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A Dynamic Model of Nutrient Digestion and Metabolism in Lactating Dairy Cows

Allan Danfær

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A Dynamic Model of Nutrient Digestion and Metabolism in Lactating Dairy Cows

En dynamisk model af næringsstoffernes fordøjelse og omsætning hos malkekøer

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København, den 14. marts 1990.

Jann Hau

Formand for fagrådet for husdyrbrugs- og veterinærvidenskab

PREFACE

Experts have
their expert fun
ex cathedra
telling one
just how nothing
can be done

(Piet Hein)

All scientists use models in their research work. Even those who persistently deny it. It is hardly possible to design an experiment and to interpret its results without any idea of how the system under investigation is functioning. Such ideas or hypotheses can be regarded as models, i.e. the scientist's conception of the real world or some part of it.

Some years ago it appeared to me that most of the available knowledge in physiology and biochemistry was not utilized to any great extent within nutrition research in dairy cows. I then became interested in modelling as a method to incorporate such knowledge into systematic and quantitative descriptions of the biology of a lactating cow and to integrate details of subunits into simulations of whole animal performance. Since that time research work within endocrinology, cell biology and biochemistry, i.e. metabolic regulation, has increased rapidly, and the need for intellectual methods to systematize and integrate new data has increased even more.

Thanks to the advancing computer technology very large quantitative models can be made operational and therefore can be used to simulate the behaviour of living systems.

For these and other reasons it became clear to me that a whole animal simulation model of a lactating cow could be useful both in theoretical and in more applied studies of dairy cow nutrition and metabolism.

The present work was carried out from 1981 and onwards at the National Institute of Animal Science, Department of Animal Physiology and Biochemistry. The Head of Department, **Dr.agro. Arnold Just** has - especially during the later stages of the process - encouraged me to complete the work and to have it published as a thesis. **Dr.med.vet. Niels Agergaard** and other colleagues in the department have evinced me great confidence, patience and encouragement.

At early phases of the work I had fruitful theoretical discussions with Professor, **Dr.scient. Mogens Flensted-Jensen** and Ass. professor **Poul Einer Hansen**, Department of Mathematics, The Royal Veterinary and Agricultural University, Copenhagen. **Lic.agro. Iver Thysen** has formulated the auxiliary SAS programs of the model, and **Mr. Lars B. Gildbjerg** has assisted me in preparing the many computer-drawn figures. The difficult manuscript was typed in a most skilful and careful manner by **Mrs. Inge Knudsen.**

Dr. John D. Oldham, The East of Scotland College of Agriculture, has been an invaluable help by reading the manuscript and suggesting many linguistic improvements.

I wish to express my sincere thanks to colleagues and good friends who have inspired, assisted and encouraged me during the work - and an apology to those who have not been mentioned here. The financial support given for 4 years by **The Joint Committee for Agricultural Research and Experiments** are also gratefully acknowledged.

Finally, I can only hope that the infinite patience of my wife and children, which has been beyond description, can be somehow rewarded.

Foulum, December 1989

Allan Danfær

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SUMMARY

Chapter 1: INTRODUCTION

The need for models. In the field of animal nutrition detailed biochemical and physiological knowledge is accumulating. Efficient utilization of new knowledge implies that it can be put into the perspective of whole animal metabolism. Therefore, there is a growing need for collection and integration of the revealed biological relationships in order to improve our current understanding of animal physiology and performance. The construction of conceptual animal models is a method to organise existing knowledge in a meaningful way.

Operational models of nutrient digestion and metabolism in an animal can provide integrated quantitative descriptions of major metabolic pathways and important interactions of different nutrients. The development and use of such models can contribute to scientific progress in several ways:

- improvement of our understanding concerned with animal digestion and metabolism
- identification of lacking or poor knowledge of quantitative nutritional relationships
- improvement of the basis for development of hypotheses and for designment of critical experiments to test them
- improvement of procedures for a more precise evaluation of experimental results.

Animal models can be provided with the property of simulating processes of digestion and metabolism, and thereby be predictive of animal performance. Use of such models - if they are sufficiently realistic - could reduce the future needs for feeding trials, which are generally long lasting and costly.

Definition of models. A model is a simplified symbolic representation of a system. In an animal model the system is the animal and some specified part of its environment, e.g. its feed.

Quantitative or mathematical models consist of equations, which describe the behaviour of the given system. Mathematical models can be classified as:

- static or dynamic
- stochastic or deterministic
- empirical or mechanistic.

Static models do not contain time as a variable, and therefore cannot describe any time-dependent behaviour of the system. Dynamic models do contain time as a variable, and are suited to simulate the continual changes and adaptations in the rates of processes occurring in living animals.

Stochastic models contain probability distributions so that not only expected values of rates and quantities, but also their variances, are predicted. Deterministic models can only give definite quantitative predictions.

Mechanistic models are explanatory as they are based on facts and/or theories about mechanisms of the underlying behaviour of the system. On the other hand, empirical models are only based on exprimental data and not any causal relationships about the observations.

Some published dynamic models. During the last 15 years many dynamic models of different biological systems have been published. Within animal science systems of different hierarchical levels are modelled: from individual pathways to the rumen and body tissues of sheep, the cow mammary gland, the lactating cow, and cattle herds.

Chapter 2: OVERALL DESCRIPTION OF THE MODEL

Nature and structure of the model. The purpose of the presented work has been to develope a dynamic, deterministic and mechanistic whole animal model of the lactating dairy cow. The objective of that model is to simulate the conversion of nutrients through digestive and metabolic processes in the cow into products of milk and body gain.

The model is composed of 9 compartments (figures 2.1-2.6) representing different organs or tissues of the cow: the rumen, intestinal lumen, intestinal wall, liver, peripheral blood and extracellular fluid, mammary gland, muscle tissue, adipose tissue, and other tissues.

Terminology of the model. The state variables in the model are either carbon or nitrogen pools. The pools of carbon are labelled C, and represent carbohydrates, lipids and other N-free organic substances. The pools of nitrogen are representing protein, peptides and amino acids (labelled A), NH_3/NH_4^+ (labelled N), and urea (labelled U).

The units of mass are moles of carbon (C) and nitrogen (N) for the carbon and nitrogen pools, respectively. All state variables of the model with names, symbols, units and initial numerical values are listed in Tables 2.1-2.9.

The rates of carbon and nitrogen flow between pools are labelled R_i (mol C/h) and R_j (mol N/h), respectively, starting at i = 100 and j=0. Flow rates integrated over 24 h are named fluxes (F_i or F_j) and are given as mol C/d or mol N/d.

General mathematical and biological principles. The dynamic behaviour of the model is achieved by using differential equations to describe the continual changes of the state variables. The rate variables are described by equations which are mathematical formulations of either Michaelis-Menten enzyme kinetics or first order mass action kinetics.

In some of the rate equations describing enzyme kinetics the numerical value of the affinity constant is regulated by the numerical value of the substrate or product pool (state variable). In this way the principle of allosteric enzyme regulation is simulated by the model.

Input parameters and output variables. Parameter values describing chemical composition of the feed, live weight of the cow and stage of lactation are required as input data to the model. With this information the model computes the numerical value of all state variables, rate variables and fluxes of matter shown in figures 2.1-2.6 at any time of the "model day".

In order to relate the simulation results to terms of whole animal performance the following output variables are calculated from relevant fluxes of matter:

- feed dry matter intake (kg/d)
- milk production (kg/d)
- milk composition (g/kg)
- live weight gain (kg/d)
- tissue energy balance (MJ/d)
- energy in milk (MJ/d)
- gross energy intake (MJ/d)
- energy losses (MJ/d)
- net energy intake (MJ/d).

Model size and programming languages. The model consists of 77 state variables and a total of about 1500 equations of which about 340 are differential equations. The computer program is written in the CSMP III simulation language, but a great deal of the computations are programmed in FORTRAN subroutines. Statistical treatments and graphical presentations of output variables are performed by means of auxiliary SAS programs.

Chapter 3: DETAILED DESCRIPTION OF THE MODEL

The procedure for constructing the model. A static model has been used as a basis for the development of the dynamic model. The static model is based on publications of Hvelplund (1983) and Danfær (1983b), and describes the daily feed intake, nutrient flow through the body, milk production and live weight change of a cow in early lactation. The assumed feed intake is 17.9 kg dry matter per d of a specified composition, the milk yield is 30.0 kg/d, and the live weight change is -0.5 kg/d. The feed is a complete mixed diet offered ad libitum.

In the next step of the procedure differential equations and auxiliary equations have been defined in the dynamic model followed by assignment of numerical values to state variables and equation parameters. The numerical values are derived from literature data or assumed as biologically probable.

Finally, the parameter values have been adjusted by means of repeated simulations until the dynamic model gave the same solutions as the static model with regard to daily feed intake, nutrient fluxes, milk production, live weight change and overall energy metabolism.

The computer programs. The main framework of the model is formulated in the CSMP III programming language and consists of 3 parts: the INITIAL, the DYNAMIC, and the TERMINAL segments.

The INITIAL segment contains those statements which are executed only once at the beginning of each run. A run is a simulation period representing the time course of 24 h. In the DYNAMIC segment FORTRAN subroutines with rate equations and regulatory equations are called for execution, and integrations of differential equations are carried out in between the execution of subroutines. All statements in the DYNAMIC segment and in the FORTRAN subroutines are computed at each integration step until the end of a run. Statements in the TERMINAL segment are only executed at the end of each run. FORTRAN subroutines called from this part of the program allow the state variables and regulated parameters to keep their numerical values obtained at the end of a run as initial values for the next run.

The output variables from the CSMP III program are organized in a data set created by means of an auxiliary SAS program. From this data set another SAS program can perform statistical treatments, further calculations, and graphical presentations of the output variables.

The computer programs are shown in Appendices 1-4.

The individual equations, state variables and parameters. In this section the model is described in detail, compartment by compartment. The individual equations are defined, and numerical values are assigned to state variables and parameters. The individual nutrient fluxes are derived primarily from the static model, and the numerical values of state variables and parameters are assumed or estimated from other literature data. All state variables and equation parameters together with their original as well as their finally adjusted values are listed in Appendices 5-8.

Chapter 4: RESULTS OF MODEL SIMULATIONS

Comparison of results from the dynamic and the static model. The results from the static model are compared to daily fluxes of matter (F_i, F_j) computed by the dynamic model. Some of the results from the dynamic model are further evaluated against literature data, which have not been used for development of the model.

The presented results from the dynamic model are means of 10 runs (run 26-35) as the first 25 runs are regarded as a period of equilibration. A complete list of all nutrient and metabolite fluxes simulated by the dynamic model is given in Appendix 9 together with results from the static model.

All results simulated by the dynamic model are almost identical to those of the static model. Daily feed intake, milk yield, live weight change and general energy metabolism are shown in Tables 4.1 and 4.2. Aspects of ruminal and intestinal digestion and absorption, liver metabolism, mammary gland metabolism, and body tissue metabolism are given in Tables 4.3-4.9.

In order to achieve that solutions of the dynamic model would be close to the results from the static model, the numerical values of state variables and equation parameters have been adjusted during repeated simulations. By this procedure a relatively small number of parameter values are changed more than 100% from the originally derived ones. Those parameters are listed in Table 4.11.

Diurnal variations of pool sizes, affinity constants, and rates of transaction. In this section examples of simulated within run variations of state variables, rates and regulated affinity constants are presented. The chosen examples are from the rumen compartment (figures 4.1-4.19), the intestinal compartments (figures 4.20-4.25), the liver compartment (figures 4.26-4.30), the peripheral blood compartment (figures 4.31-4.41), and the mammary gland and body tissue compartments (figures 4.42-4.47).

The very distinct diurnal variations in rumen nutrient pool sizes and in absorption rates from the rumen caused by the pattern of feed intake (figure 4.1) are more or less smoothed out in nutrient pool sizes of the blood and in rates of nutrient uptake by the tissues.

Although the simulated fluctuations during the "model day" of the parameter values in some cases are very large and irregular, all parameters return to or approach their initial values at the end of the "day".

Stability of the model. The dynamic model is evaluated with regard to stability by examination of the reproducibility of the simulations through sequential runs. Mean values, standard deviations, and minumum and maximum values of some of the output variables during 10 runs of simulation (run 26-35) are shown in Table 4.12. The between run variations of the selected simulation results are small and representative for all other output variables in the model. In addition to this the model stability is evaluated after 500 runs of simulation. Mean values, standard deviations, maximum and minimum values for dry matter intake, milk production and live weight gain are given for every 50 runs as well as for all 500

runs (Table 4.13). The trends of stability in these output variables are illustrated in figure 4.48.

Chapter 5: USE OF THE MODEL

This chapter deals with the use of the dynamic model to simulate situations different from those presumed in the definition of the model (a nonpregnant cow at 44 days post partum fed ad libitum on a complete mixed diet of a specified composition).

Simulation of animal performance at different stages of lactation. The altered nutrient partition during progressing lactational stages is regulated in the model by means of simulated changes of plasma concentrations of metabolic hormones. In this way the model can simulate declining milk yields and increasing live weight gains during the lactational period.

Results of 2 simulations are presented. In the first one, animal performance (milk yield, live weight gain and body weight) at different stages of lactation is simulated by the original version of the model as described in chapter 4. In the second simulation, the numerical value of a few equation parameters are changed in order to mimic an altered tissue responsiveness to metabolic hormones. The changes imply that the performance of a cow with a higher potential for milk yield and a lower potential for body gain is simulated. The resulting curves of milk yield, live weight gain and body weight during lactation are shown in figure 5.1.

The differences between the 2 sets of simulated curves illustrate how cows with different tissue sensitivity to metabolic hormones, i.e. different genetic capacity for milk production, respond to the same feed during lactation.

Simulation of growth hormone treatments. Short-term administration of growth hormone is imitated by the model at 2 lactational stages, 73 and 257 days post partum. In these simulations milk yield is increased by increasing levels of treatment in a curvilinear fashion, both in early and in late lactation (figures 5.2 and 5.3). The relative responses in milk yield to increasing "doses" of growth hormone are much higher in late than in early lactation. Other simulated treatment effects are: unchanged feed intake, decreased energy balance, decreased plasma glucose and insulin concentrations, and increased plasma concentration of free fatty acids.

The efficiency of milk production (kg milk per unit of net energy intake) can be regarded as a measure of nutrient partitioning between the mammary gland and the body tissues. It is therefore expected that this parameter is positively correlated to the ratio of growth hormone and insulin concentrations. Such a relationship is simulated by the model (figure 5.4).

Simulation of a feeding experiment. In this section the model is used to simulate the results from one specific feeding experiment published by Krohn & Konggaard (1987). The cows in that experiment were offered a total mixed diet ad libitum. The results of 3 simulations are presented. In the first simulation, the model is used

in its original version except for those parameter values concerned with the specific experimental conditions. The second simulation is performed after a change of some internal model parameters to simulate a different nutrient partition. In the third simulation, more parameter values concerned with nutrient uptake and adipose tissue metabolism have been altered.

The first simulation underestimates the milk yield and overestimates the live weight gain. The second simulation underestimates the rate of daily gain. In the final simulation, the deviations between the observed and the simulated results (feed intake, milk yield, milk composition, live weight gain) are very small (Table 5.3).

Simulated regulation of gluconeogenesis. The significance of amino acids as substrates for glucose synthesis is an important factor in the utilization of protein for milk production. This aspect of the intermediary metabolism is not fully clarified by the present experimental knowledge. Therefore, the model is used to elucidate the following questions:

- How much of the synthesized glucose is derived from propionate and from amino acids when different diets are fed?
- How are the contributions of propionate and amino acids to glucose synthesis regulated?

For that purpose an experiment is simulated in which 3 different rations are fed to dairy cows in early lactation. The experimental diets are characterized (Table 5.4) by a high starch content (diet HS), a high protein content (diet HP), and by starch and protein partly protected against rumen fermentation (diet BSP).

The simulated results (Table 5.5) suggest that the rate of gluconeogenesis is higher with diet HS (16 mol glucose/d) than with the other 2 diets (13-14 mol/d), that the contribution of propionate to glucose synthesis is higher on diet HS (81%) than on the other diets (65%), and that the contribution of amino acids to glucose synthesis is lowest on diet HS (3%) and highest on diet HP (20%). The availability of propionate is highest with diet HS, whereas the availability of amino acids is almost the same for all diets. The ratio of glucagon to insulin concentrations in blood plasma is highest on diet HP and lowest on diet BSP.

In the model, the contributions of propionate and amino acids to gluconeogenesis are regulated partly by the substrate availability and partly by the metabolic hormones, glucagon and insulin. This explains the simulated differences between the diets.

The inclusion of rumen bypass starch and protein in diet BSP increases the simulated milk yield as well as the efficiency of energy and protein utilization. In another simulated experiment the effects of incremental degrees of dietary starch protection are examined. The simulated effects (figures 5.5-5.8) of increasing levels of unfermentable starch can be summarized as follows:

- decreased feed intake, and decreased absorption of propionate and amino acids
- increased absorption of glucose, and decreased rate of gluconeogenesis
- increased milk yield, but decreased milk energy secretion
- varying net energy content per kg feed dry matter of the same chemical composition.

Chapter 6: DISCUSSION AND CONCLUSIONS

Model objectives and evaluation criteria. The chapter is initiated with a brief review of the methodology of the modelling process and the basic principles of model evaluation.

The main objective of the presented model is to simulate the conversion of nutrients through digestive and metabolic processes in the lactating dairy cow into intermediate substances, and further into waste products, and products of milk and tissue constituents. Several minor objectives can be attained with such a general model:

(i) Prediction of the effects of different diets on animal performance at different lactational stages.
(ii) Evaluation of current physiological and biochemical concepts causal to animal performance.
(iii) Evaluation of new hypotheses about the regulations of nutrient digestion and metabolism in dairy cows.

The criteria for validation of the model depend on the modelling objectives. The evaluation in relation to objective (i) can be performed by comparing the simulation results with a wide range of quantitative experimental data from feeding trials, digestibility studies, and studies of visceral and peripheral tissue metabolism. The model can be evaluated with regard to objective (ii) by examining subunit behaviour against data on the regulation of nutrient metabolism in individual tissues. When these minor objectives have been achieved, the model can be accepted as regards to its main objective. The usefulness of the model in relation to objective (iii) will increase as the model is developed towards achie-

vement of the main objective.

Evaluation of the model. A number of simulated processes in the digestive tract, the liver and the peripheral tissues are compared to literature data in order to evaluate the model in anticipation of the predictive purpose (objective i). The simulation results are within ranges of experimental values for the following processes:

The digestive tract

- Apparent rumen digestibility of organic matter
- VFA production in the rumen
- Microbial net growth and protein synthesis in the rumen
- Degradation of dietary protein in the rumen
- Digestibility of amino acids in the small intestine.

The liver

- Contribution of propionate and amino acids to glucose synthesis
- Urea synthesis
- Heat production.

The mammary gland

- Glucose uptake and partition between intracellular pathways.

The simulated contribution of amino acids to liver gluconeogenesis is much higher than the lowest of the experimental values used for the comparison. In the mammary gland, the simulated rates of uptake and oxidation of acetate and ketone bodies are considerably higher than corresponding experimental figures. These differences

between modelling results and literature data are discussed, and it is questioned, if the in vivo estimates have general validity.

The simulated diurnal variations of some output variables are evaluated in relation to concepts used in the model about the behaviour of subunits (objective ii). Comparisons with data from the literature show that the diurnal variations in the rate of feed intake, and in the blood plasma concentrations of insulin, glucose, ketone bodies, lactate, amino acids and urea are imitated in a realistic way. Hence, the underlying physiological and biochemical concepts are supported. The comparisons show further, that the model is somewhat insufficient in its concepts of free fatty acid release from the adipose tissue.

The predictive ability of the model is evaluated further by simulation of results from a specific feeding experiment. After adjustment of some parameter values in the model, the simulated feed intake, milk yield, milk composition and live weight gain are as observed in the experiment.

Quantitative (objective i) as well as qualitative (objective ii) aspects of model behaviour are evaluated by simulations of animal performance at different stages of lactation, and by simulations of animal performance after growth hormone treatments.

The simulated curves of milk yield and live weight gain during the lactational period are similar to in vivo observations. The ability of the model to simulate different lactational milk yields and weight gains of cows having the same feed intake points to the possibility of using the model to formulate hypotheses about the physiological background for different genetic capacities of milk

yield.

The simulated effects of short-term growth hormone treatments on animal performance are similar to in vivo observations with regard to:

- dose-dependent, curvilinear responses in milk yield both in early and late lactation
- relatively higher increases in milk yield in late than in early lactation
- unchanged feed intake and decreased energy balance
- increased plasma concentration of free fatty acids.

However, the simulated effects on the plasma concentrations of growth hormone, insulin and glucose are not in accordance with experimental findings. Within these aspects of hormonal regulation the model can only be partly accepted in relation to its purpose of prediction (objective i) and of concept evaluation (objective ii).

Important questions concerned with the regulation of gluconeogenesis and the extent of amino acid contribution to glucose synthesis have been identified. The model is used to elucidate these questions as they are not fully clarified in the literature. The results of the performed simulations can be partly confirmed by experimental data, and suggest the following:

- amino acids can be quantitatively important as substrates for glucose synthesis
- the need for liver gluconeogenesis is reduced by inclusion of protected starch and protein in the diet
- the efficiency of energy and protein utilization is increased by inclusion of protected starch and protein in the diet

- diets of identical chemical compositions, but with different starch degradabilities, have different net energy values.

It is concluded from these results, that a sufficiently realistic dynamic, mechanistic model could be the best tool for evaluation of different feeds and diets for lactating cows.

Advantages and drawbacks of the model. Some of the qualitative properties of the model are discussed in this section. A general advantage is that with modelling it is possible to avoid a classical problem in animal science, namely that an object cannot be studied in detail without affecting the object itself. It is admitted, however, that experimental data obtained by traditional methods are requested for the construction and evaluation of models. Other general qualities confined to dynamic models are the great flexibility of such models, and further that quantitative impacts of acute metabolic changes on whole animal performance (i.e. metabolic regulations) can be simulated. In the present model a simple principle to simulate metabolic regulation is introduced. This principle is based on the biological phenomena of allosteric enzyme regulation.

The defects of the model are related to the general structure of the model, regulation of food intake, microbial growth in the digestive tract, metabolism of minerals and vitamins, regulation of hormone secretion, regulation of mammary gland capacity for milk synthesis, and regulation of energy metabolism. The general structure of the model is suffering from an improper weighting of the description of the peripheral tissues compared to the visceral tissues. Another problem is that the model is difficult to evaluate completely because of its size and complexity. The rate of

feed intake in the model is regulated only by rumen fill and not by products of digestion and metabolism. The simulated rate of microbial growth is directly proportional to the rate of ATP synthesis ignoring the ATP requirement for maintenance. The metabolism of minerals and vitamins are not included in the model, hence these are not considered as limiting factors. The levels of metabolic hormones in the blood during the lactational period are in the model based upon empirical data rather than being determined by intrinsic and mechanistic elements. The model regulates the rate of milk synthesis only by substrate availability, and the synthetic capacity within the mammary tissue is not changed with progressing lactation. A serious drawback of the model is that rates of substrate oxidation are not regulated at the tissue level by the requirement for energy in synthetic pathways. This means that rates of synthetic processes are also not regulated by the availability of ATP and reduced cofactors produced by substrate oxidations. Therefore the model simulations are not expected to be satisfactory in situations such as fasting or very low feed intakes, where energy supply is the limiting factor.

Perspectives for use of the model. In the future the model can be used in two areas of scientific work:

1) Stimulation of thinking, formulation and evaluation of hypotheses, and identification of lacking or false knowledge.

2) Prediction of animal performance.

Within the second area the model could be a useful tool in screening of new feed rations, for finding the optimum composition of feed rations, and for development of a complete feed evaluation system based upon the metabolism of absorbed nutrients.

Conclusions. The following can be concluded from the discussion of the presented work:

- A dynamic, deterministic and mechanistic whole animal model has been developed in accordance with its main objective: to simulate the conversion of nutrients through digestion and metabolism in the cow into intermediate substances and further into waste products and products of milk and tissue constituents. However, this objective is not fully achieved, and the model needs further development and adjustments.

- The model is based on a static model of nutrient digestion and metabolism in the lactating dairy cow. The solutions of the dynamic model are the same as those of the static model with regard to daily flux rates of matter through all modelled transactions.

- The results of a specific feeding experiment are simulated accurately by the model after some parameter adjustments.

- A number of simulated results concerned with digestion, liver metabolism, mammary gland metabolism, hormonal regulations and lactational performance are in agreement with independent literature data.

- The simulated rates of glucose synthesis from amino acids in the liver and acetate metabolism in the mammary gland differ from some in vivo observations. The general validity of the experimental results is doubtful, and more work should be devoted to these questions.

- The model is very flexible and possesses a new, simple principle of modelling allosteric regulations of pool sizes and rates of transaction.

- In future work the model can be utilized in theoretical research as well as for predictive purposes. This could lead to the development of a complete feed evaluation system based on dynamic modelling.

- Knowledge of animal digestion and metabolism can be efficiently improved by combining different experimental methods with the modelling approach.

SAMMENDRAG

Kapitel 1: INDLEDNING

Er der behov for modeller? Detaljeret biokemisk og fysiologisk viden inden for området husdyrernæring øges mere og mere. En effektiv udnyttelse af denne viden forudsætter, at den kan vurderes i perspektivet af dyrenes totale stofskifte. Der er derfor et voksende behov for at integrere nye erkendelser om biologiske sammenhænge for dermed at forbedre forståelsen af husdyrenes fysiologi og livsytringer. Opbygning af teoretiske dyremodeller er en metode til at organisere eksisterende viden på en fornuftig måde.

Operationelle modeller af næringsstoffernes fordøjelse og omsætning i et dyr kan integrere kvantitative beskrivelser af vigtige stofskifteprocesser samt vekselvirkninger mellem forskellige næringsstoffer. Udvikling og brug af sådanne modeller kan bidrage til videnskabelige fremskridt på flere måder:

- forbedring af vores forståelse af husdyrernes fordøjelse og næringsstofomsætning
- erkendelse af manglende eller mangelfuld viden om kvantitative ernæringsmæssige sammenhænge
- forbedring af grundlaget for at opstille hypoteser samt for at planlægge kritiske forsøg til at afprøve disse
- muligheder for en mere præcis tolkning af forsøgsresultater.

Dyremodeller kan konstrueres således, at de kan simulere fordøjelses- og stofskifteprocesser og dermed forudsige dyrenes livsytringer. Anvendelse af sådanne modeller - forudsat at de er tilstrækkeligt realistiske - kunne formindske det fremtidige behov for langvarige og kostbare fodringsforsøg.

Definition af modeller. En model er en simplificeret symbolsk afbildning af et system. Systemet, der repræsenteres af en dyremodel, er dyret selv samt en angivet del af dyrets miljø, f.eks. foderet.

Kvantitative eller matematiske modeller består af ligninger, som beskriver det givne systems reaktioner på forskellige stimuli eller input. Matematiske modeller kan klassificeres som:

- statiske eller dynamiske
- stokastiske eller deterministiske
- empiriske eller mekanistiske.

Statiske modeller indeholder ikke tiden som en variabel og kan derfor ikke beskrive tidsafhængige reaktioner i systemet. Dynamiske modeller indeholder tiden som en variabel og er velegnede til at simulere de kontinuerte ændringer og tilpasninger, som finder sted i levende dyrs stofskifteprocesser.

Stokastiske modeller indeholder sandsynlighedsfordelinger således, at modellerne forudsiger ikke blot de forventede værdier af mængder og hastigheder, men også disses varianser. Deterministiske modeller kan kun give entydige kvantitative forudsigelser.

Mekanistiske modeller er forklarende, da de er baserede på viden og/eller teorier om de mekanismer, der bestemmer systemets reaktioner. Empiriske modeller er derimod kun baserede på eksperimentelle observationer og ikke på disses årsagssammenhænge.

Publicerede dynamiske modeller. Adskillige dynamiske modeller af forskellige biologiske systemer er publiceret i løbet af de sidste 15 år. På husdyrområdet er der udarbejdet modeller med meget forskellig detaljeringsgrad (hierarkisk niveau): enkelte stofskifteveje, vommen og kropsvæv hos får, mælkekirtlen hos køer, den lakterende ko samt hele kvægbesætninger.

Kapitel 2: OVERORDNET BESKRIVELSE AF MODELLEN

Modellens art og struktur. Hensigten med det præsenterede arbejde har været at udvikle en dynamisk, deterministisk og mekanistisk model af en lakterende ko. Modellens formål er at simulere næringsstoffernes omdannelse gennem koens fordøjelses- og stofskifteprocesser til mælk og tilvækst.

Modellen er sammensat af 9 delmodeller (figurerne 2.1-2.6), som repræsenterer forskellige organer og væv i koen: formaver, tarmlumen, tarmvæg, lever, blod og ekstracellulær væske, mælkekirtel, muskelvæv, fedtvæv samt andre væv.

Modellens terminologi. Modellens tilstandsvariable er enten kulstof- eller kvælstofpuljer. Kulstofpuljerne er mærkede med C og repræsenterer kulhydrater, lipider og andre N-fri organiske stoffer. Kvælstofpuljerne repræsenterer proteiner, peptider og aminosyrer (mærkede A), NH_3/NH_4^+ (mærkede N) samt urinstof (mærkede U).

De anvendte enheder for masse er mol kulstof (C) og mol kvælstof (N) for henholdsvis kulstof- og kvælstofpuljerne. Alle modellens tilstandsvariable med navne, symboler, enheder og initiale numeriske værdier er anført i tabellerne 2.1-2.9.

Strømningshastighederne af kulstof og kvælstof mellem puljer er mærkede med henholdsvis R_i (mol C/time) og R_j (mol N/time) begyndende med i = 100 og j = 0. En strømningshastighed integreret over 24 timer benævnes en flux (F_i eller F_j) og angives som mol C/dag eller mol N/dag.

Generelle matematiske og biologiske principper. Modellens dynamiske egenskaber opnås ved anvendelse af differentialligninger til at beskrive kontinuerte ændringer i de tilstandsvariable. De hastighedsvariable er beskrevet ved hjælp af ligninger, som er matematiske formuleringer af enten Michaelis-Menten enzymkinetik eller første ordens massevirkningskinetik.

I nogle af hastighedsligningerne, der beskriver enzymkinetik, reguleres affinitetskonstantens numeriske værdi af den aktuelle masse af substrat- eller produktpuljen (en tilstandsvariabel). Modellen kan på denne måde simulere princippet for allosterisk enzymregulering.

Input parametre og output variable. Parameterværdier til beskrivelse af foderets kemiske sammensætning samt koens legemsvægt og laktationsstadium er nødvendige som modellens input data. Ud fra denne information beregner modellen på ethvert tidspunkt af et "modeldøgn" den numeriske værdi af alle tilstandsvariable, hastighedsvariable samt stofstrømme (fluxer) vist i figurerne 2.1-2.6.

Følgende variable beregnes herudover ud fra relevante stofstrømme for at relatere simuleringsresultaterne til dyrets samlede livsytringer:

- tørstofoptagelse (kg/dag)
- mælkeydelse (kg/dag)
- mælkens sammensætning (g/kg)
- tilvækst (kg/dag)
- energibalance (MJ/dag)
- energi i mælk (MJ/dag)
- optagelse af bruttoenergi (MJ/dag)
- energitab (MJ/dag)
- optagelse af nettoenergi (MJ/dag).

Modellens størrelse og de anvendte programmeringssprog. Modellen består af 77 tilstandsvariable og mere end 1500 ligninger, hvoraf ca. 340 er differentialligninger. Det tilhørende EDB-program er formuleret i programmeringssproget CSMP III, men en stor del af beregningerne er programmeret som FORTRAN subrutiner. Statistiske beregninger og grafisk fremstilling af output variable udføres ved hjælp af særlige SAS programmer.

apitel 3: DETALJERET BESKRIVELSE AF MODELLEN

remgangsmåde for modellens opbygning. En statisk model er anvendt
om grundlag for udviklingen af den dynamiske model. Den statiske
odel, der er baseret på publikationer af Hvelplund (1983) og Dan-
r (1983b), beskriver foderoptagelse, næringsstofstrøm gennem
oppen, mælkeydelse og tilvækst hos en malkeko i tidlig lakta-
on. Den daglige foderoptagelse er 17.9 kg tørstof af en given
mmensætning, mælkeydelsen er 30 kg/dag, og vægtændringen er -0.5
/dag. Foderrationen er et fuldfoder givet efter ædelyst.

fferentialligninger og hjælpeligninger i den dynamiske model er
rnæst definerede, hvorefter tilstandsvariable og ligningsparame-
e er tildelt numeriske værdier. De numeriske værdier er udledt
a litteraturen eller antaget som værende biologisk sandsynlige.

delig er parameterværdierne justeret efter gentagne simulerin-
r, indtil den dynamiske model har givet de samme løsninger som
n statiske model med hensyn til foderoptagelse, næringsstof-
rømme, mælkeydelse og tilvækst samt generel energiomsætning.

B-programmer. Modellens hoveddel er beskrevet i programmerings-
roget CSMP III og består af 3 segmenter: INITIAL, DYNAMIC og
MINAL.

TIAL segmentet indeholder de ordrer (statements), som kun udfø-
én gang ved begyndelsen af hver simuleringskørsel (run). En
rsel er en simuleringsperiode, der svarer til 1 "modeldøgn".

FORTRAN subrutiner med hastighedsligninger og regulerende ligninger kaldes til udførelse fra DYNAMIC segmentet, og integration af differentialligninger foretages ind imellem beregning af subrutiner. Alle ordrer i DYNAMIC segmentet og i FORTRAN subrutinerne udføres for hvert integrationstrin indtil afslutningen af en kørsel. Ordrer i TERMINAL segmentet udføres kun i slutningen af hver kørsel. FORTRAN subrutiner, der kaldes fra denne del af programmet, tillader tilstandsvariable og regulerede parametre at beholde de ved slutningen af en kørsel opnåede numeriske værdier som begyndelsesværdier i den efterfølgende kørsel.

Output variable fra CSMP III programmet organiseres i et datasæt, som dannes ved hjælp af et SAS program. De variable kan fra dette datasæt underkastes statistiske behandlinger, yderligere beregninger samt grafisk fremstilling med et andet SAS program.

De anvendte programmer er vist i Appendiks 1-4.

De enkelte ligninger, tilstandsvariable og parametre. I dette afsnit er modellen beskrevet i detaljer, hver delmodel for sig. De enkelte ligninger er definerede, og tilstandsvariable samt parametre er tillagt numeriske værdier. De individuelle næringsstofstrømme er primært udledt fra den statiske model, og de numeriske værdier af tilstandsvariable og parametre er bestemt ved skøn eller ud fra litteraturen. Alle tilstandsvariable og ligningsparametre med deres oprindelige såvel som deres endeligt justerede værdier er vist i Appendiks 5-8.

Kapitel 4: RESULTATER AF MODELSIMULERINGER

Sammenligning af resultater fra den dynamiske og den statiske model. Resultaterne fra den statiske model er sammenlignet med de stofstrømme (F_i,F_j), som er beregnet af den dynamiske model. Nogle af resultaterne fra den dynamiske model er yderligere vurderet i forhold til eksperimentelle data, der ikke har været anvendt som grundlag for udvikling af modellen.

De præsenterede resultater fra den dynamiske model er gennemsnit af 10 simuleringskørsler (run 26-35), idet de første 25 kørsler betragtes som en periode til indstilling af modellens ligevægt. En fuldstændig fortegnelse over alle næringsstofstrømme simuleret af den dynamiske model er vist i Appendiks 9 sammen med resultater fra den statiske model.

Alle dynamiske simuleringsresultater er næsten identiske med de tilsvarende beregnet i den statiske model. Daglig foderoptagelse, mælkeydelse, vægtændring samt generel energiomsætning er anført i tabellerne 4.1 og 4.2. Aspekter af fordøjelse og absorption fra fordøjelseskanalen samt af næringsstofomsætningen i lever, mælkekirtel og kropsvæv er vist i tabellerne 4.3-4.9.

De numeriske værdier af tilstandsvaribale og ligningsparametre er blevet justeret under gentagne simuleringer med det formål, at de dynamiske modelløsninger skulle være tættest muligt på resultaterne fra den statiske model. Ved denne fremgangsmåde er et relativt lille antal parameterværdier ændret mere end 100% fra de oprindeligt udledte værdier. Disse parametre er anført i tabel 4.11.

Døgnvariationer i næringsstofpuljer, affinitetskonstanter og proceshastigheder. Eksempler på variationer inden for en simuleringskørsel af tilstandsvariable, hastighedsvariable samt regulerede affinitetskonstanter er præsenteret i dette afsnit. De valgte eksempler er fra delmodeller af formaverne (figurerne 4.1-4.19), tarmkanalen (figurerne 4.20-4.25), leveren (figurerne 4.26-4.30), det perifere blod (figurerne 4.31-4.41) samt mælkekirtlen og kropsvævene (figurerne 4.42-4.47).

De meget tydelige døgnvariationer i formavernes næringsstofpuljer og absorptionshastigheder forårsaget af foderoptagelsesmønstret (figur 4.1) er mere eller mindre udjævnede i blodets næringsstofpuljer samt i vævenes næringsstofoptagelse.

Alle parameterværdier vender tilbage til eller nærmer sig deres begyndelsesværdier ved slutningen af en kørsel, selv om de simulerede fluktuationer af parametrene i nogle tilfælde er meget store og uregelmæssige i løbet af "modeldøgnet".

Modellens stabilitet. Den dynamiske model er vurderet med hensyn til stabilitet ved at undersøge simuleringernes reproducerbarhed i flere på hinanden følgende kørsler. Middelværdier, standardafvigelser samt minimum- og maksimumværdier af nogle output variable fra 10 simuleringskørsler (run 26-35) er vist i tabel 4.12. Variationerne mellem kørsler af de udvalgte simuleringsresultater er små og repræsentative for alle andre output variable i modellen. Modelstabiliteten er desuden vurderet efter 500 simuleringskørsler. Middelværdier, standardafvigelser, minimum- og maksimumværdier for tørstofoptagelse, mælkeydelse samt tilvækst er anført for såvel hver 50 som for alle 500 kørsler (tabel 4.13). Stabilitetens udvikling for disse output variable er vist grafisk i figur 4.48.

Kapitel 5: ANVENDELSE AF MODELLEN

Dette kapitel omhandler modellens anvendelse til simulering af situationer med andre forudsætninger end de, der ligger til grund for modellens opbygning (d.v.s. en ikke-drægtig ko, der fodres efter ædelyst med et fuldfoder af en given sammensætning, 44 dage efter kælving).

Simulering af mælkeydelse og tilvækst gennem laktationsperioden.
Den ændrede næringsstoffordeling hen igennem laktationsperioden er i modellen reguleret ved hjælp af simulerede ændringer i koncentrationen af cirkulerende stofskiftehormoner. Modellen kan herved simulere en faldende mælkeydelse og stigende tilvækst med øget afstand fra kælving.

Der er præsenteret resultater af 2 simuleringer. I den første er mælkeydelse, tilvækst og koens legemsvægt simuleret i forskellige stadier af laktationsperioden med den oprindelige version af modellen, som den er beskrevet i kapitel 4. I den anden simulering er de numeriske værdier af nogle få parametre ændrede for at efterligne en ændret følsomhed i vævene for de regulerende stofskiftehormoner. Disse ændringer medfører, at modellen kan simulere livsytringerne hos en ko med højere kapacitet for mælkeydelse og mindre kapacitet for tilvækst. De resulterende kurver for mælkeydelse, tilvækst og legemsvægt gennem laktationen er vist i figur 5.1.

De 2 sæt simulerede kurver viser, hvordan køer med forskellig vævsfølsomhed for stofskiftehormoner (forskellig genetisk kapaci-

tet for mælkeproduktion) kan reagere på det samme foder i løbet af laktationsperioden.

Simulering af væksthormonbehandling. Kortvarig behandling med væksthormon på 2 tidspunkter i laktationen, 73 og 257 dage efter kælving, er simuleret med modellen. Mælkeydelsen øges kurvilineært med stigende "doser" væksthormon - både i tidlig og sen laktation (figurerne 5.2 og 5.3). Den relative stigning i mælkeydelse er meget højere i sen end i tidlig laktation. Andre simulerede virkninger af behandlingen er: uændret foderoptagelse, lavere energibalance, lavere koncentrationer af glukose og insulin i blodet samt forøget koncentration af frie fedtsyrer.

Foderets udnyttelse til mælkeproduktion (udtrykt som kg mælk pr. enhed nettoenergi) kan betragtes som et mål for fordelingen af næringsstoffer mellem mælkekirtel og kropsvæv. Det kan derfor forventes, at denne parameter er positivt korreleret med forholdet mellem koncentrationerne af væksthormon og insulin i blodet. Figur 5.4 viser, at modellen kan simulere en sådan sammenhæng.

Simulering af et fodringsforsøg. Modellen er i dette afsnit anvendt til at efterligne resultaterne af et fodringsforsøg publiceret af Krohn & Konggaard (1987). Køerne i dette forsøg blev tilbudt et fuldfoder efter ædelyst. Resultater af 3 simuleringer er præsenteret. I den første simulering er modellen anvendt i sin oprindelige version med undtagelse af de parameterværdier, som beskriver forsøgsbetingelserne (foderets sammensætning samt køernes vægt og laktationsstadium). Den anden simulering er udført efter ændringer af nogle interne modelparametre, der medfører en ændret næringsstoffordeling. Andre parameterværdier, der har betydning

for næringsstofoptagelse og fedtvævets stofskifte, er ændret ved den tredie simulering.

Den første simulering undervurderer mælkeydelsen og overvurderer den opnåede tilvækst. Den anden simulering underestimerer tilvæksten. I den tredie simulering (tabel 5.3) er forskellene meget små mellem de eksperimentelle og de simulerede resultater (foderoptagelse, mælkeydelse og -sammensætning samt tilvækst).

Simuleret regulering af glukoneogenesen. Aminosyrernes betydning som substrater for syntesen af glukose er en vigtig faktor for proteinudnyttelsen til mælkeproduktion. Dette aspekt af det intermediære stofskifte er ikke fuldt klarlagt af den nuværende eksperimentelle viden. Modellen er på denne baggrund anvendt til at belyse følgende spørgsmål:

- Hvor meget glukose dannes i leveren ud fra henholdsvis propionat og aminosyrer under forskellige fodringsbetingelser?
- Hvordan reguleres dannelsen af glukose fra henholdsvis propionat og aminosyrer?

Med dette formål er der simuleret et forsøg, hvori 3 forskellige foderrationer er anvendt til malkekøer i tidlig laktation. Disse rationer (tabel 5.4) er karakteriserede ved 1) et højt stivelsesindhold (HS), 2) et højt proteinindhold (HP), og ved 3) at stivelse og protein er delvist beskyttet mod forgæring i formaverne (BSP).

Simuleringsresultaterne (tabel 5.5) viser, at glukoneogenesens hastighed er større med ration HS (16 mol glukose/dag) end med de 2

øvrige rationer (13-14 mol/dag), at bidraget fra propionat til dannelsen af glukose er højere med ration HS (81%) end med de andre rationer (65%), samt at bidraget fra aminosyrer er mindst med ration HS (3%) og størst med ration HP (20%). Tilgængeligheden af propionat er størst med ration HS, hvorimod tilgængeligheden af aminosyrer er næsten den samme ved alle 3 rationer. Forholdet mellem koncentrationerne af glukagon og insulin i blodet er højest med ration HP og lavest med ration BSP.

Bidragene fra henholdsvis propionat og aminosyrer til syntesen af glukose er i modellen reguleret dels af substrattilgængeligheden og dels af stofskiftehormonerne, glukagon og insulin. Dette forklarer de simulerede forskelle mellem de anvendte foderrationer.

Ration BSP, som indeholder beskyttet stivelse og protein, øger såvel den simulerede mælkeydelse som den simulerede udnyttelsesgrad af energi og protein. Virkningerne af at øge stivelsens beskyttelsesgrad er undersøgt i et andet simuleringsforsøg. Resultaterne heraf er vist i figurerne 5.5-5.8 og kan resumeres som følger:

- nedsat foderoptagelse samt nedsat absorption af propionat og aminosyrer
- øget absorption af glukose og nedsat glukoneogenese
- øget mælkeydelse, men nedsat energiudskillelse i mælken
- forskelligt indhold af nettoenergi i tørstof med samme kemiske sammensætning.

Kapitel 6: DISKUSSION OG KONKLUSIONER

Modelformål og vurderingskriterier. Kapitlet indledes med en kort gennemgang af metodikken ved opbygningen af modeller samt af de grundlæggende principper for modelevaluering.

Hovedformålet med den præsenterede model er at simulere næringsstoffernes omdannelse gennem fordøjelses- og stofskifteprocesser i den lakterende ko til intermediære stoffer og videre til affaldsstoffer samt til mælke- og vævskomponenter. En sådan generel model kan samtidigt opfylde flere delmål:

(i) Forudsigelse af forskellige foderrationers virkning på koens livsytringer i forskellige laktationsstadier.
(ii) Vurdering af den fysiologiske og biokemiske forståelse af grundlæggende faktorer for dyrenes livsytringer.
(iii) Vurdering af nye hypoteser om regulering af næringsstoffernes fordøjelse og omsætning hos malkekøer.

Kriterierne for vurdering af modellen afhænger af dens formål. En vurdering i forhold til formål (i) kan foretages ved at sammenligne simuleringsresultaterne med et bredt udsnit af eksperimentelle data fra fodringsforsøg, fordøjelighedsforsøg samt stofskifteundersøgelser i viscerale og perifere væv. Modellen kan bedømmes med hensyn til formål (ii) ved at undersøge de simulerede delprocessers funktioner i forhold til data om regulering af næringsstofomsætningen i individuelle væv. Når disse delmål er nået, kan modellen accepteres til sit hovedformål. Modellens anvendelighed, hvad formål (iii) angår, vil forbedres efterhånden, som modellen udvikles til at opfylde hovedformålet.

Bedømmelse af modellen. Et antal simulerede processer i fordøjelseskanalen, leveren og de perifere væv er sammenlignet med data fra litteraturen for at vurdere modellens egenskaber med henblik på forudsigelse af koens livsytringer (formål i). Følgende simulerede processer er i overensstemmelse med eksperimentelle resultater:

Fordøjelseskanalen

- Tilsyneladende fordøjelighed af organisk stof i formaverne
- VFA-produktion i formaverne
- Mikrobiel vækst og proteinsyntese i formaverne
- Nedbrydning af foderprotein i formaverne
- Fordøjelighed af aminosyrer i tyndtarmen.

Leveren

- Dannelse af glukose ud fra propionat og aminosyrer
- Urinstofsyntese
- Varmeproduktion.

Mælkekirtlen

- Optagelse af glukose
- Glukosens omsætning i forskellige stofskifteveje.

Det simulerede bidrag fra aminosyrer til syntesen af glukose i leveren er meget større end de laveste eksperimentelle værdier, der er anvendt til sammenligning. Den simulerede optagelse og oxidation af acetat og ketonstoffer i mælkekirtlen er betydelig højere end tilsvarende eksperimentelle målinger. Disse forskelle mellem model- og forsøgsresultater er diskuteret, og de sidstnævntes generelle gyldighed er draget i tvivl.

De simulerede døgnvariationer i nogle output variable er diskuteret med henblik på en vurdering af modellens mekanistiske egenskaber på detailniveau (formål ii). Sammenligninger med data fra litteraturen viser, at døgnvariationerne er simuleret realistisk for foderoptagelsen samt for koncentrationerne i blodet af insulin, glukose, ketonstoffer, laktat, aminosyrer og urinstof. Modellens fysiologiske og biokemiske forudsætninger kan derfor delvis accepteres. Sammenligningerne viser videre, at modellens funktion er noget ufuldstændig med hensyn til fedtvævets mobilisering af frie fedtsyrer.

Modellens egnethed til forudsigelser er yderligere bedømt ved simulering af et bestemt fodringsforsøg. De simulerede resultater (foderoptagelse, mælkeydelse og -sammensætning samt tilvækst) er - efter justering af nogle af modellens parameterværdier - som fundet i forsøget.

Kvantitative (formål i) såvel som kvalitative (formål ii) aspekter af modellens egenskaber er belyst ved at simulere koens livsytringer, dels i forskellige laktationsstadier og dels som resultat af behandling med væksthormon.

De simulerede laktationskurver over mælkeydelse og tilvækst ligner virkelige observationer. Modellens evne til at simulere forskellige laktationsydelser og tilvækster for køer med samme foderoptagelse peger på muligheden af at anvende modellen som støtte til formulering af hypoteser om den fysiologiske baggrund for forskellig genetisk ydelseskapacitet.

De simulerede virkninger af kortvarig behandling med væksthormon er i overensstemmelse med eksperimentelle resultater med hensyn

til:

- kurvilineær stigning i mælkeydelse med øget væksthormondosis, både i tidlig og sen laktation
- relativt større effekt på mælkeydelsen i sen end i tidlig laktation
- uændret foderoptagelse og faldende energibalance
- øget koncentration af frie fedtsyrer i blodet.

De simulerede virkninger på blodets indhold af væksthormon, insulin og glukose er imidlertid ikke som fundet i forsøgene. De aspekter af modellen, der vedrører den hormonale regulering, kan derfor kun delvis accepteres, hvad angår dens formål til forudsigelse (delmål i) og dens mekanistiske forudsætninger (delmål ii).

Der er fremsat nogle vigtige spørgsmål vedrørende glukoneogenesens regulering og omfanget af aminosyrernes bidrag til syntesen af glukose. Modellen er anvendt til at belyse disse spørgsmål, da de ikke er fuldt klarlagt i litteraturen. Resultaterne af de foretagne simuleringer kan delvis bekræftes af eksperimentelle data og antyder følgende:

- aminosyrer kan have stor kvantitativ betydning som substrater for syntesen af glukose
- behovet for glukoneogenese i leveren reduceres ved fodring med beskyttet stivelse og protein
- koens energi- og proteinudnyttelse forbedres ved beskyttelse af foderets stivelse og protein
- foderrationer med identisk kemisk sammensætning, men med forskellig nedbrydningsgrad af stivelse, har forskelligt indhold af nettoenergi.

Det konkluderes ud fra disse resultater, at en dynamisk, mekani-

stisk model, der er tilstrækkeligt realistisk, kunne være det bedste redskab til at vurdere værdien af fodermidler og foderrationer til malkekøer.

Modellens fordele og mangler. Nogle af modellens kvalitative egenskaber er diskuteret i dette afsnit. Et generelt fortrin ved at arbejde med modeller er, at det er muligt at undgå et klassisk videnskabeligt problem, nemlig at et objekt ikke kan studeres i detaljer, uden at objektet selv derved påvirkes. Eksperimentelle data opnået ved traditionelle metoder er imidlertid nødvendige for modellers opbygning og efterfølgende afprøvning. Andre generelle fordele ved dynamiske modeller er deres store fleksibilitet samt deres mulighed for at simulere akutte stofskifteændringers kvantitative virkninger på de samlede livsytringer (d.v.s. regulering af stofskiftet). Den præsenterede model indeholder et nyt, simpelt princip til simulering af stofskifteregulering. Dette princip er baseret på allosterisk regulering af enzymaktivitet.

Modellens mangler vedrører dens generelle struktur, regulering af foderoptagelsen, mikrobiel vækst i fordøjelseskanalen, mineral- og vitaminstofskiftet, regulering af hormonsekretion, regulering af mælkekirtlens syntesekapacitet samt regulering af energistofskiftet. Svagheden ved modellens generelle struktur er, at der er lagt ulige vægt på beskrivelsen af processer i de perifere væv sammenlignet med de viscerale væv. Et andet problem er, at modellen er vanskelig at bedømme til bunds på grund af dens størrelse og kompleksitet. Foderoptagelsens hastighed er i modellen kun reguleret ved fysisk og ikke ved metabolisk kontrol. Den simulerede mikrobielle vækshastighed er direkte proportional med syntesehastigheden af ATP, idet der ikke tages hensyn til mikrobernes basale ATP-behov. Omsætningen af mineralstoffer og vitaminer er ikke inkluderet i modellen, og disse anses derfor ikke som begrænsende faktorer.

Koncentrationen af stofskiftehormoner i blodet gennem laktationsperioden er i modellen baseret på empiriske data i stedet for at være bestemt af interne, mekanistiske faktorer. Syntesehastigheden af mælkekomponenter reguleres kun af substrattilgængeligheden i modellen, og syntesekapaciteten i selve mælkekirtlen ændres derfor ikke i løbet af laktationsperioden. En alvorlig mangel ved modellen er, at oxidationsprocesser i vævene ikke reguleres af behovet for energi til synteseprocesser. Dette betyder samtidigt, at synteseprocessernes hastighed ikke er reguleret af tilgængeligheden af ATP og reducerede cofaktorer dannet ved oxidationsprocesser. Simuleringerne kan derfor ikke forventes at være tilfredsstillende i situationer som faste eller meget lav foderoptagelse, hvor energiforsyningen er den begrænsende faktor.

Perspektiver for modellens anvendelse. Modellen kan i fremtiden anvendes inden for 2 områder af videnskabeligt arbejde:

1) Støtte for teoretiske overvejelser, formulering og vurdering af hypoteser samt erkendelse af manglende eller "falsk" viden.

2) Forudsigelse af malkekoens samlede livsytringer.

På det sidstnævnte område kunne modellen blive et nyttigt hjælpemiddel til en førstehåndsvurdering af nye foderrationer, til at optimere foderrationers sammensætning og til at udvikle et fuldstændigt system til foderværdibestemmelse baseret på omsætningen af de absorberede næringsstoffer.

Konklusioner. Diskussionen af det præsenterede arbejde fører til følgende konklusioner:

- Der er udviklet en dynamisk, deterministisk og mekanistisk model af en lakterende ko i overensstemmelse med hovedformålet: at kunne simulere næringsstoffernes omdannelse ved fordøjelses- og stofskifteprocesser til intermediære stoffer, affaldsprodukter, mælk og vævsbestanddele. Dette mål er imidlertid ikke fuldt opnået, og modellen må yderligere udvikles og justeres.

- Modellen er baseret på en statisk model af næringsstoffordøjelse og -omsætning i en lakterende ko. Den dynamiske models løsninger er de samme som den statiske models med hensyn til daglig strøm af stof gennem alle modelbeskrevne stofskifteveje.

- Resultater fra et bestemt fodringsforsøg er simuleret korrekt af modellen efter justering af nogle parameterværdier.

- Et antal simuleringsresultater vedrørende fordøjelse, omsætning i lever og mælkekirtel, hormonal regulering samt laktationsydelser er i overensstemmelse med uafhængige eksperimentelle data.

- Simuleringsresultater vedrørende glukoneogenese fra aminosyrer i leveren samt omsætning af acetat i mælkekirtlen afviger fra nogle forsøgsresultater. Disses generelle gyldighed er draget i tvivl, og yderligere forskning i disse spørgsmål anses for påkrævet.

- Modellen er meget fleksibel og indeholder et nyt, simpelt princip til simulering af allosterisk regulering af puljestørrelser og proceshastigheder.

- Modellen kan i fremtiden udnyttes dels ved teoretisk forskning og dels til forudsigelse af malkekøers produktion. Dette kunne føre til udviklingen af et fuldstændigt system til foderværdibe-

stemmelse baseret på dynamisk modelarbejde.

- Viden om husdyrenes fordøjelse og stofskifte kan forbedres mere effektivt, hvis forskellige eksperimentelle metoder kombineres med anvendelsen af modeller.

1 INTRODUCTION

1.1 The need for models

As detailed biochemical and physiological knowledge in the field of animal nutrition increases it becomes increasingly difficult to obtain a comprehensive view of whole animal metabolism. The increase in knowledge is followed by a growing need for collection and integration of the revealed biological relationships in order to improve our understanding of animal physiology and performance.

One method to organise knowledge is to construct conceptual models of the system in question. Models of nutrient digestion and metabolism in an animal can provide integrated quantitative descriptions of the major metabolic pathways and of the most important interactions between different nutrients. Working to develop such models is a way to a better understanding, but besides this there are some more specific advantages to the scientific process:

- discovery of weak points in the knowledge of quantitative, nutritional relationships
- improvement of the basis for construction of hypotheses and critical experiments to test them
- improvement of procedures for a more precise evaluation of experimental results.

The usefulness of animal models increases further when they are made to simulate the key processes of digestion and metabolism. In this way models can be predictive of animal performance, and if sufficiently realistic models are obtained, the need for long lasting and expensive feeding trials could be reduced.

1.2 Definition of models

A model is a simplified symbolic representation of a system - the system being for instance an animal and some specified part of its environment.

Quantitative or mathematical models are composed of equations representing the behaviour of the given system. According to Thornley & France (1984) mathematical models can be classified into the following, distinct types:

- static or dynamic
- stochastic or deterministic
- empirical or mechanistic.

Static models do not take time into explicit consideration, but can only describe a system of constant rates within the observed period of time - e.g. the daily feed intake of an animal. Dynamic models on the other hand are well suited for simulation of the continual changes (regulation) of processes occurring in living animals. Use of differential equations provides the mathematical tool for the description of such dynamic behaviour.

Stochastic models contain probability distributions so that not only expected values but also variances of rates and quantities are predicted. Deterministic models do not contain probability distributions and therefore give definite and unique answers.

Empirical models are based on experimental observations, typically from feeding trials designed to reveal input-output relationships. They do not reveal causal relationships. The predicitive tools of these models are often regression equations fitted to observed data. Mechanistic models are explanatory, because they are based on facts and/or theories of biological events in compartments and subcompartments of the whole model.

A mechanistic whole animal model could for instance contain descriptions of interorgan nutrient transport, processes in individual tissues and regulation of pathways in subcellular organelles.

1.3 Some published dynamic models

During the last 15 years many dynamic models in biological sciences have been published. Some are concerned with the regulation of individual pathways (Dibrov et al. 1982, Phillipson 1982, Schauer & Heinrich 1983, Okamoto & Hayashi 1984, Reichl & Reiser 1984) and of hormone concentrations (Smith 1983). Some deal with ruminal digestion in sheep (Baldwin et al. 1977, Black et al. 1980-81, Beever et al. 1980-81, France et al. 1982, Murphy et al. 1986), with body tissue metabolism in sheep (Gill et al. 1984), and with nitrogen utilization in grazing ruminants (Morris et al. 1975). The lactating cow has also been a subject for modelling - the

mammary gland alone (Neal & Thornley 1983, Waghorn & Baldwin 1984) and the whole animal (Koong et al. 1982, Baldwin & Bauman 1984, Baldwin et al. 1987 a,b&c). In addition to this, simulation models for larger systems such as cattle herds are available (Kahn & Spedding 1983, Kahn & Spedding 1984).

These few references do not represent a complete review of the subject, but are mentioned to give an impression of the different biological systems that have been modelled. The level of detail and description differs widely between models. It is clear that models of biochemical pathways are normally much more detailed than whole animal models, otherwise the latter would be enormous. Some models of rather large systems have many biochemical details - e.g. the rumen model of Baldwin et al. (1977), while others - e.g. the whole animal model of Koong et al. (1982) - represent the main digestive and metabolic routes much more simply.

2 OVERALL DESCRIPTION OF THE MODEL

2.1 Nature and structure of the model

The purpose of the work presented here has been to construct a dynamic, deterministic and mechanistic whole animal model simulating the conversion of nutrients through digestive and metabolic processes in the cow into products of milk and body gain. The model is outlined below and described in full detail in the following chapter.

The model is composed of 9 compartments (figures 2.1 - 2.6) representing different organs or tissues of the cow: the rumen, intestinal lumen, intestinal wall, liver, peripheral blood and extracellular fluid, mammary gland, muscle tissues, adipose tissues, and other tissues. A subcompartment in the rumen represents the rumen microbes (figure 2.1).

The small boxes within the compartments are state variables representing metabolic pools. Arrowed lines show the biochemical transactions - that is the flow of nutrients and metabolites between the different pools. The "clouds" shown outside and inside compartments are reservoirs of matter supplying or draining the model: feed, faeces, urine, milk and gases of fermentation and oxidation. In the ruminal and intestinal compartments ATP from microbial fermentations is shown in small ellipses.

2.2 Terminology of the model

The state variables of the model are either carbon or nitrogen pools. The pools of carbon are labelled C and represent carbohydrates, lipids and other N-free organic substances. There are three types of nitrogen pools to represent amino acids, peptides and protein (labelled A), NH_3/NH_4^+ (labelled N) and urea (labelled U).

The units of mass are moles of carbon (C) and nitrogen (N) for the carbon and nitrogen pools, respectively. A total listing of the state variables with names, symbols, units and initial numerical values in the model is given in Tables 2.1 - 2.9.

The rates of carbon and nitrogen flow between pools are labelled R_i (mol C/h) and R_j (mol N/h), respectively, starting at 100 for i and at 0 for j. Flow rates integrated over 24 h are named fluxes (F_i or F_j) and are given in mol C/d or mol N/d. Names, symbols and simulated flux rates of all transactions in the model are listed in Appendix 9.

Table 2.1 State variables in rumen compartment

Substance	Symbol	Initial numerical value in model	Unit
Unfermentable carbohydrates and lipids	C1	261.1	mol C
Fermentable sugars	SU2	3.847	"
Fermentable starch	ST2	0.4336	"
Fermentable cell wall carbohydrates	CE2	29.99	"
Fermentable carbohydrates	C2 1)	34.27	"
Microbial carbohydrates and lipids	C3	19.77	"
Acetate	AC4	10.49	"
Propionate	PR4	6.684	"
Butyrate	BU4	3.837	"
Methane	CH4	0.9331	"
Carbon dioxide	CO4	2.055	"
Microbial fermentation end products	C4 2)	24.00	"
Unfermentable protein	A1	7.308	mol N
Fermentable protein, peptides and amino acids	A2	2.194	"
Microbial amino acids and peptides	A3	0.0010	"
Microbial protein and nucleic acids	A4	11.25	"
Ruminal NH_3/NH_4^+	N1A	0.7349	"
Microbial NH_3/NH_4^+	N1B	0.1165	"
Ruminal urea	U1	0.2175	"

1) C2 = SU2 + ST2 + CE2
2) C4 = AC4 + PR4 + BU4 + CH4 + CO4

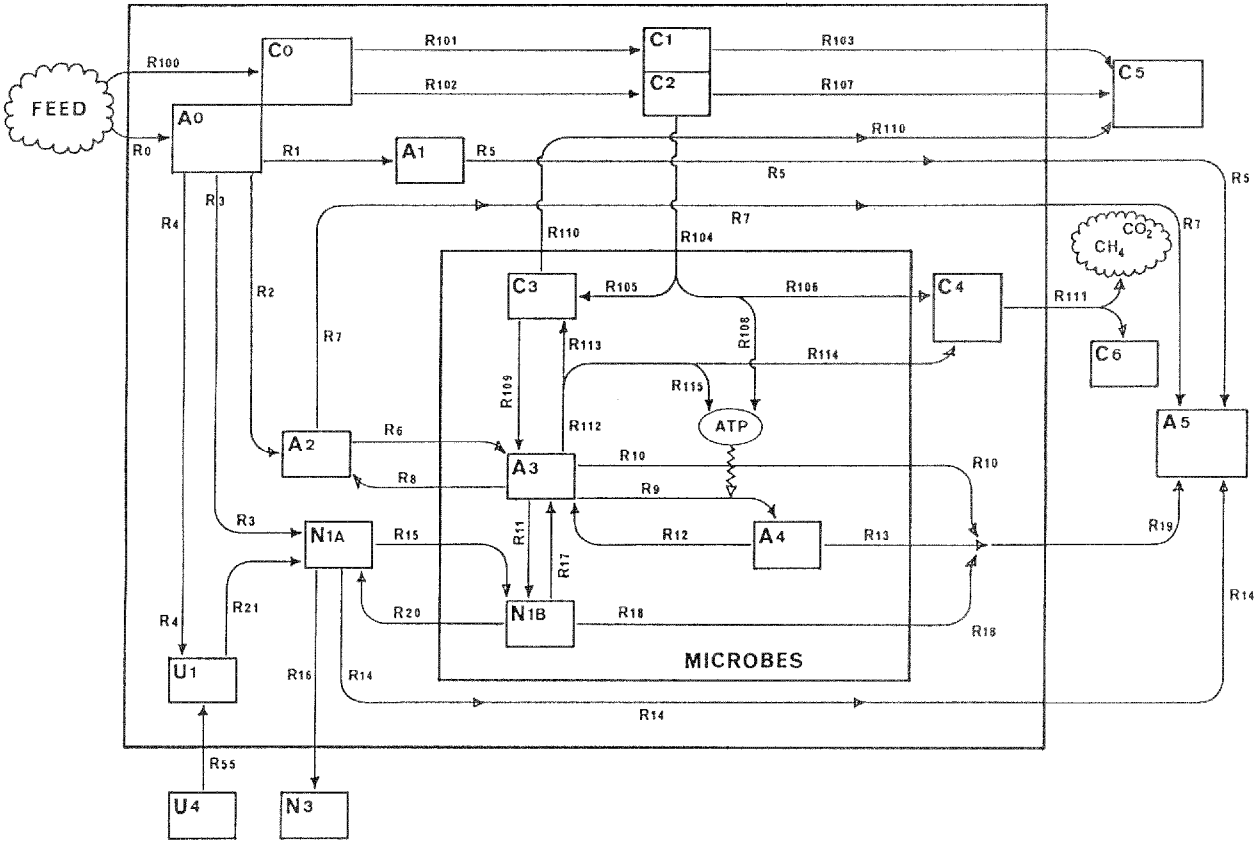


Figure 2.1. Diagram of the rumen compartment

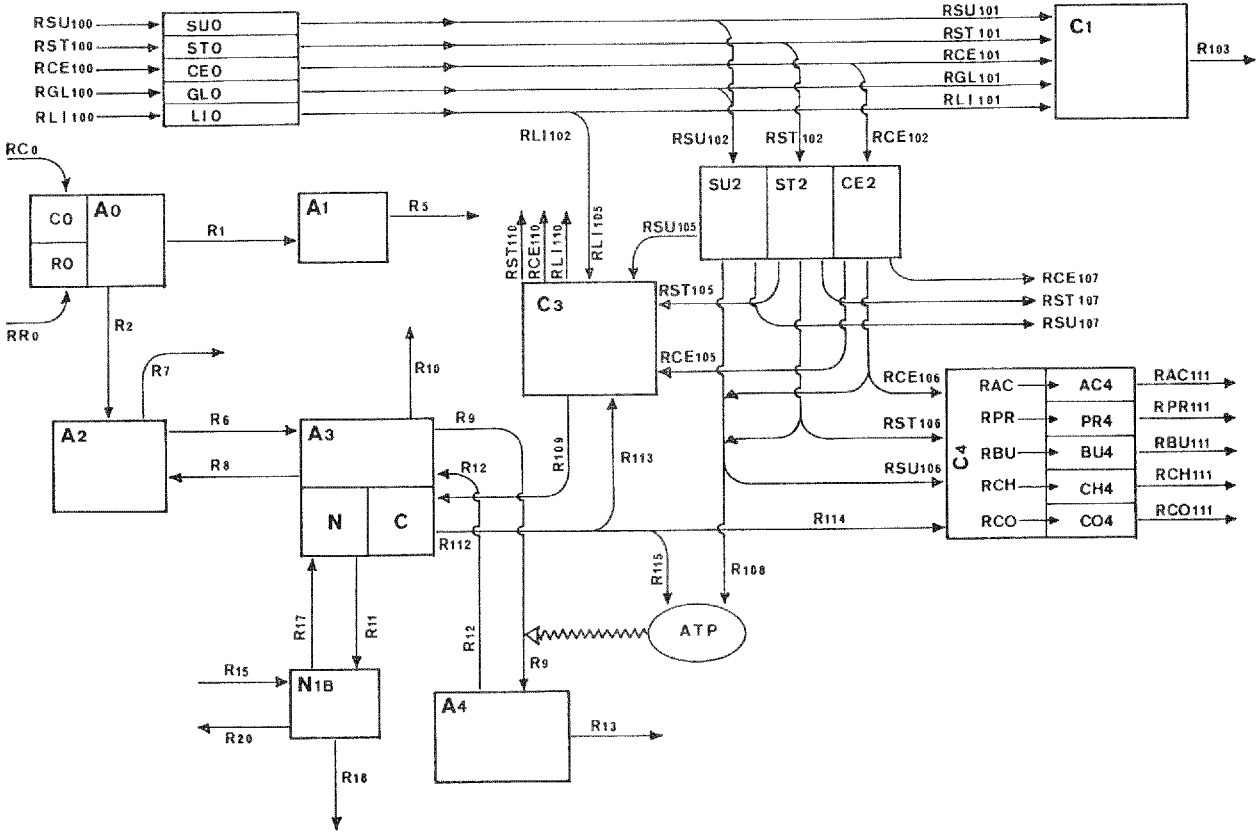


Figure 2.2. Details of the rumen compartment

Table 2.2 State variables in intestinal lumen compartment

Substance	Symbol	Initial numerical value in model	Unit
Indigestible carbohydrates and lipids	C7	29.58	mol C
Digestible carbohydrates	C8	0.07452	"
Digestible lipids	C9	0.9132	"
Undigested + microbial carbohydrates and lipids	C10B	56.65	"
Indigestible protein	A6	1.531	mol N
Digestible protein	A7	0.8568	"
Undigested protein (feed, microbial, endogen.) in hind gut	A8	3.825	"
Indigestible endogenous protein	A10	0.07762	"
Digestible endogenous protein	A11	0.2821	"
NH_3/NH_4^+ in small intestine	N2A	0.05850	"
NH_3/NH_4^+ in hind gut	N2B	0.2607	"
Urea in hind gut	U2	0.03928	"

Nutrient pools which are not state variables:

Unfermented + microbial carbohydrates and lipids (C5)
Volatile fatty acids in portal blood (C6)
Volatile fatty acids, methane and carbon dioxide in hind gut(C10A)
Unfermented feed protein, microbial protein and NH_3/NH_4^+ in small intestine (A5)
Endogenous protein (A9)

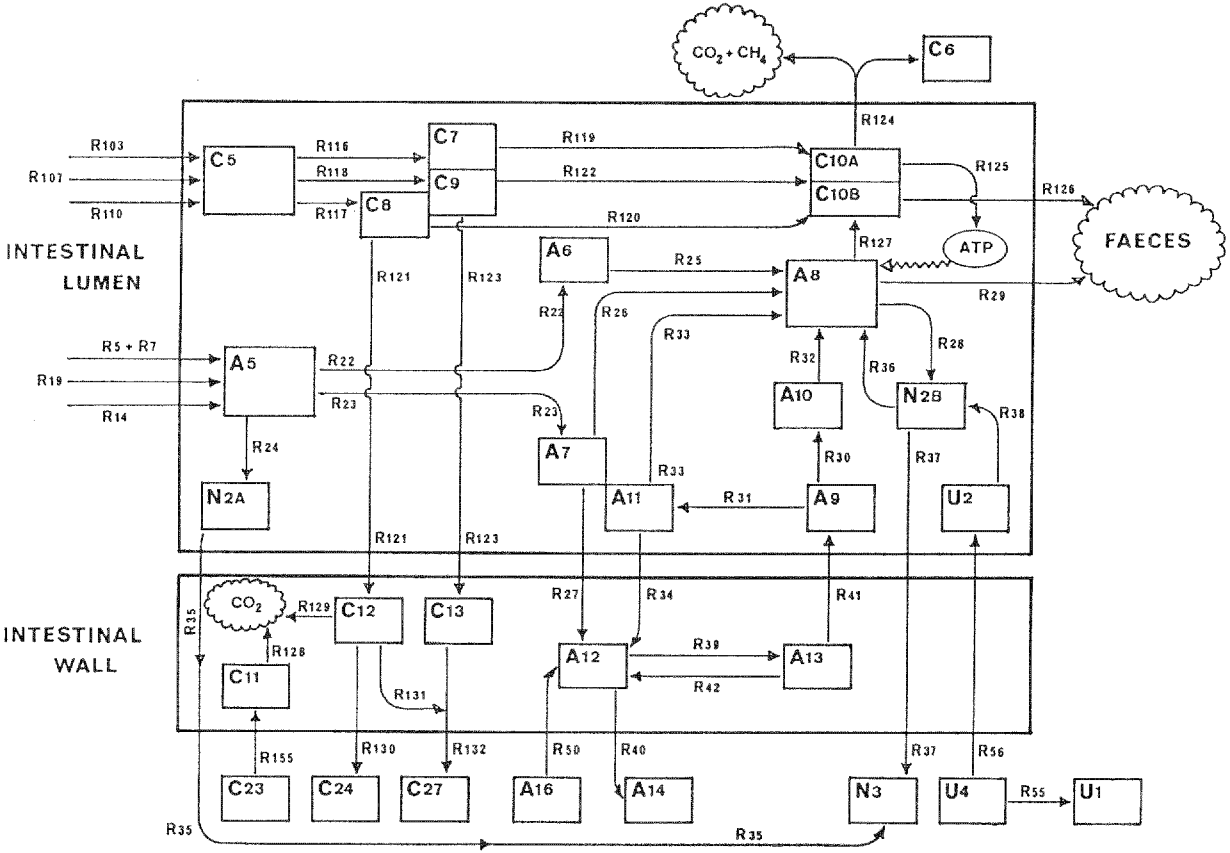


Figure 2.3. Diagram of the intestinal compartments

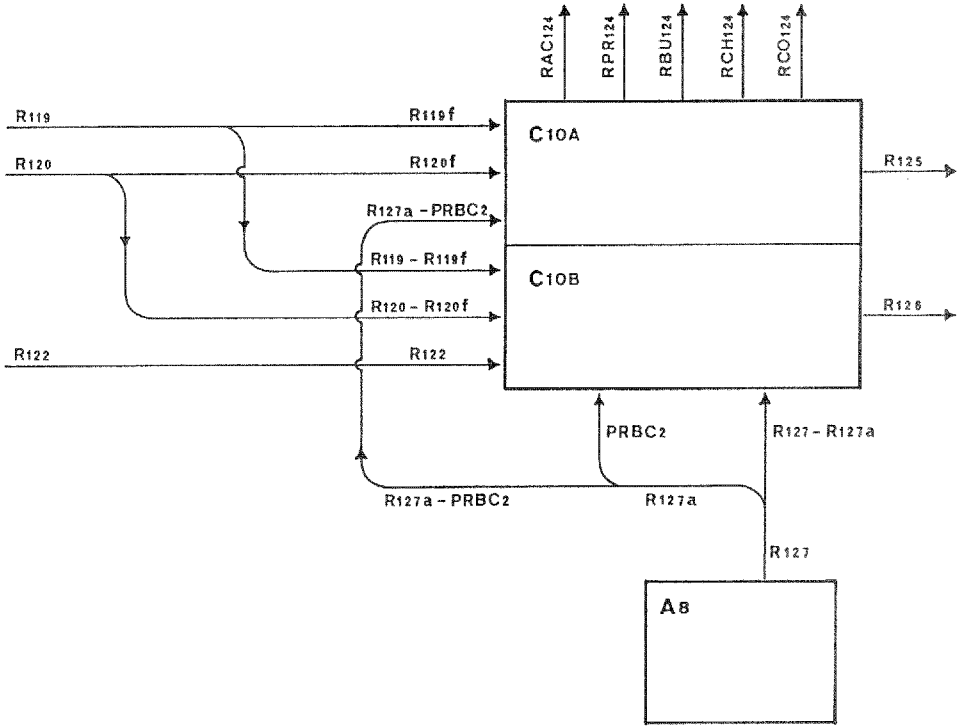


Figure 2.4. Details of the intestinal lumen compartment

Table 2.3 State variables in intestinal wall compartment

Substance	Symbol	Initial numerical value in model	Unit
Acetate + ketone bodies	C11	0.01430	mol C
Glucose	C12	0.02556	"
Amino acids	A12	0.9393	mol N
Intestinal protein	A13	55.95	"

Nutrient pool which is not a state variable:

Fatty acids (C13)

Table 2.4 State variables in liver compartment

Substance	Symbol	Initial numerical value in model	Unit
Propionate	C14	0.1846	mol C
Glucose + glycogen	C16	1.154	"
Keto acids	C17	0.1168	"
Glycerol + lactate	C18	0.09737	"
Fatty acids	C19	0.1684	"
Triglyceride in liver fat	C20	15.04	"
Triglyceride in lipoproteins	C21	5.307	"
Acetate + ketone bodies	C22	0.03738	"
Amino acids	A14	0.1994	mol N
Liver protein	A15	19.82	"
NH_3/NH_4^+	N3	0.04838	"
Urea	U3	0.3509	"

Nutrient pool which is not a state variable:

Butyrate (C15)

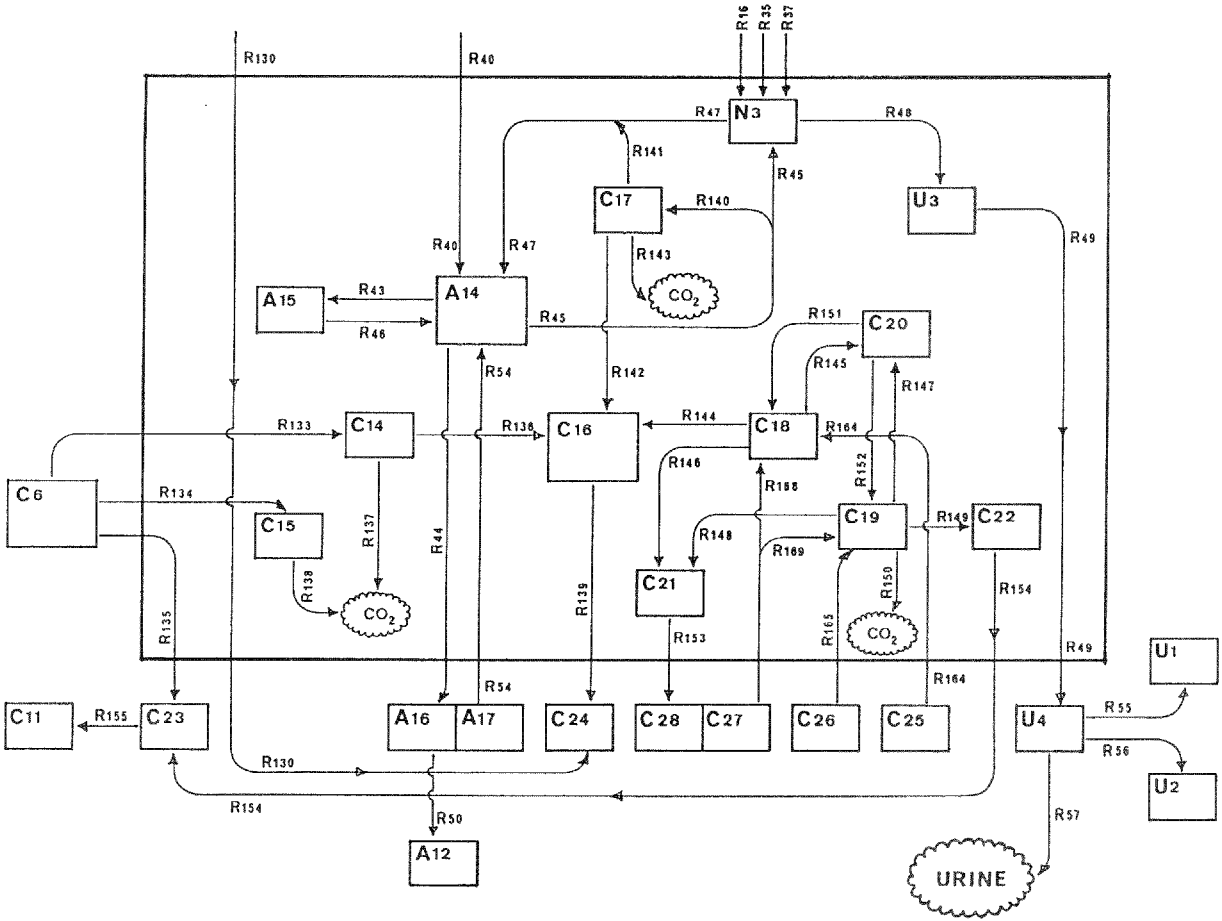


Figure 2.5. Diagram of the liver compartment

Table 2.5 State variables in peripheral blood compartment

Substance	Symbol	Initial numerical value in model	Unit
Acetate + ketone bodies	C23	0.9192	mol C
Glucose	C24	3.252	"
Glycerol + lactate	C25	0.2542	"
Fatty acids	C26	1.355	"
Triglyceride in chylomicrons	C27	0.4959	"
Triglyceride in liver lipoproteins	C28	0.6487	"
Amino acids to peripheral tissues	A16	0.5023	mol N
Amino acids from peripheral tissues	A17	0.5226	"
Urea	U4	2.048	"

Table 2.6 State variables in mammary gland compartment

Substance	Symbol	Initial numerical value in model	Unit
Acetate + ketone bodies	C29	0.1485	mol C
Glucose	C30	0.1782	"
Fatty acids	C31	0.1230	"
Lactose	C33	1.010	"
Triglyceride in milk fat	C34	55.87	"
Amino acids	A18	0.5780	mol N
Milk protein	A19	0.2320	"

Nutrient pool which is not a state variable:

Glycerol (C32)

Table 2.7. State variables in muscle tissue compartment

Substance	Symbol	Initial numerical value in model	Unit
Acetate + ketone bodies	C35	1.550	mol C
Glucose	C36	1.860	"
Fatty acids	C37	0.3490	"
Lactate	C38	3.270	"
Amino acids	A20	4.251	mol N
Muscle protein	A21	498.0	"

Nutrient pool which is not a state variable:

NH_3/NH_4^+ (N4)

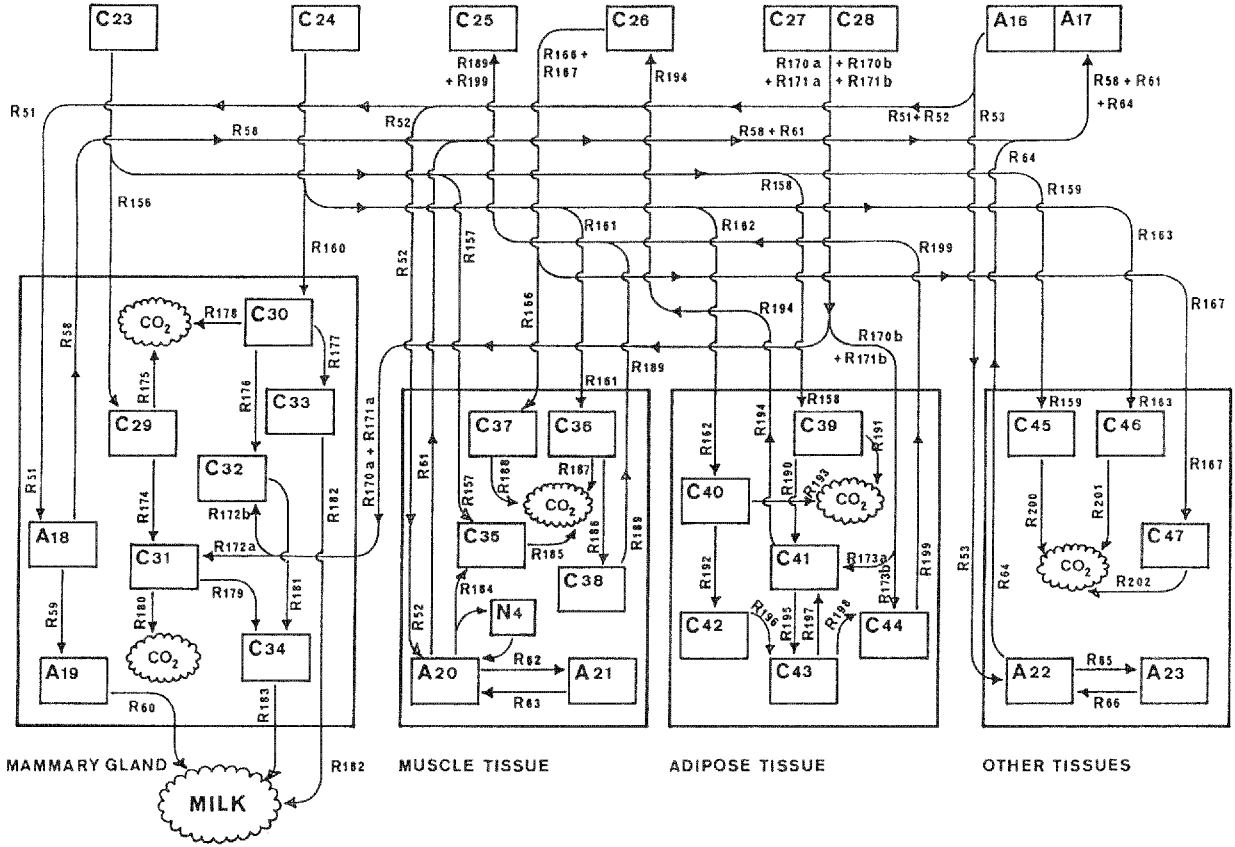


Figure 2.6. Diagram of the peripheral tissue compartments

Table 2.8. State variables in adipose tissue compartment

Substance	Symbol	Initial numerical value in model	Unit
Acetate + ketone bodies	C39	0.2210	mol C
Glucose	C40	0.2650	"
Fatty acids	C41	3.040	"
Triglyceride in depot fat	C43	3030	"
Glycerol	C44	0.0460	"

Nutrient pool which is not a state variable:

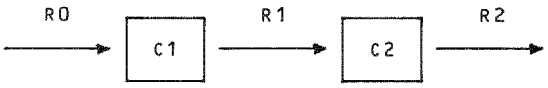
Glycerol-P (C42)

Table 2.9. State variables in other tissue compartment

Substance	Symbol	Initial numerical value in model	Unit
Acetate + ketone bodies	C45	0.2000	mol C
Glucose	C46	0.2400	"
Fatty acids	C47	0.0450	"
Amino acids	A22	2.817	mol N
Tissue protein	A23	330.0	"

2.3 General mathematical and biological principles

The dynamic behaviour of the model is achieved by using differential equations to describe the continual changes of the state variables. The simplified example below will illustrate the principle:



Two state variables C1 and C2 are given. Material from C1 is transferred to C2 with the rate $R1 = R1_{(max)}*C1/(K1+C1)$ and material is transferred from C2 with the rate R2 = K2*C2, where R1(max), K1 and K2 are parameters with constant values. The 2 rate equations are mathematical formulations of biological processes with different kinetics: the description for R1 is analogous to that for Michaelis-Menten enzyme kinetics and R2 follows first order mass action kinetics.

At time = t the state variables have the numerical values C1(t) and C2(t), and the rates at time = t can be calculated:

$$R1(t) = R1_{(max)}*C1(t)/(K1+C1(t))$$
$$R2(t) = K2*C2(t)$$

In the next time interval (dt) such that accumulated time = t+dt, the values of the state variables change according to the differential equations:

$$dC1(t)/dt = R0(t)-R1(t)$$
$$dC2(t)/dt = R1(t)-R2(t)$$

New values of C1 and C2 at time = t_1 are then found by integration:

$$C1(t_1) = C1(t) + \int_{t}^{t_1} (R0(t) - R1(t))dt$$

$$C2(t_1) = C2(t) + \int_{t}^{t_1} (R1(t) - R2(t))dt$$

The reaction rates R1 and R2 at time = t_1 are now calculated from the new values of C1 and C2, and the procedure goes on throughout the simulation period. In this way reaction rates are continually regulated by the changing size of substrate pools.

Another example will show how rates and pools can be regulated by feed-back inhibition. Consider the rate $R1 = R1_{(max)} * C1/(K1+C1)$ in the same system as above. The following conditions about the product pool C2 are introduced:

if $C2_{(max)} \leq C2$ then $K1 = K1 + dK1$
if $C2_{(max)} > C2 > C2_{(min)}$ then $K1 = K1$
if $C2 \leq C2_{(min)}$ then $K1 = K1 - dK1$

In this system the value of R1 will depend not only on C1, but also on C2. If C2 increases to or above $C2_{(max)}$, the increase in K1 will decrease the rate R1 and in turn decrease the input to C2. If C2 decreases to or below $C2_{(min)}$, the smaller value of K1 will increase the rate R1 and thus the input to C2.

The biological parallel to this principle is that of allosteric enzyme regulation where some modifying factors can change an enzyme's affinity for its substrate.

2.4 Input parameters and output variables

The model requires as input data parameters describing chemical composition of the feed, live weight of the cow and stage of lactation. From this information the model calculates, at any time of the "model day", the value of all state variables, rates and fluxes shown in figures 2.1 - 2.6.

In order to relate the simulation results to terms of whole animal performance the following output variables are computed from relevant fluxes:

- feed dry matter intake (kg/d)
- feed unit intake (SFU/d)
- milk production (kg/d)
- milk lactose production (g/d)
- milk fat production (g/d)
- milk fat content (g/kg milk)
- milk protein production (g/d)
- milk protein content (g/kg milk)
- live weight gain (kg/d)
- maintenance requirement for net energy (MJ/d)
- tissue energy balance (MJ/d)
- energy in milk (MJ/d)
- gross energy intake (MJ/d)
- faecal energy (MJ/d)
- digestible energy (MJ/d)
- methane energy (MJ/d)
- urinary energy (MJ/d)
- metabolizable energy intake (MJ/d)
- heat production (MJ/d)
- net energy intake (MJ/d).

2.5 Model size and programming languages

The model consists of 77 state variables and a total of more than 1500 equations of which 341 are differential equations. The computer program is written in the CSMP III simulation language (Speckhart & Green 1976), but some of the computations are programmed in FORTRAN subroutines, because the size of the model exeeds the maximum capacity of CSMP III. Because of its special facilities SAS (Statistical Analysis System) is used for statistical treatment and presentation of the output variables.

All computations have been performed at UNI-C, a computing centre at the Technical University of Denmark.

3 DETAILED DESCRIPTION OF THE MODEL

The objectives of the model are 1) to describe quantitatively the continous processes of nutrient metabolism and interactions between different nutrients in individual tissues, and 2) to predict the feed intake, milk production and change in live weight of cows in a specified lactational stage given a diet of a specified chemical composition.

3.1 The procedure for constructing the model

The essential feature of a dynamic model is a set of differential equations describing the rates of flow of matter in the system. When the equations are defined, numerical values must be assigned to the equation parameters. Two principially different methods can be applied for this process. One is that all parameters are treated as unknown quantities, the values of which are found by computer iterations for given model inputs and outputs. Another method is to assign experimental or estimated values to the parameters in advance and then use the resulting output as a test of how well the model is constructed.

For the present model a combination of these 2 methods was used. Firstly, a static model of a lactating dairy cow was made. This static model describes the daily amounts of feed consumed, nutrient flow through the body, milk production and live weight change. Secondly, differential equations and auxiliary equations were de-

fined, and thirdly, state variables and equation parameters were given numerical values derived from the literature or assumed as biologically probable. Finally, the parameters were adjusted by means of repeated simulations until the dynamic model gave the same solutions as the static model with regard to daily feed intake, nutrient fluxes, milk production and live weight change. The static model is based on publications of Hvelplund (1983) and Danfær (1983b) and describes the processes of digestion and metabolism in a 600 kg cow in early lactation consuming 17.9 kg dry matter, producing 30 kg milk and loosing 0.5 kg body weight per day. The ration chosen had a fixed composition of fodder beets (37%), grass silage (15%), beet top silage (12%), barley straw (9%) and concentrates (27% of feed dry matter). Calculations of energy utilization (see figure 3.1) based on the amounts of metabolized nutrients show that the energy losses (in methane, faeces, urine and heat) are in good agreement with corresponding experimental values from the literature (Coppock et al. 1964, Flatt et al. 1969).

The energy value of the feed ration chosen for the model was 16.0 Scandinavian Feed Units (SFU) calculated from the chemical composition of the feed, but only 14.8 SFU when estimated on the basis of the production and live weight of the model cow. The lower value is an expression of the true net energy content in the feed, and the ratio of the 2 values, 14.8/16.0 = 0.92 is the same as that found by Danfær (1983a) in an analysis of results from 2 large Danish feeding experiments (Østergaard 1979, Kristensen 1983). This analysis showed that the ratio is 1 at a feeding level of 10-12 SFU per cow per day - the level of feed intake where most feeding experiments used to determine the SFU value of feedstuffs have been performed - but at higher feeding levels the ratio decreases according to a second degree polynomial (Danfær 1983a).

From these and other calculations it was concluded that, for the chosen ration, the static model developed by Hvelplund (1983) and Danfær (1983b) gave realistic predictions of the nutrient and energy metabolism in a high-yielding dairy cow in early lactation, and therefore could be used as a basis for the dynamic model.

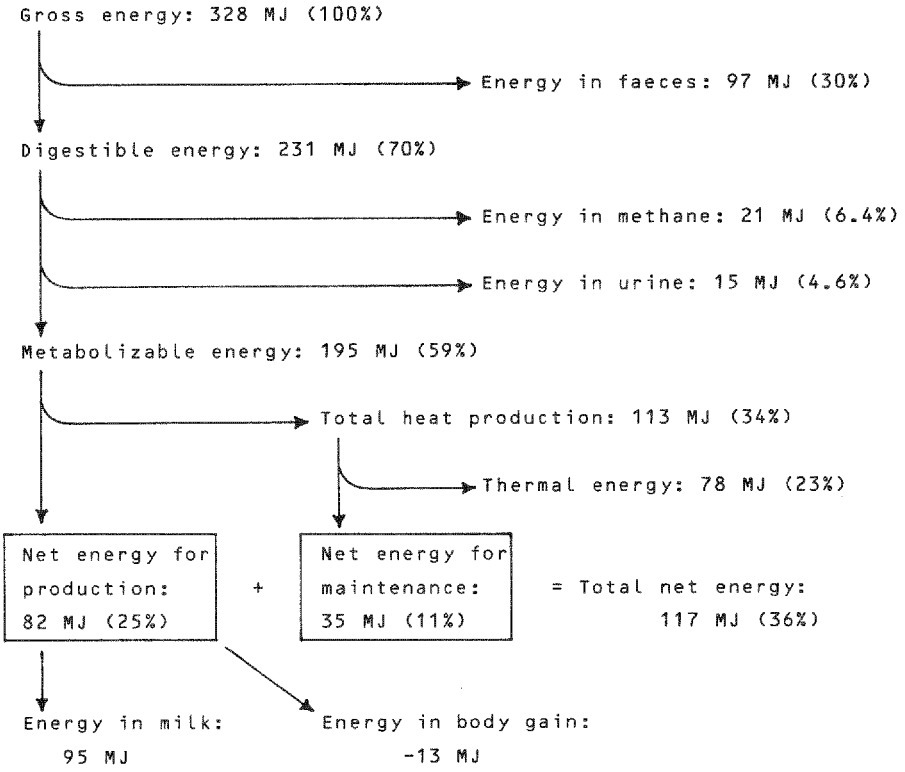


Figure 3.1. Energy utilization of a lactating 600 kg cow consuming 17.9 kg dry matter and producing 30 kg milk according to the static model (Danfær 1983b)

3.2 The computer programs

This section will describe briefly the construction and function of the CSMP III, FORTRAN and SAS computer programs. The programs are shown in full in the Appendices.

3.2.1 The main program and the subroutines

The main framework of the model is formulated in the CSMP III programming language (Speckhart & Green 1976) and consists of 3 parts: the INITIAL, the DYNAMIC, and the TERMINAL segments (see Appendix 1).

The INITIAL segment contains those statements which are executed only at the beginning of each run - a run being one simulation period terminated when the chronological variable TIME reaches the numerical value of the symbol FINTIM. In this model FINTIM is defined as 24 h, and therefore a run represents the time course of 1 day.

The equation parameters and state variables which are given initial numerical values are grouped under PARAM, CONSTANT and INCON. The initial values are those assigned at the beginning of each run, when TIME = 0 h. In the PARAM group are equation parameters (e.g. K106I, K6I) whose values are regulated and therefore variable during a run, and equation parameters (KCA, KATP, YATPM) which are necessary for computations in the INITIAL segment. The state variables (e.g. C1I, SU2I) are listed in the CONSTANT group,

and in the INCON group there are 3 parameters giving the live weight of the cow (BW, kg), the rate of feed intake during periods of eating (FT, kg dry matter/h) and a factor for esterification of milk fat (L179).

The segment is completed with a list of equations, which transfer the initial values of parameters and state variables to their proper names in the respective rate equations (e.g. K106 = K106I, C1 = C1I), together with some parameters which are derived from state variables (C2, CA3, YATP, X1, X2, X3, CA20).

In the DYNAMIC segment FORTRAN subroutines (see Appendix 2) with rate equations and regulatory equations are called for execution, and in between the execution of subroutines, integrations of differential equations are carried out in the DYNAMIC segment.

The first subroutine, RATE1, contains the rate equations of the rumen compartment (e.g. RSU100 = FT*KSU*LSU, RST100 = FT*KST*LST), and after the subroutine has been called and executed, the main program continues with the integration of rate equations from the rumen compartment in order to find new values for its state variables (e.g. C1 = C1I+INTGRL(0.0, DC1), where DC1 = R101-R103). The same procedure is then used for the other compartments: intestinal lumen and intestinal wall (subroutine RATE2), liver and extracellular fluid (subroutine RATE3), and mammary gland, muscle tissue, adipose tissue and other tissues (subroutine RATE4).

The DYNAMIC segment continues with the integration of individual flow rates (e.g. R100, R103, mol C/h) calculated in the subroutines, leading to daily fluxes of matter (e.g. F100 = INTGRL (0.0, R100), F103 = INTGRL(0.0, R103), mol C/d).

After these integrations other FORTRAN subroutines are called. Subroutines POOL1, POOL2, POOL3 and POOL4 prevent numerical values of the state variables becoming zero or negative (e.g. IF(SU2.LT.0.01) SU2 = 0.01), while subroutines REGUL1, REGUL2 and REGUL3 regulate the numerical values of variable parameters and prevent these parameter values becoming zero or negative (e.g. IF(K106.LT.0.00001) K106 = 0.00001). The variable parameters are those given initial values in the INITIAL segment and the principle behind their regulation during a run is as illustrated by the example in section 2.3. The following sequence shows the FORTRAN formulation:

```
      R106 = R106M*C2/(K106+C2)
      IF(C2.LT.C2MX) GO TO 1
        K106 = K106-0.1
        GO TO 2
1     IF(C2.GT.C2MN) GO TO 2
        K106 = K106+0.1
        GO TO 2
2     CONTINUE
```

The variable parameter K106 is thus decreased by 0.1 when the state variable C2 becomes equal to or greater than C2MX, and K106 is increased by 0.1 when C2 becomes equal to or less than C2MN. As a consequence of this the rate R106 will increase or decrease respectively.

The subroutine REGUL1 also regulates when and how much the cow will eat:

```
      IF(NIGHT.EQ.0.) GO TO 11
        FT = 0.0
        GO TO 13
11    IF(UNFERM.LT.MAX) GO TO 12
```

```
        FT = 0.0
        GO TO 13
12    IF(UNFERM.GT.MIN) GO TO 13
        FT = 3.3
        GO TO 13
13    CONTINUE
```

The variable NIGHT = STEP(1.)-STEP(5.) is defined in the DYNAMIC segment and will have the value 1 when TIME is between 1 and 5 h, and the value 0 at all other times. When NIGHT = 1 the cow will not eat because FT = 0. When NIGHT = 0 the value of FT will be 3.3, if the variable UNFERM is equal to or less than MIN, and FT will be 0 when UNFERM becomes equal to or greater than MAX. This means that except for a period between 1 and 5 h the cow will eat at a rate of 3.3 kg dry matter per h when the amount of unfermented organic matter in the rumen (UNFERM = A1+A*A2+C1+C*C2) decreases to or below a lower limit (MIN). But the cow will stop eating when the unfermented matter increases to or above an upper limit (MAX).

All statements in the DYNAMIC segment and in the subroutines called from it are executed at each integration step until the end of a run, when the variable TIME equals the preset value of FINTIM.

The TERMINAL segment contains statements that are only executed at the end of each run. The first 4 of these statements are specifications about the integration method, number of runs, and output presentation. FINTIM = 24 means that each run represents 24 h; PRDEL = 24 means that results can be printed for each run at TIME = 0 and TIME = 24 h in the CSMP III program output; OUTDEL = 0.05 means that results at 0.05 h intervals can be printed or plotted as output from a SAS data set generated from the CSMP III program; and DELT = 0.05 means that the integration time interval is 0.05 h

or 3 min. METHOD ADAMS defines a second order integration method:

$Y_{t+dt} = Y_t + dt/2*(3*(dY/dt)_t - (dY/dt)_{t-dt})$,

and IF(RUN.GT.35.) GO TO 50 means that the simulations stop when 35 runs have been performed.

The FORTRAN subroutines named END1, END2, END3 and END4 called from the TERMINAL segment allow the state variables and the regulated parameters to keep their numerical values obtained at the end of a run as initial values for the subsequent run, when the statement CALL RERUN initiates a new run (e.g. C1I = C1, K106I = K106).

The variables listed after PREPARE in the main program (e.g. RUN, F100) are transferred to and presented as output from a SAS data set. The statement RANGE will give the minimum and maximum values in each run of the listed variables (e.g. C1, SU2) as an output from the CSMP III program.

3.2.2 Auxiliary programs

The SAS program shown in Appendix 3 is connected to the CSMP III program and creates a data set containing the output variables listed after the PREPARE statement in the TERMINAL segment of the main program. From this data set another SAS program (see Appendix 4) can perform statistical treatments, further calculations, and graphical presentations of the output variables.

3.3 The individual equations, state variables and parameters

In this section the compartments of the model will be described in detail by the definition of equations and the assignment of numerical values to state variables and equation parameters. The original values estimated from the literature or otherwise assumed are given as well as the values finally adopted after repeated simulations. The individual rates of nutrient metabolism are derived primarily from the static model of Hvelplund (1983) and Danfær (1983b). It is assumed that all nutrient pools are in a steady state.

3.3.1 The rumen compartment

Diagrams of state variables and flows of nutrients in the rumen compartment are shown in figures 2.1 and 2.2. Numerical values and dimensions of the state variables and equation parameters are shown in Appendix 5.

The chemical composition of the feed - a complete diet offered ad libitum - is calculated on the basis of the individual feedstuffs (see section 3.1) according to Hvelplund (1983):

	Per cent of feed dry matter
Sugar	22.35
Starch	3.13
Cell wall carbohydrates	42.68
Glycerol	0.47
Fatty acids	4.00

Protein (N*6.25)	17.88
Ashes	9.49
Total	100.00

Carbon transactions

The equations describing the intake of carbohydrates and lipids are:

```
RSU100 = FT*KSU*LSU        (intake of sugar, mol C/h)
RST100 = FT*KST*LST        (intake of starch, mol C/h)
RCE100 = FT*KCE*LCE        (intake of cell wall carbohydrates,
                            mol C/h)
RGL100 = FT*KGL*LGL        (intake of glycerol, mol C/h)
RLI100 = FT*KLI*LLI        (intake of fatty acids, mol C/h)
R100 = RSU100+RST100+RCE100+RGL100+RLI100
                           (intake of carbohydrates and
                            lipids, mol C/h)
```

The assumed rate of **feed intake during periods of eating** (FT) is based on the work of Tibor (1980), who found rates of eating varying from 3.15 to 3.38 kg DM per hour in lactating cows consuming from 16.0 to 18.1 kg DM per day:

```
FT = 3.3 kg DM/h.
```

The contents of nutrients in the feed are described as fractions of the dry matter according to the chemical composition of the diet:

```
KSU = 0.2235 kg sugar/kg DM
KST = 0.0313 kg starch/kg DM
```

KCE = 0.4268 kg cell wall carbohydrates/kg DM
KGL = 0.0047 kg glycerol/kg DM
KLI = 0.0400 kg fatty acids/kg DM.

The carbon content in the dietary nutrients is calculated as the number of carbon atoms per mole divided by the respective molecular weights:

LSU = 1000*12/342 = 35.087 mol C/kg sugar
LST = 1000*6/162 = 37.037 mol C/kg starch
LCE = 1000*6/162 = 37.037 mol C/kg cell wall carbohydrates
LGL = 1000*3/92.1 = 32.573 mol C/kg glycerol
LLI = 1000*16/256.4 = 62.402 mol C/kg fatty acids.

As the dry matter intake is 17.9 kg/d according to the static model (see section 3.1), the simulated rate of **carbohydrate and lipid intake** is:

R100 = 17.9*(0.2235*35.087+(0.0313+0.4268)*37.037+
0.0047*32.573+0.0400*62.402) =
491.49 mol C/d = 20.479 mol C/h.

The time used to consume this amount of food is: 17.9/3.3 = 5.42 h.

The individual groups of nutrients are divided into **unfermentable and fermentable fractions** by the parameters MSU, MST, MCE and MLI:

RSU101 = MSU*RSU100 (unfermentable sugar, mol C/h)
RST101 = MST*RST100 (unfermentable starch, mol C/h)
RCE101 = MCE*RCE100 (unfermentable cell wall carbohydrates, mol C/h)
RGL101 = MSU*RGL100 (unfermentable glycerol, mol C/h)

```
RLI101 = MLI*RLI100          (unfermentable fatty acids, mol C/h)
R101 = RSU101+RST101+RCE101+RGL101+RLI101
                             (unfermentable carbohydrates and
                             lipids, mol C/h)
RSU102 = (1-MSU)*(RSU100+RGL100)
                             (fermentable sugar and glycerol,
                              mol C/h)
RST102 = (1-MST)*RST100      (fermentable starch, mol C/h)
RCE102 = (1-MCE)*RCE100      (fermentable cell wall
                              carbohydrates, mol C/h)
RLI102 = (1-MLI)*RLI100      (fermentable fatty acids, mol C/h)
R102 = RSU102+RST102+RCE102+RLI102
                             (fermentable carbohydrates and
                              lipids, mol C/h)
```

Sugar, starch and glycerol are assumed to be **totally fermentable:**

```
MSU = MST = 0.
```

Cell wall constituents are **60% fermentable** (Mertens & Ely 1979), and fatty acids are **10% fermentable** (Hvelplund 1983):

```
MCE = 0.40
MLI = 0.90.
```

The pool of **unfermentable carbohydrates and lipids** is represented by the state variable C1, and the rate of **nutrient outflow** (R103) from this pool to the intestinal compartment is described as a first order mass action process. **Outflow rates of the individual nutrients** in the pool are calculated in proportion to their occurrence in the feed:

R103 = K103*C1 (outflow of unfermentable carbohydrates and lipids, mol C/h)

RSU103 = R103*RSU101/R101 (outflow of unfermentable sugar, mol C/h)

RST103 = R103*RST101/R101 (outflow of unfermentable starch, mol C/h)

RCE103 = R103*RCE101/R101 (outflow of unfermentable cell wall carbohydrates, mol C/h)

RGL103 = R103*RGL101/R101 (outflow of unfermentable glycerol, mol C/h)

RLI103 = R103*RLI101/R101 (outflow of unfermentable fatty acids, mol C/h)

In the FORTRAN subroutine (see Appendix 2) these rates are expressed by the parameters KSU, LSU, MSU etc., because the rate R101 will be zero in periods with no feed intake. The **outflow rate of unfermentable carbohydrates and lipids** is calculated on the basis of the static model (Hvelplund 1983):

R103 = 6.39 mol C/h.

The **fractional turnover rate constant** (K103) is assumed to be 2.5% per h - a value estimated by Lindberg (1981) and used by Kristensen (1984) in a dynamic simulation of feed intake of cows on pasture:

$K103 = 0.025\ h^{-1}$.

The **size of the pool** is then derived as:

C1 = R103/K103 = 6.39/0.025 = 255.6 mol C.

The **pools of fermentable** (but not necessarily fermented) **sugar, starch and cell wall carbohydrates** are represented by the state variables SU2, ST2 and CE2. Nutrients from these pools are either **incorporated into microbial carbohydrates and lipids** (R105), **fermented to volatile fatty acids, methane and carbon dioxide** (R106), or **transported out of the rumen in the liquid phase** (R107):

```
RSU105 = K105*SU2          (microbial uptake of sugar, mol C/h)
RST105 = K105*ST2          (microbial uptake of starch, mol C/h)
RCE105 = K105*CE2          (microbial uptake of cell wall
                            carbohydrates, mol C/h)
RLI105 = RLI102            (microbial uptake of fatty acids,
                            mol C/h)
R105 = RSU105+RST105+RCE105+RLI105
                           (microbial uptake of carbohydrates
                            and lipids, mol C/h)

RSU107 = K107*SU2          (outflow of fermentable sugar,
                            mol C/h)
RST107 = K107*ST2          (outflow of fermentable starch,
                            mol C/h)
RCE107 = K107*CE2          (outflow of fermentable cell wall
                            carbohydrates, mol C/h)
R107 = RSU107+RST107+RCE107
                           (outflow of fermentable carbohy-
                            drates, mol C/h)
C2 = SU2+ST2+CE2           (pool of fermentable carbohydrates,
                            mol C)
```

The estimation of **pool sizes in the rumen** is based on the following assumptions:

1) The mass of total rumen contents is 85.0 kg of which 11.0 kg is dry matter, and 10.0 kg is organic matter (Meissner et al. 1979, Egan et al. 1983, Hvelplund 1984a).

2) Total rumen N is 0.278 kg (Ibrahim & Ingalls 1972, Holter et al. 1982) of which 0.013 kg is NH_3-N (Armstrong 1976), and 0.265 kg is non-ammonia N.

3) Microbial N mass is 0.143 kg (Hungate 1966, Maeng & Baldwin 1976a), and microbial organic matter is 1.5 kg of which 40% (= 0,6 kg) is carbohydrates and lipids (Hvelplund 1983, Hvelplund 1984a, Nørgaard 1984).

4) The amount of carbohydrates and lipids in the rumen is derived as organic matter less protein, amino acids and nucleic acids: 10.0-0.265*6.25 = 8,3 kg.

5) Total volatile fatty acids in rumen liquor are 0.5 kg (Hvelplund 1983).

6) Unfermented carbohydrates and lipids (state variables C1 and C2) are therefore: 8.3-(0.6+0.5) = 7.2 kg.

7) Unfermented protein, amino acids and nucleic acids (state variables A1 and A2) are: (0.265-0.143)*6.25 = 0.8 kg.

The daily feed intake in the static model is 17.9 kg dry matter of which 13.0 kg is carbohydrates and lipids (R100). Carbohydrates and lipids taken together are 63.9% digested in the rumen (Hvelplund 1983) and the **unfermented part** is therefore:

R103+R107 = 13.0*0.361 = 4.69 kg/d equivalent to 7.91 mol C/h.

The outflow rate of unfermentable carbohydrates and lipids (R103)

is 6.39 mol C/h equivalent to 3.70 kg/d, and the **outflow rate of fermentable carbohydrates** is estimated as:

R107 = 4.69-3.70 = 0.99 kg/d equivalent to
7.91-6.39 = 1.52 mol C/h.

The **mass of the unfermentable pool of carbohydrates and lipids** (C1) and the **mass of the fermentable carbohydrate pool** (C2) are:

C1 = R103/K103 = (3.70/24)/0.025 = 6.2 kg
C2 = 7.2-6.2 = 1.0 kg.

The **rate constant for fermentable carbohydrate outflow** is then derived as:

$K107 = R107/C2 = (0.99/24)/1.0 = 0.041\ h^{-1}$.

The fraction of sugar and starch digested in the rumen is taken as 0.98 (Armstrong & Smithard 1979), and the **outflow rates of the individual groups of fermentable carbohydrates** are estimated as:

RSU107 = (1-0.98)*RSU102 = 0.02*5.96 = 0.12 mol C/h
RST107 = (1-0.98)*RST102 = 0.02*0.86 = 0.02 mol C/h
RCE107 = 1.52-(0.12+0.02) = 1.38 mol C/h.

The **pool sizes of the individual groups of fermentable carbohydrates** are then derived as:

SU2 = RSU107/K107 = 0.12/0.041 = 2.93 mol C
ST2 = RST107/K107 = 0.02/0.041 = 0.49 mol C
CE2 = RCE107/K107 = 1.38/0.041 = 33.66 mol C
C2 = 2.93+0.49+33.66 = 37.08 mol C.

The rates of **carbohydrate utilization in microbial syntheses and fermentations** are:

R105-RLI105+R106 = RSU102+RST102+RCE102-R107 =
13.90-1.52 = 12.38 mol C/h.

The **microbial incorporation of carbohydrates** is 21% of the total utilization (Czerkawski 1978, Danfær 1979):

R105-RLI105 = RSU105+RST105+RCE105 = 12.38*0.21 =
2.60 mol C/h,

and the **rate constant for microbial uptake of carbohydrates** is derived as:

K105 = (RSU105+RST105+RCE105)/C2 = 2.60/37.08 = 0.070 h^{-1}.

The simulated rate of **carbohydrate fermentation** (R106) is expressed as an enzymatic process, where the maximal rate (R106M) depends on the mass of the microbial population (A4):

R106 = R106M*C2/(K106+C2) (fermentation of carbohydrates, mol C/h)
R106M = L106*A4
RSU106 = R106*X1*EXP(-G*X3) (fermentation of sugar, mol C/h)
RST106 = R106*X2*EXP(-G*X3) (fermentation of starch, mol C/h)
RCE106 = R106*(1-EXP(-G*X3)) (fermentation of cell wall carbohydrates mol C/h)
X1 = SU2/(SU2+ST2)
X2 = ST2/(SU2+ST2)
X3 = CE2/(SU2+ST2)

The rates of fermentation of the individual groups of carbohydrates depend on the proportions of sugar+starch and cell wall carbohydrates in the rumen so that the digestion of cell walls is re-

duced when the level of sugar+starch is increased (Thomsen & Nørgaard 1983, Ternrud & Neergaard 1986). In the above mathematical formulation the ratio (X3) of cell wall carbohydrates (CE2) and easily fermentable carbohydrates (SU2+ST2) will affect the relative fermentation rates of these groups. If the amount of sugar and/or starch is increased, the ratio X3 decreases, and the cell wall fermentation rate will decrease exponentially, reaching zero when X3 = 0.

The **carbohydrate fermentation** rate is derived as the total utilization rate less the rate of microbial incorporation:

R106 = 12.38-2.60 = 9.78 mol C/h.

This rate is assumed to be 80% of the **maximal rate:**

R106M = 9.78/0.80 = 12.23 mol C/h,

and as the mass of the microbial protein pool (A4) is estimated to be 10.04 mol N (see later), the **maximal fermentation rate factor** is:

L106 = R106M/A4 = 12.23/10.04 = 1.218 mol C/(mol N*h).

The **affinity constant for carbohydrate fermentation** is then calculated:

K106 = (R106M/R106-1)*C2 = (12.23/9.78-1)*37.08 = 9.270 mol C.

The rates of **fermentation of the individual carbohydrate groups** are estimated as:

RSU106 = RSU102-(RSU105+RSU107) = 5.64 mol C/h
RST106 = RST102-(RST105+RST107) = 0.81 mol C/h

RCE106 = RCE102-(RCE105+RCE107) = 3.33 mol C/h.

From these values a preliminary estimate of the **parameter G** is: 0.04.

The simulated fraction of cell wall carbohydrates digested in the rumen is: (RCE105+RCE106)/RCE100 = (2.36+3.33)/11.79 = 0.48 - as reported by Thomsen (1980).

The rates of **formation of fermentation products:** volatile fatty acids, methane, carbon dioxide and ATP, **from each class of carbohydrates** are defined as follows:

SUAC1 = ACSU*RSU106	(formation of acetate from sugar, mol C/h)
SUPR1 = PRSU*RSU106	(formation of propionate from sugar, mol C/h)
SUBU1 = BUSU*RSU106	(formation of butyrate from sugar, mol C/h)
SUCH1 = CHSU*RSU106	(formation of CH_4 from sugar, mol C/h)
SUCO1 = COSU*RSU106	(formation of CO_2 from sugar, mol C/h)
SUATP1 = ATPSU*RSU106	(formation of ATP from sugar, mol ATP/h)
STAC1 = ACST*RST106	(formation of acetate from starch, mol C/h)
STPR1 = PRST*RST106	(formation of propionate from starch, mol C/h)
STBU1 = BUST*RST106	(formation of butyrate from starch, mol C/h)

```
STCH1 = CHST*RST106          (formation of CH4 from starch,
                              mol C/h)
STCO1 = COST*RST106          (formation of CO2 from starch,
                              mol C/h)
STATP1 = ATPST*RST106        (formation of ATP from starch,
                              mol ATP/h)

CEAC1 = ACCE*RCE106          (formation of acetate from cell
                              wall carbohydrates, mol C/h)
CEPR1 = PRCE*RCE106          (formation of propionate from cell
                              wall carbohydrates, mol C/h)
CEBU1 = BUCE*RCE106          (formation of butyrate from cell
                              wall carbohydrates, mol C/h)
CECH1 = CHCE*RCE106          (formation of CH4 from cell wall
                              carbohydrates, mol C/h)
CECO1 = COCE*RCE106          (formation of CO2 from cell wall
                              carbohydrates, mol C/h)
CEATP1 = ATPCE*RCE106        (formation of ATP from cell wall
                              carbohydrates, mol ATP/h)
```

Numerical values of the parameters (ACSU, PRSU, ..., ATPCE) are derived from fermentation equations given by Baldwin et al. (1970) (see Appendix 5).

The simulated rate of **protein fermentation** is defined as an enzymatic process (R112), and the substrate pool is the carbon of microbial amino acids and peptides (CA3 = KCA*A3):

```
R112 = R112M*CA3/(K112+CA3)
```

In estimating the **masses of microbial pools** the following assump-

tions are made:

1) Mass of microbial nitrogen pools (A3, N1B and A4) is 0.143 kg N equivalent to 10.21 mol N.

2) Protein concentration in microbial dry matter is 51% (Hvelplund 1983).

3) The concentration of intracellular free amino acid N and peptide N (A3) is 80 mmol per kg microbial dry matter (Blake et al. 1983).

4) The concentration of intracellular ammonia N (N1B) is 15 mmol per kg microbial dry matter (Blake et al. 1983).

5) The molar ratio (KCA) of carbon and nitrogen in proteins is taken as 3.8 mol C/mol N (Reichl & Baldwin 1975, Danfær 1979).

Hence **pool sizes** of A3, N1B, A4 and CA3 can be derived as:

A3 (amino acids and peptides) = 0.143*6.25*80/(0.51*1000)
= 0.140 mol N

N1B (NH_3/NH_4^+) = 0.143*6.25*15/(0.51*1000) = 0.026 mol N

A4 (protein) = 10.21-(0.14+0.03) = 10.04 mol N

CA3 (carbon in amino acids and peptides) = 3.8*0.140
= 0.532 mol C.

The overall fermentation of carbon from carbohydrates and protein into VFA, CH_4 and CO_2 (R106+R114) is 281.5 mol C/d or 11.73 mol C/h in the static model (Hvelplund 1983). The contribution to this from protein (R114) is: 11.73-9.78 = 1.95 mol C/h, but the total fermentation of protein (R112) is higher, because it is assumed

that some of the protein is fermented to branched-chain fatty acids (BCFA) which are taken up and used in microbial synthetic processes (R113).

The content of carbon in protein is: 3.8/(6.25*14.01) = 0.043 mol C/g, and the formation of VFA, CH_4 and CO_2 by protein fermentation is 0.037 mol C/g protein (Baldwin et al. 1970). The simulated rate of total **protein fermentation** can therefore be estimated as:

R112 = 1.95*0.043/0.037 = 2.26 mol C/h,

which is assumed to be 85% of the **maximal possible rate:**

R112M = 2.26/0.85 = 2.66 mol C/h.

The **affinity constant for protein fermentation** is then calculated:

K112 = 0.0939 mol C.

The rates of **formation of VFA, BCFA, CH_4, CO_2 and ATP from protein fermentation** are defined as follows:

```
PRAC1 = AC*R112          (formation of acetate, mol C/h)
PRPR1 = PR*R112          (formation of propionate, mol C/h)
PRBU1 = BU*R112          (formation of butyrate, mol C/h)
PRBC1 = BC*R112          (formation of BCFA, mol C/h)
PRCH1 = CH*R112          (formation of CH4, mol C/h)
PRCO1 = CO*R112          (formation of CO2, mol C/h)
PRATP1 = ATPPR*R112      (formation of ATP, mol ATP/h)
```

Numerical values of the fermentation parameters (AC, PR,....,

ATPPR) are derived from Baldwin et al. (1970) (see Appendix 5).

The rates of **formation of the individual VFA, BCFA, CH_4, CO_2 and ATP from the overall fermentation of carbohydrates and protein** are found by summations:

```
RAC = SUAC1+STAC1+CEAC1+PRAC1   (formation of acetate, mol C/h)
RPR = SUPR1+STPR1+CEPR1+PRPR1   (formation of propionate,
                                 mol C/h)
RBU = SUBU1+STBU1+CEBU1+PRBU1   (formation of butyrate, mol C/h)
RCH = (SUCH1+STCH1+CECH1+PRCH1)*K
                                (formation of CH4, mol C/h)
RCO = SUCO1+STCO1+CECO1+PRCO1-RCH*(1-1/K)
                                (formation of CO2, mol C/h)
R108 = SUATP1+STATP1+CEATP1     (formation of ATP from carbohy-
                                 drates, mol ATP/h)
R113 = PRBC1                    (formation of BCFA from protein,
                                 mol C/h)
R114 = R112-R113                (formation of VFA, CH4 and CO2
                                 from protein, mol C/h)
R115 = PRATP1                   (formation of ATP from protein,
                                 mol ATP/h)
```

The amount of CH_4 produced according to the fermentation equations is reduced by 25% (K = 0.75), and the amount of CO_2 produced according to the fermentation equations is correspondingly increased, because some hydrogen is used for reduction of coenzymes and hydrogenation of unsaturated fatty acids rather than for methane formation (Hvelplund 1983).

The **net fermentation of carbon** (R112-R109) from the pool of amino

acids and peptides (A3) is equal to the amount of **carbon from the net deamination of amino acids** (R11-R17):

```
R109 = R112-KCA*(R11-R17)      (use of microbial carbohydrates
                                and lipids for amino acid
                                synthesis, mol C/h)
```

As the net fermentation rate of amino acids to NH_3-N (R11-R17) is 0.147 mol N/h (see later), the rate of **conversion of microbial non-protein carbon into amino acids** will be:

```
R109 = 2.26-3.8*0.147 = 1.70 mol C/h.
```

The **outflow rate of microbial carbohydrates and lipids** (R110) is proportional to the pool size (C3):

```
R110 = K110*C3                 (outflow of microbial carbohy-
                                drates and lipids, mol C/h)
RST110 = L110*R110             (outflow of microbial starch,
                                mol C/h)
RCE110 = M110*R110             (outflow of microbial cell wall
                                carbohydrates, mol C/h)
RLI110 = N110*R110             (outflow of microbial lipids,
                                mol C/h)
```

The simulated outflow rate of **microbial carbohydrates and lipids from the rumen** is found by balancing the pool (C3):

```
R110 = R105+R113-R109 = 2.79+0.16476*2.26-1.70 = 1.46 mol C/h.
```

The **rate constant** is (see later):

$K110 = 0.0828\ h^{-1}$,

and the **pool size of microbial carbohydrates and lipids** can be calculated as:

$C3 = R110/K110 = 1.46/0.0828 = 17.59$ mol C.

The proportions of starch (L110 = 0.08), cell wall carbohydrates (M110 = 0.44), and lipids (N110 = 0.48) in the microbes are estimated from the work of Hvelplund (1983).

The rates of **VFA absorption and disappearance of fermentation gases** from the rumen are defined as:

```
RAC111 = KAC111*AC4          (outflow of acetate, mol C/h)
RPR111 = KPR111*PR4          (outflow of propionate, mol C/h)
RBU111 = KBU111*BU4          (outflow of butyrate, mol C/h)
RCH111 = KCH111*CH4          (outflow of CH4, mol C/h)
RCO111 = KCO111*CO4          (outflow of CO2, mol C/h)
R111 = RAC111+RPR111+RBU111+RCH111+RCO111
                             (outflow of VFA, CH4 and CO2,
                              mol C/h)
```

The **VFA absorption constants** are assumed to be proportional to the pK_a values of the individual acids because it is suggested that the undissociated acids are absorbed more easily than their anions (Phillipson 1970):

$KAC111 = 0.4504\ h^{-1}$
$KPR111 = 0.4627\ h^{-1}$

KBU111 = 0.4561 h^{-1}.

The **absorption rates of VFA** are presumed to be equal to their production rates:

RAC111 = RAC = 4.23 mol C/h
RPR111 = RPR = 2.50 mol C/h
RBU111 = RBU = 1.71 mol C/h.

From these figures the **VFA pool sizes** can be calculated:

AC4 = RAC111/KAC111 = 4.23/0.4504 = 9.39 mol C
PR4 = RPR111/KPR111 = 2.50/0.4627 = 5.40 mol C
BU4 = RBU111/KBU111 = 1.71/0.4561 = 3.76 mol C.

Consequently, the total amount of VFA (AC4+PR4+BU4) in the rumen is 7.4 moles of acids equivalent to: 7.4/74 = 0.1 moles per l rumen liquor as found in many experiments (Hungate 1966, Bauman et al. 1971, Chamberlain et al. 1983, Counotte et al. 1983).

The amount of methane forms 30-40% of the total gas present in the rumen (Phillipson 1970), and it is suggested here that CH4 = 0.5*C04. As the **disappearance rates of fermentation gases** are equal to their production rates:

RCH111 = RCH = 0.92 mol C/h
RCO111 = RCO = 2.32 mol C/h,

it can be deduced that KCO111 = 1.263*KCH111. It is assumed that the value of KCH111 is higher than the VFA absorption constants and is assessed at 1.0 h^{-1}. Then the **rate constants for fermentation gas disappearance** are:

KCH111 = 1.000 h^{-1}

KCO111 = 1.263 h^{-1},

and the **fermentation gas pool sizes** are:

CH4 = RCH111/KCH111 = 0.92/1.000 = 0.92 mol C/h
CO4 = RCO111/KCO111 = 2.32/1.263 = 1.84 mol C/h.

Nitrogen transactions

The rate of **crude protein intake** is defined as:

RO = RCO+RRO	(intake of crude protein, mol N/h)
RCO = FT*KC*LC	(intake of crude protein in concentrates, mol N/h)
RRO = FT*KR*LR	(intake of crude protein in roughages, mol N/h)

The parameters KC and KR give the **concentration in ration dry matter of crude protein** in concentrates and roughages, respectively, while LC and LR are the **nitrogen content in protein** from concentrates and roughages, respectively. According to the static model:

KC = 0.1000 kg crude protein in concentrates/kg ration DM
KR = 0.0788 kg crude protein in roughages/kg ration DM, and
LC = LR = 11.423 mol N/kg crude protein.

Hence, the simulated rate of **protein intake** is:

RO = 17.9*(0.100+0.0788)*11.423 = 36.56 mol N/d =
1.523 mol N/h.

The dietary crude protein is divided into **unfermentable** (R1) and **fermentable protein** (R2), **ammonium-N** (R3), **and urea-N** (R4):

```
R1 = MC*RCO+MR*RRO          (unfermentable protein, mol N/h)
R3 = M3*RO                  (ammonium, mol N/h)
R4 = M4*RO                  (urea, mol N/h)
R2 = RO-R1-R3-R4            (fermentable protein, mol N/h)
```

Based on the composition of the feed and factors of protein degradability given by Armstrong (1979), the dietary protein is assumed to be 80% fermentable. As the ration contains no ammonium salts or urea, M3 = M4 = 0, and R3 = R4 = 0 mol N/h. Hence, the **flows of fermentable and unfermentable protein** are:

```
R2 = 0.80*RO = 0.80*1.523 = 1.218 mol N/h
R1 = RO-R2 = 1.523-1.218 =  0.305 mol N/h.
```

The **unfermentable fraction of roughage protein** is assumed to be:

```
MR = 0.10,
```

and the **unfermentable fraction of concentrate protein** can then be calculated as:

```
MC = (R1-MR*RRO)/RCO = (0.305-0.10*0.671)/0.852 = 0.2788.
```

The state variables A1 and A2 represent the unfermentable and fermentable protein pools, respectively. The **protein escaping degradation in the rumen** is removed at a rate, R5+R7, which is 35% of the protein intake (Hvelplund 1983):

R5 = K5*A1 (outflow of unfermentable protein, mol N/h)

R7 = K7*A2 (outflow of fermentable protein, mol N/h)

The simulated **outflow rate of unfermentable protein** is found by balancing the pool (A1):

R5 = R1 = 0.305 mol N/h, and

the **outflow rate of fermentable protein** is found by difference:

R7 = (0.35*R0)-R5 = (0.35*1.523)-0.305 = 0.228 mol N/h.

The turnover rate constant for the liquid phase in the rumen has been estimated at 11% per hour (Hartnell & Satter 1979, Tamminga 1979). The outflow rate of fermentable protein is believed to follow closely the outflow rate of rumen liquor, and the **rate constant for fermentable protein outflow** is therefore:

$K7 = 0.11\ h^{-1}$.

The **pool size of fermentable protein** is derived as:

A2 = R7/K7 = 0.228/0.11 = 2.077 mol N.

As stated previously the mass of unfermented protein in the rumen (A1+A2) is 0.80 kg or 9.138 mol N. Hence, the **pool size of unfermentable protein** is:

A1 = 9.138-2.077 = 7.061 mol N, and

the **rate constant for unfermentable protein outflow** will be:

$K5 = R5/A1 = 0.305/7.061 = 0.043\ h^{-1}$.

The rates describing **microbial N metabolism in the rumen** are as follows:

R6 = R6M*A2/(K6+A2)	(microbial uptake of amino acids and peptides, mol N/h)
R8 = R8M*A3/(K8+A3)	(microbial excretion of amino acids, mol N/h)
R9 = R9M*A3/(K9+A3)	(microbial protein synthesis, mol N/h)
R9M = YATP*M9*(R108+R115)	(mol N/h)
R10 = K10*A3	(outflow of microbial amino acids and peptides, mol N/h)
R11 = R11M*A3/(K11+A3)	(degradation of microbial amino acids, mol N/h)
R12 = K12*A4	(degradation of microbial protein, mol N/h)
R13 = K13*A4	(outflow of microbial protein, mol N/h)
R15 = R15M*N1A/(K15+N1A)	(microbial uptake of NH_3/NH_4^+, mol N/h)
R17 = R17M*N1B/(K17+N1B)	(microbial amino acid synthesis, mol N/h)
R18 = K18*N1B	(outflow of microbial NH_3/NH_4^+, mol N/h)
R19 = R10+R13+R18	(outflow of microbial total nitrogen, mol N/h)
R20 = R20M*N1B/(K20+N1B)	(microbial excretion of NH_3/NH_4^+, mol N/h)

The **masses of the nitrogen pools** are as estimated previously:

A3 (microbial amino acids and peptides) = 0.140 mol N
A4 (microbial protein and nucleic acids) = 10.04 mol N
N1B (microbial NH_3/NH_4^+) = 0.026 mol N
N1A (extracellular rumen NH_3/NH_4^+) = 0.013 kg N = 0.928 mol N.

Free amino acids which are not utilized for protein synthesis in protozoa are excreted to the rumen liquor (Tamminga 1979). The rate of this proces (R8 in the model) is estimated from Coleman (1975) to be 10% of the rate of **microbial uptake of amino acids and peptides** (R6 in the model). Balancing the pool of fermentable protein and amino acids in the rumen liquor (A2) gives:

R6-R8 = R2-R7 = 0.990 mol N/h, and
R6 = 0.990/(1-0.10) = 1.100 mol N/h.

The rate of **amino acid excretion** is then derived as:

R8 = R6*0.10 = 1.100*0.10 = 0.110 mol N/h.

The transport of N-compounds through microbial cell walls and membranes is assumed to be by carrier-mediated processes following Michaelis-Menten (saturation) kinetics (Eckert & Randall 1978, Russel & Hespell 1981). The microbial amino acid transport mechanisms are assumed to be 70% saturated, which means that the **maximal rates of microbial uptake and excretion of amino acids and peptides** are:

R6M = 1.100/0.70 = 1.572 mol N/h
R8M = 0.110/0.70 = 0.157 mol N/h.

The **affinity constants for microbial amino acid exchange** are finally calculated:

K6 = 0.890 mol N

K8 = 0.060 mol N.

The **total yield of microbial N from the rumen** has been estimated by Danfær (1979), Hvelplund (1983) and Robinson & Sniffen (1985). The following value for this rate has been adopted in the model:

R19 = 0.845 mol N/h.

The microbial N pools (A3+A4+N1B) are 10.206 mol N, and the **rate constant for microbial outflow from the rumen** is consequently:

$K10 = K13 = K18 = K110 = 0.845/10.206 = 0.0828\ h^{-1}$.

Hence, the simulated **outflow rates of microbial amino acids and peptides** (R10), **protein** (R13), and **NH_3/NH_4^+** (R18) are:

R10 = 0.0828*0.140 = 0.012 mol N/h
R13 = 0.0828*10.04 = 0.831 mol N/h
R18 = 0.0828*0.026 = 0.002 mol N/h.

Eighty per cent of the synthesized microbial protein passes from the rumen to the intestines, and 20 per cent is turned over within the rumen (Armstrong 1976). The simulated **rate of protein synthesis** can therefore be calculated as:

R9 = R13/0.80 = 0.831/0.80 = 1.039 mol N/h.

The maximal rate (R9M) is assumed to depend on ATP availability (R108+R115) and on the efficiency of ATP utilization (YATP*M9). YATP depends in turn on the concentrations of amino acids (A2) and NH_3/NH_4^+ (N1A) in the rumen fluid (Maeng & Baldwin 1976 b&c, Mehrez et al. 1977, Owens & Bergen 1983):

YATP = YATPM*A2*N1A/(KATP+A2*N1A).

As stated, A2 = 2.077 mol N and N1A = 0.928 mol N. YATP is, on average, 26 g cell DM/mol ATP for mixed rumen microbial populations, and YATPM is approximately 8% higher: 28 g cell DM/mol ATP (Hespell & Bryant 1979). The affinity constant can then be estimated as: KATP = 0.1483 (mol N)^2. The concentration of crude protein in cell DM is 50% (Hvelplund 1983), and the **nitrogen content in microbes** is accordingly:

M9 = 0.50/(6.25*14.0) = 5.742*10^{-3} mol protein-N/g cell DM.

The simulated rate of ATP formation (R108+R115) is 7.294 mol ATP/h, and the **maximal rate of protein synthesis** is derived as:

R9M = 26*5.742*7.294/1000 = 1.089 mol N/h.

Hence, the **affinity constant** is calculated as:

K9 = 0.0068 mol N.

This value is low compared to the substrate pool size (A3), which is also the case for the affinity constants of most rumen bacteria (Russell & Hespell 1981).

The rate of **microbial protein degradation** in the model is:

R12 = R9-R13 = 1.039-0.831 = 0.208 mol N/h,

and the **rate constant** for the process will be:

K12 = R12/A4 = 0.208/10.04 = 0.0207 h^{-1}.

Contrary to protozoa rumen bacteria are not able to transport free amino acids through their cell walls into the rumen fluid. Excess amino acids are therefore degraded intracellularly and the nitrogen is excreted to the medium as NH_3/NH_4^+ (Tamminga 1979). In order to simulate this situation the model requires both an extracellular (N1A) as well as an intracellular (N1B) pool of NH_3/NH_4^+. The rate of net incorporation of ammonium-N into microbial protein is 230 g/d equivalent to 0.684 mol/h (Hvelplund 1983). This is assumed to be 80% of the gross rate of **microbial amino acid synthesis** from intracellular NH_3/NH_4^+ (Armstrong 1976, Tamminga 1979):

R17 = 0.684/0.80 = 0.855 mol N/h.

K_m values of the two known enzymes for utilization of ammonium-N by rumen microbes: glutamate dehydrogenase and glutamine synthetase, are 5mM and 0.2 mM, respectively (Baldwin & Denham 1979). Using an average value (2.6 mM) the **affinity constant for microbial amino acid synthesis** can be estimated as:

K17 = 2.6*1.75*0.8/(0.2*1000) = 0.0182 mol N,

when microbial cell DM is 1.75 kg (Hvelplund 1983), and microbial metabolic water is 80% of the total cell mass (Blake et al. 1983).

The **maximal rate of microbial amino acid synthesis** is then derived from the rate equation:

R17M = 1.454 mol N/h.

Now, the simulated rate of **microbial amino acid degradation** is calculated by balancing the pool A3:

R11 = R6+R12+R17-(R8+R9+R10) = 1.002 mol N/h.

This is assumed to be 70% of the **maximal rate:**

R11M = R11/0.70 = 1.002/0.70 = 1.432 mol N/h,

and the **affinity constant for degradation of microbial amino acids** is consequently:

K11 = 0.06 mol N.

Processes of **urea uptake** and **ammonia absorption** are defined as follows:

R14 = K14*N1A	(outflow of NH_3/NH_4^+, mol N/h)
R16 = K16*(N1A/V1)	(absorption of NH_3/NH_4^+, mol N/h)
R21 = R21M*U1/(K21+U1)	(hydrolysis of urea, mol N/h)
R55 = K55*(U4/V4-U1/V1)	(uptake of urea, mol N/h)

The rumen ammonia flux rate (R14+R15+R16 = R20+R21) is 276 g N/d equivalent to 0.821 mol N/h (Oldham et al. 1980). The rate of **urea hydrolysis** (R21) equals the rate of **urea uptake** (R55), which is taken from Hvelplund (1983) as 62 g N/d:

R21 = R55 = 62/(14.01*24) = 0.184 mol N/h.

The simulated rate of **microbial NH_3/NH_4^+ excretion** to the rumen fluid is then:

R20 = 0.821-0.184 = 0.637 mol N/h,

which is assumed to be 85% of the **maximal rate:**

R20M = R20/0.85 = 0.637/0.85 = 0.749 mol N/h.

From this the **affinity constant for excretion of intracellular NH_3/NH_4^+** is derived as:

$K20 = 0.0046$ mol N.

The simulated rate of **microbial NH_3/NH_4^+ uptake** from the rumen fluid is found by balancing the intracellular NH_3/NH_4^+ pool (N1B):

$R15 = R17+R18+R20-R11 = 0.492$ mol N/h.

Affinities of ruminal bacteria for ammonium-N range from 5 to 45 µM (Russell & Hespell 1981). An average value (25 µM) is used in the model for estimation of the **affinity constant** (rumen water: V1 = 85-11 = 74 kg):

$K15 = 25*10^{-6}*74 = 0.002$ mol N,

and the **maximal rate of microbial NH_3/NH_4^+ uptake** is calculated as:

$R15M = 0.493$ mol N/h.

The **outflow of NH_3/NH_4^+** from the rumen (R14) follows the **liquid turnover rate** (K7):

$K14 = K7 = 0.11\ h^{-1}$
$R14 = 0.11*0.928 = 0.102$ mol N/h.

Ammonium is absorbed from the rumen by diffusion and depends therefore on the ruminal concentration, i.e. N1A/V1 (Houpt 1970, Huntington 1986). The simulated rate of **NH_3/NH_4^+ absorption** is found by balancing the pool N1A:

R16 = R20+R21-(R14+R15) = 0.227 mol N/h,

and the **rate constant for absorption** will be:

K16 = R16/(N1A/V1) = 0.227/0.0125 = 18.154 l/h.

Ruminal urea-N concentration is about 3 mM (Houpt 1970), and the **urea pool in the rumen** is then:

U1 = 3*74/1000 = 0.222 mol N.

The maximal capacity of ruminal bacteria for urea degradation is 1 g per l per h (Jones 1967, c.f. Owens & Bergen 1983). From this information the **maximal rate of urea hydrolysis** can be estimated as:

R21M = 1*74*2/60.1 = 2.463 mol N/h,

and the **affinity constant for urea hydrolysis** is accordingly:

K21 = 2.743 mol N.

The high ureolytic activity of rumen wall bacteria is inversely related to the level of ammonia in the rumen fluid (Wallace et al. 1979), and according to this the affinity constant K21 is regulated by the size of N1A (see subroutine REGUL1, Appendix 2).

Urea transport from the blood into the rumen is proportional to the concentration gradient (Houpt 1970), and in the model formulation this is assumed to be valid for transport via saliva as well as directly through the rumen wall (R55). The urea-N concentration in the blood is 14 mM (Møller 1973, Harmeyer & Martens 1980, Holter et al. 1982, Oltner & Wiktorsson 1983). The **volume of the**

extracellular fluid compartment is assumed to be 25% of the live weight (600 kg):

V4 = 0.25*600 = 150 l,

and, hence, the **urea pool in the extracellular fluid** is:

U4 = 150*14/1000 = 2.100 mol N.

The rate of urea uptake into the rumen (R55) is estimated previously as 0.184 mol N/h, and the **diffusion constant** is finally calculated:

K55 = R55/(U4/V4-U1/V1) = 0.184/(0.014-0.003) = 16.765 l/h.

Feed energy content

The **gross energy content in the feed** is calculated by the last equations of the rumen compartment subroutine:

```
ESU100 = (RSU100/LSU)*CSU      (energy intake in sugar, MJ/h)
EST100 = (RST100/LST)*CST      (energy intake in starch, MJ/h)
ECE100 = (RCE100/LCE)*CCE      (energy intake in cell walls,
                                MJ/h)
ELI100 = (RGL100*(1/LGL-18.02/1000)+RLI/LLI)*CLI
                               (energy intake in lipids, MJ/h)
EPRO = ((R1+R2)/LC)*CPR        (energy intake in protein, MJ/h)
RGE = ESU100+EST100+ECE100+ELI100+EPRO
                               (gross energy intake, MJ/h)
```

The parameters CSU, CST, CCE, CLI and CPR are factors describing heats of combustion of the individual nutrients: CSU = 16.6 MJ/kg sugar, CST = 17.6 MJ/kg starch (Bach Knudsen 1986), CCE = 18.8

MJ/kg cell wall carbohydrates, CLI = 39.75 MJ/kg fat and CPR = 23.93 MJ/kg protein (Schiemann et al. 1972). According to the above equations the rate of **gross energy intake** can be calculated:

RGE = 13.596 MJ/h = 326.30 MJ/d.

3.3.2 The intestinal compartments

Diagrams of state variables and the flow of nutrients in the intestinal compartments are shown in figures 2.3 and 2.4. Numerical values and dimensions of the state variables and equation parameters are shown in Appendix 6.

Carbon transactions

The nutrients passing from the rumen into the intestines are unfermented feed carbohydrates and fatty acids (R103+R107), microbial carbohydrates and lipids (R110), unfermented feed protein (R5+R7), microbial crude protein (R19), and ruminal NH_3/NH_4^+ (R14).

The rates of **digestion and hind gut fermentation of carbohydrates and lipids** are defined as follows:

```
R116 = RCE103+RCE107+RCE110+K116*(RLI103+RLI110*48/51)
                            (indigestible cell wall carbohydrates
                             and fatty acids, mol C/h)
R117 = RSU103+RST103+RGL103+RSU107+RST107+RST110+RLI110*3/51
                            (digestible sugar, starch and
                             glycerol, mol C/h)
```

```
R118 = (1-K116)*(RLI103+RLI110*48/51)
                                (digestible fatty acids, mol C/h)
R119 = K119*C7                  (intestinal flow of indigestible cell
                                 wall carbohydrates and fatty acids,
                                 mol C/h)
R119F = L119*R119               (hind gut fermentation of cell wall
                                 carbohydrates and fatty acids,
                                 mol C/h)
R120 = K120*C8                  (intestinal flow of digestible sugar,
                                 starch and glycerol, mol C/h)
R120F = L120*R120               (hind gut fermentation of sugar,
                                 starch and glycerol, mol C/h)
R121 = R121M*C8/(K121+C8)       (uptake from the lumen of glucose,
                                 mol C/h)
R122 = K122*C9                  (intestinal flow of digestible fatty
                                 acids, mol C/h)
R123 = K123*C9                  (uptake from the lumen of fatty
                                 acids, mol C/h)
```

The values of the state variables, C7 (indigestible cell wall carbohydrates and fatty acids), C8 (digestible sugar, starch and glycerol), and C9 (digestible fatty acids) are estimated as follows:

1) The volume of digesta fluid in the small intestine is assumed to be 21.3 l (Phillipson 1970, Crampton & Lloyd 1959 c.f. Neimann-Sørensen 1983): V2A = 21.3 l.

2) Digesta in the small intestine contains 4.4% dry matter (Hvelplund et al. 1976, Hvelplund 1984b) and 95.6% water (equivalent to V2A = 21.3 l).

3) Hence, the volume of digesta in the small intestine is cal-

culated as: 21.3/0.956 = 22.3 l, and digesta dry matter is: 22.3-21.3 = 1.0 kg.

4) Digesta organic matter is assumed to be - as in the rumen - 90% of the dry matter, i.e. 0.90 kg organic matter in the small intestine.

5) Protein content in the digesta is 25% of dry matter (Agergaard et al. 1984), i.e. 0.25 kg protein in the small intestine.

6) Consequently, the amount of carbohydrates and lipids in the small intestine is: C7+C8+C9 = 0.90-0.25 = 0.65 kg, equivalent to 29.8 mol C.

According to the static model (Hvelplund 1983) fatty acids are digested in the small intestine at a rate (R123) of 46.6 mol C/d equivalent to 1.942 mol C/h, representing 90% of the entry rate of the digestible (but not digested) fatty acids (R118) from the rumen (Brumby et al. 1979). The simulated total entry rate of fatty acids (indigestible and digestible) into the small intestine (RLI103+RLI110*48/51) is 2.332 mol C/h, and therefore the **fraction of indigestible fatty acids** can be calculated as:

K116 = (2.332-1.942/0.90)/2.332 = 0.0745.

The entry rates of **indigestible and digestible carbohydrates and lipids** are then estimated:

R116 = 6.738(indig. carbohydrates)+
0.0745*2.332(indig. fatty acids) = 6.912 mol C/h
R117 = 0.119(dig. sugar)+0.134(dig. starch)+
0.041(dig. glycerol) = 0.294 mol C/h
R118 = (1-0.0745)*2.332 = 2.158 mol C/h.

Ninety per cent of the digestible carbohydrates are actually digested in the small intestine (Pehrson & Knutson 1980, Hvelplund 1983), and therefore the rate of **glucose uptake from the intestinal lumen** will be:

$$R121 = 0.90*R117 = 0.90*0.294 = 0.265 \text{ mol C/h},$$

and the remaining 10% are transported to the hind gut, i.e. the **intestinal flow of digestible carbohydrates** is:

$$R120 = R117-R121 = 0.294-0.265 = 0.029 \text{ molC/h}.$$

The simulated rate of **fatty acid uptake from the intestinal lumen** is:

$$R123 = 0.90*R118 = 0.90*2.158 = 1.942 \text{ mol C/h},$$

and the **intestinal flow of digestible fatty acids** to the hind gut is then:

$$R122 = R118-R123 = 2.158-1.942 = 0.216 \text{ mol C/h}.$$

The rate of **intestinal flow of indigestible carbohydrates and fatty acids** to the hind gut is:

$$R119 = R116 = 6.912 \text{ mol C/h},$$

and the **rate constant for digesta flow in the small intestine** is calculated as:

$$K119 = K120 = K122 = (R119+R120+R122)/(C7+C8+C9) = (6.912+0.029+0.216)/29.8 = 0.24 \text{ h}^{-1}.$$

Now, the pools in the small intestine of **indigestible carbohydra-**

tes and fatty acids (C7), **digestible carbohydrates and glycerol** (C8), and **digestible fatty acids** (C9) can be estimated:

C7 = R119/K119 = 6.912/0.24 = 28.800 mol C
C8 = R120/K120 = 0.029/0.24 = 0.123 mol C
C9 = R122/K122 = 0.216/0.24 = 0.899 mol C.

Twenty-two per cent of the cell wall carbohydrates and 100% of the sugar and starch present in the hind gut are fermented (Hvelplund 1983). Hence, the values used in the model for the **fermented fractions of cell wall carbohydrates and of starch** are, respectively:

L119 = 0.22
L120 = 1.00.

Consequently, the simulated **fermentation rates of carbohydrates and fatty acids** in the hind gut are:

R119F = 0.22*6.912 = 1.521 mol C/h
R120F = 1.00*0.029 = 0.029 mol C/h.

The maximal capacity for carbohydrate digestion is estimated by Pehrson & Knutsson (1980) as 1200 g glucose per d. The transport of glucose from the lumen into the intestinal epithelium is an active process mediated by a carrier protein (Stryer 1981, Christensen 1984) leading to saturation (Michaelis-Menten) kinetics. The **maximal rate of glucose uptake from the lumen** is then:

R121M = 1200*6/(180*24) = 1.667 mol C/h,

and the **affinity constant** can be calculated as:

K121 = 0.6515 mol C.

The **rate constant for fatty acid uptake from the lumen** is finally derived:

$$K123 = R123/C9 = 1.942/0.899 = 2.160\ h^{-1}.$$

The **formation of fermentation products from hind gut fermentations** of starch and cell wall carbohydrates is described by the following equations:

STAC2 = ACST*R120F	(formation of acetate from starch, mol C/h)
STPR2 = PRST*R120F	(formation of propionate from starch, mol C/h)
STBU2 = BUST*R120F	(formation of butyrate from starch, mol C/h)
STCH2 = CHST*R120F	(formation of CH_4 from starch, mol C/h)
STCO2 = COST*R120F	(formation of CO_2 from starch, mol C/h)
STATP2 = ATPST*R120F	(formation of ATP from starch, mol ATP/h)
CEAC2 = ACCE*R119F	(formation of acetate from cell wall carbohydrates, mol C/h)
CEPR2 = PRCE*R119F	(formation of propionate from cell wall carbohydrates, mol C/h)
CEBU2 = BUCE*R119F	(formation of butyrate from cell wall carbohydrates, mol C/h)
CECH2 = CHCE*R119F	(formation of CH_4 from cell wall carbohydrates, mol C/h)
CECO2 = COCE*R119F	(formation of CO_2 from cell wall carbohydrates, mol C/h)
CEATP2 = ATPCE*R119F	(formation of ATP from cell wall carbohydrates, mol ATP/h)

```
R125 = STATP2+CEATP2          (formation of ATP from starch and
                               cell wall carbohydrates, mol ATP/h)
```

Numerical values of the parameters (ACST, PRST, --- , ATPCE) are derived from fermentation equations given by Baldwin et al. (1970) (see Appendix 5).

The rate of **faecal excretion of carbohydrates and lipids** is defined as:

```
R126 = K126*C10B              (excretion of undigested
                               carbohydrates and lipids, mol C/h)
```

The **rate constant** and the **pool size** are, respectively, (see later):

$K126 = 0.114\ h^{-1}$

C10B = 55.756 mol C.

The following equations are concerned with **intestinal wall metabolism, and absorption of glucose and fatty acids:**

```
R128 = R128M*C11/(K128+C11)   (oxidation of acetate and
                               ketone bodies, mol C/h)
R129 = R129M*C12/(K129+C12)   (oxidation of glucose, mol C/h)
R130 = R130M*C12/(K130+C12)   (absorption of glucose, mol C/h)
R131 = K131*R123              (formation of glycerol for
                               esterification of fatty acids,
                               mol C/h)
R132 = R123+R131              (absorption of lipids, mol C/h)
```

R155 = K155*(C23/V4) (uptake of acetate and ketone bodies from the blood, mol C/h)

The rate of acetate and ketone body oxidation (R128) is assumed to be equivalent to the basal metabolism in the digestive tract, which according to Webster et al. (1975) can be estimated as $0.062*(0.90*600)^{0.75}$ = 7.0 MJ/d in a 600 kg cow. The amount of substrate which must be oxidized to produce this quantity of heat is calculated by using heat combustion values for acetate and 3-OH-butyrate, and the relative amounts of these nutrients available from absorption as well as from endogenous production (see section 3.3.3). In this way the **oxidation rate of acetate and ketone bodies** is calculated as:

R128 = 0.642 mol C/h,

which is assumed to be 90% of the **maximal rate of oxidation:**

R128M = 0.642/0.90 = 0.713 mol C/h.

The intracellular concentration of acetate and ketone bodies (C11/VD) in the intestinal wall is assumed to be only 20% of the concentration in the extracellular fluid (C23/V4), which is taken to be 5.8 mmol C/l (Bickerstaffe et al. 1974, Annison et al. 1974, Lomax & Baird 1983, Ray et al. 1983, Rulquin 1983). The **intracellular concentration** is therefore:

C11/VD = 5.8*0.20 = 1.16 mmol C/l.

The **volume of the intracellular fluid** (VD) is derived from the tissue weight = 14.5 kg (Lobley et al. 1980, Crampton & Lloyd 1959 c.f. Neimann-Sørensen 1983), and from the tissue dry matter content = 150 g/kg (Rothschild & Reichl 1983). Hence,

VD = 14.5*0.85 = 12.3 l.

Consequently, the **intracellular pool size of acetate and ketone bodies** is calculated as:

C11 = 1.16*VD = 1.16*12.3/1000 = 0.014 mol C,

and the **affinity constant** is:

K128 = 0.00156 mol C.

Fatty acids are esterified with glycerol during their absorption through the intestinal wall. The glycerol moieties are synthesized from glucose with a rate (R131) proportional to the rate of fatty acid uptake (R123). The **proportionality factor** is:

K131 = 3/(3*16) = 0.0625,

and the **formation rate of glycerol** is therefore:

R131 = 0.0625*1.942 = 0.121 mol C/h.

The amount of glucose not used in glycerol synthesis is: R129+R130 = R121-R131 = 0.265-0.121 = 0.144 mol C/h, and the rate of **glucose oxidation** is assumed to be 5% of this:

R129 = 0.144*0.05 = 0.0072 mol C/h,

which in turn is assumed to be 50% of the **maximal glucose oxidation** rate:

R129M = 0.0072/0.50 = 0.0144 mol C/h.

The intracellular glucose concentration in the intestinal wall (C12/VD) is further assumed to be a little higher than the glucose concentration in the digesta (C8/V2A), which is: 0.123/21.3 = 0.0058 mol C/l. According to this the **intracellular glucose concentration** is taken to be:

C12/VD = 0.007 mol C/l,

and the **pool size of intracellular glucose** is therefore:

C12 = 0.007*VD = 0.007*12.3 = 0.086 mol C.

The **affinity constant for glucose oxidation** is then calculated as:

K129 = 0.086 mol C.

Hence, the simulated rate of **glucose absorption** is:

R130 = R121-R131-R129 = 0.144-0.0072 = 0.137 mol C/h.

The **maximal rate of glucose transport** across the intestinal epitheluim is:

R130M = R121M = 1.667 mol C/h,

and the **affinity constant** can then be derived as:

K130 = 0.9665 mol C.

The membrane transport of acetate and ketone bodies is independent of carriers (Giesecke 1983), and is assumed to be proportional to their concentrations in the blood (King et al. 1985). The rate of **acetate and ketone body uptake from the blood** equals the rate of oxidation:

R155 = R128 = 0.642 mol C/h,

and the **rate constant** is:

K155 = R155/(C23/V4) = 0.642/0.0058 = 110.60 l/h.

The volume of the extracellular fluid (V4) is 150 l (see section 3.3.1), and the **pool size of acetate and ketone bodies** is consequently:

C23 = 0.0058*V4 = 0.0058*150 = 0.87 mol C.

Nitrogen transactions

The **digestion and hind gut fermentations of nitrogenous compounds** are described as follows:

R22 = (1-K23*L23)*(R5+R7)+(1-M23*L23)*(R10+R13) (indigestible dietary and microbial protein, mol N/h)

R23 = K23*L23*(R5+R7)+M23*N23*(R10+R13) (digestible dietary and microbial protein, mol N/h)

R24 = R14+R18 (NH_3/NH_4^+ from rumen liquor and from rumen microbes, mol N/h)

R25 = K25*A6 (intestinal flow of indigestible dietary and microbial protein, mol N/h)

R26 = K26*A7 (intestinal flow of digestible dietary and microbial protein, mol N/h)

R27 = R27M*A7/(K27+A7) (uptake from the lumen of dietary and microbial amino acids, mol N/h)

R28 = R28M*A8/(K28+A8)	(protein degradation in the hind gut, mol N/h)
R29 = K29*A8	(faecal excretion of undigested protein, mol N/h)
R32 = K32*A10	(intestinal flow of indigestible endogenous protein, mol N/h)
R33 = K33*A11	(intestinal flow of digestible endogenous protein, mol N/h)
R34 = R34M*A11/(K34+A11)	(uptake from the lumen of endogenous amino acids, mol N/h)
R35 = K35*(N2A/V2A)	(absorption of NH_3/NH_4^+ from the small intestine, mol N/h)
R36 = R36M*N2B/(K36+N2B)	(microbial amino acid synthesis in the hind gut, mol N/h)
R36M = L36*R125	(mol N/h)
R127 = KCA*(R28-R36)	(net protein degradation in the hind gut, mol C/h)
R127A = K127A*R127	(fermentation of protein-C in the hind gut, mol C/h)

The **proportions of amino acids** in undegraded dietary protein and in microbial protein are taken to be 0.80 and 0.70, respectively (Hvelplund 1983):

K23 = 0.80
M23 = 0.70.

Both dietary and microbial amino acids are assumed to be 100% **digestible** (although not 100% digested):

L23 = N23 = 1.0.

According to these values and the rate of N inflow from the rumen, the **flow rates of indigestible protein, digestible protein, and**

NH_3/NH_4^+ can be calculated:

R22 = 0.20*0.533+0.30*0.843 = 0.360 mol N/h
R23 = 0.80*0.533+0.70*0.843 = 1.016 mol N/h
R24 = 0.102+0.002 = 0.104 mol N/h.

The total amount of crude protein in the digesta of the small intestine is 245 g (Agergaard et al. 1984). This amount is equivalent to the **pools of dietary and microbial protein** (A6+A7), **endogenous protein** (A10+A11), **and NH_3/NH_4^+** (N2A):

A6+A7+A10+A11+N2A = 245 g protein = 2.79 mol N.

The **content of NH_3/NH_4^+** is taken as 2.4% of total digesta nitrogen (Teller et al. 1979, Brandt & Rohr 1981, Brandt et al. 1981), which means that

N2A = 2.79*0.024 = 0.067 mol N.

The indigestible protein of dietary and microbial origin is transported down the small intestine at the rate, R25 = R22 = 0.360 mol N/h. The **rate constant for this intestinal flow** has been estimated previously:

$K25 = K26 = K32 = K33 = K119 = 0.24\ h^{-1}$,

and the **pool size of indigestible protein** can be derived as:

A6 = R25/K25 = 0.360/0.24 = 1.50 mol N.

Undegraded dietary amino acids and microbial amino acids are digested with an efficiency of 86% and 75%, respectively (Hvelplund 1983). The rate of **amino acid uptake from the lumen** across the

mucousal membrane can therefore be expressed as:

R27 = 0.86*K23*(R5+R7)+0.75*M23*(R10+R13) = 0.809 mol N/h.

The **flow rate of digestible protein to the hind gut** can then be calculated by difference:

R26 = R23-R27 = 1.016-0.809 = 0.207 mol N/h,

and the **pool size of digestible protein** from the rumen will be:

A7 = R26/K26 = 0.207/0.24 = 0.863 mol N.

Amino acids are taken up into cells by facilitated transport mechanisms showing Michaelis-Menten kinetics (Munck 1976, Bergen 1978, Eckert & Randall 1978, Christensen 1982). Rothschild & Reichl (1983) have investigated the kinetics of amino acid uptake in intestinal tissue from cattle, and they found V_{max} values for individual amino acids ranging from 36 to 206 µmol/h per g tissue dry matter. Using an average value of 120 µmol/h, the previously estimated intestinal tissue weight (14.5 kg) and its dry matter content (150 g/kg), a **maximal rate of uptake** (V_{max}) for 20 amino acids can be calculated:

$$R27M = 20*120*14.5*150*10^{-6} = 5.22 \text{ mol amino acids/h} = 6.98 \text{ mol N/h.}$$

The **affinity constant for amino acid uptake** is then derived as:

K27 = 6.581 mol N,

which for a single amino acid is equivalent to: 6.581*1000/(20*21.3) = 15.4 mmol N/l = 11.6 mmol amino acids/l. This latter value falls in the middle of the range of K_m values for 13 individual amino acids experimentally determined by Rothschild & Reichl (1983): 0.7 - 22.1 mmol/l.

The rate of protein degradation in the hind gut (R28) is estimated as 0.364 mol N/h (see later), and the ratio R28/R28M is assumed to be the same as the ratio R11/R11M for the corresponding process in the rumen (see section 3.3.1). The **maximal rate of protein degradation in the hind gut** (R28M) is therefore:

$$R28M = R28*R11M/R11 = 0.364*1.432/1.002 = 0.5205 \text{ mol N/h.}$$

The digesta volume in the hind gut is 14.1 l (Phillipson 1970, Crampton & Lloyd 1959 c.f. Neimann-Sørensen 1983), and the nitrogen content is 4 g/l digesta (Phillipson 1970, Hvelplund 1984b). Consequently, the **total amount of nitrogen in the hind gut** is:

$$A8+N2B = 14.1*4/14.01 = 4.03 \text{ mol N.}$$

As 6.5% of this is made up of NH_3/NH_4^+ (Ben-Ghedalia et al. 1974) the **pool size of NH_3/NH_4^+ in the hind gut** is:

$$N2B = 4.03*0.065 = 0.262 \text{ mol N,}$$

and the **pool size of undigested protein in the hind gut** is:

$$A8 = 4.03-0.262 = 3.77 \text{ mol N.}$$

The **affinity constant for protein degradation in the hind gut** is then estimated:

$$K28 = 1.616 \text{ mol N.}$$

The apparant protein digestibility is 71.7% in the static model (Hvelplund 1983), and according to this the rate of **nitrogen excretion in the faeces** is:

$$R29 = R0*(1-0.717) = 1.523*0.283 = 0.431 \text{ mol N/h.}$$

Hence, the **faecal excretion rate constant** is calculated as:

$$K29 = K126 = R29/A8 = 0.431/3.77 = 0.114\ h^{-1}.$$

The pools of endogenous protein in the small intestine (A10+A11) is found by subtraction from the total amount of crude protein: A10+A11 = 2.79-(A6+A7)-N2A = 2.79-2.36-0.067 = 0.363 mol N. As K32 = K33 = 0.24 h^{-1}, the **flow rate of undigested endogenous protein** can be derived as:

$$R32+R33 = (A10+A11)*0.24 = 0.363*0.24 = 0.087\ mol\ N/h.$$

The amount of endogenous protein actually digested (R34) is estimated by Danfær (1979) as 77% of the endogenous protein secreted (R41): R34 = 0.77*R41, and (R32+R33) = (1-0.77)*R41. Solution of these equations gives the rate of **secretion of endogenous protein:**

$$R41 = 0.087/0.23 = 0.379\ mol\ N/h,$$

and the rate of **uptake of endogenous amino acids:**

$$R34 = 0.77*0.379 = 0.292\ mol\ N/h.$$

The **maximal rate** and the **affinity constant for amino acid uptake from the intestinal lumen** have been estimated previously:

$$R34M = R27M = 6.98\ mol\ N/h,\ and$$
$$K34 = K27 = 6.581\ mol\ N.$$

The **pool size of digestible endogenous protein** is then derived as:

$$A11 = 0.287\ mol\ N,$$

and the **pool size of indigestible endogenous protein** is found by

difference:

A10 = 0.363-0.287 = 0.076 mol N.

The **intestinal flow rates of undigested** (indigestible (R32) as well as digestible (R33)) **endogenous protein** are finally calculated:

R32 = 0.076*0.24 = 0.018 mol N/h
R33 = 0.287*0.24 = 0.069 mol N/h.

The rate of **NH_3/NH_4^+ absorption from the small intestine** equals the rate of inflow from the rumen:

R35 = R24 = 0.104 mol N/h,

and the **absorption rate constant** is derived as:

K35 = R35/(N2A/V2A) = 0.104/(0.067/21.3) = 33.142 l/h.

The **metabolism of microbial N in the hind gut** is quantified as follows:

1) The difference between rates of protein degradation and amino acid synthesis in the hind gut is found by balancing the pool of undigested protein (A8): R28-R36 = R25+R26+R32+R33-R29 = 0.222 mol N/h.

2) The microbial amino acids synthesized in the hind gut cannot be absorbed to the blood (Ulyatt et al. 1975), and are supposed to be excreted in the faeces.

3) Of the faecal nitrogen about 50% is of microbial origin (Mason

et al. 1977): R29/2 = 0.431/2 = 0.216 mol N/h.

4) The flow rate of undigested microbial protein from the rumen is: (R10+R13)*M23*(1-0.75) = 0.843*0.70*0.25 = 0.148 mol N/h, and 50% of this is assumed to avoid degradation to NH_3/NH_4^+ and to be excreted in the faeces: 0.148/2 = 0.074 mol N/h.

The rate of **microbial amino acid synthesis** (R36) is therefore the total microbial faecal nitrogen less the undigested microbial nitrogen from the rumen excreted in the faeces:

R36 = 0.216-0.074 = 0.142 mol N/h.

An argument for the assumption that microbial protein from the rumen is more degradable than microbial protein synthesized in the hind gut is, that the rumen microbes have been exposed to acid digestion in the abomasum. The **degradation rate of protein and other N-compounds** to NH_3/NH_4^+ is found as:

R28 = (R28-R36)+R36 = 0.222+0.142 = 0.364 mol N/h.

The availability of ATP from hind gut fermentations affects the maximal rate of microbial protein synthesis: R36M = L36*R125, where the proportionality factor (L36 = YATPM*M9) expresses the amount of microbial protein-N synthesized per mol ATP made available from fermentation. The maximal microbial cell yield (YATPM) is 28 g cell DM/mol ATP, the nitrogen concentration in cell dry matter (M9) is $5.742*10^{-3}$ mol N/g cell DM (see section 3.3.1), and R125 = 1.092 mol ATP/h. Consequently, the **maximal rate of microbial protein synthesis in the hind gut** is:

R36M = $28*5.742*10^{-3}*1.092$ = 0.1756 mol N/h.

The **pool size of NH_3/NH_4^+ in the hind gut** has been estimated pre-

viously:

N2B = 0.262 mol N,

and the **affinity constant for microbial protein synthesis** can finally be derived:

K36 = 0.06212 mol N.

Carbon transactions

The simulated rate of **net protein degradation in the hind gut** (R127) is calculated as KCA*(R28-R36), where KCA = 3.8 mol C/mol N:

R127 = 3.8*0.222 = 0.845 mol C/h.

The rate of **protein-C fermentation** (R127A = K127A*R127) is derived from the fermentation equations (see later):

R127A = 0.115 mol C/h,

and the **fraction of protein-C fermented** will be:

K127A = R127A/R127 = 0.1361.

Rates of **formation of fermentation products from protein fermentation in the hind gut** are defined below:

PRAC2 = AC*R127A	(formation of acetate, mol C/h)
PRPR2 = PR*R127A	(formation of propionate, mol C/h)
PRBU2 = BU*R127A	(formation of butyrate, mol C/h)
PRBC2 = BC*R127A	(formation of BCFA, mol C/h)

```
PRCH2 = CH*R127A                (formation of CH4, mol C/h)
PRCO2 = CO*R127A                (formation of CO2, mol C/h)
```

Numerical values of the fermentation parameters (AC,PR, ---, CO) are derived from Baldwin et al. (1970) (see Appendix 5).

Absorption of VFA and disappearance of fermentation gases from the hind gut are calculated by summations:

```
RAC124 = STAC2+CEAC2+PRAC2      (outflow of acetate, mol C/h)
RPR124 = STPR2+CEPR2+PRPR2      (outflow of propionate, mol C/h)
RBU124 = STBU2+CEBU2+PRBU2      (outflow of butyrate, mol C/h)
RCH124 = (STCH2+CECH2+PRCH2)*K
                                (outflow of CH4, mol C/h)
RCO124 = STCO2+CECO2+PRCO2-RCH124*(1-1/K)
                                (outflow of CO2, mol C/h)
R124 = RAC124+RPR124+RBU124+RCH124+RCO124
                                (outflow of VFA, CH4 and CO2,
                                 mol C/h)
```

The amount of CH_4 produced according to the fermentation equations (Baldwin et al. 1970) is reduced by 25% (K = 0.75), and the amount of CO_2 produced is correspondingly increased as in the rumen compartment (section 3.3.1).

From the static model (Hvelplund 1983) it can be estimated that 23% of the carbon in carbohydrates and lipids is fermented in the hind gut, so that R124 = (R119+R120+R122)*0.23 = 7.157*0.23 = 1.646 mol C/h. In the present dynamic model carbon from fermented protein is also contributing to the hind gut production of VFA and fermentation

gases. From the above equations for the formation and outflow of VFA, CH_4 and CO_2, the **total outflow rate of fermentation products** can be expressed as:

R124 = STAC2+CEAC2+STPR2+CEPR2+STBU2+CEBU2+
STCH2+CECH2+STCO2+CECO2+(1-BC)*R127A =
1.550+0.83524*R127A = 1.646 mol C/h.

This equation makes it possible to estimate the simulated rate of **protein-C fermentation:**

R127A = (1.646-1.550)/0.83524 = 0.115 mol C/h.

The rate of **incorporation of branched-chain fatty acids** (BCFA) **into microbial cells** (see figure 2.4) is:

PRBC2 = 0.16476*0.115 = 0.019 mol C/h,

and the rate of **carbohydrate and lipid faecal excretion** can now be calculated by balancing the pool of undigested carbon (C10B):

R126 = K126*C10B = (R119-R119F)+(R120-R120F)+R122+
(R127-R127A)+PRBC2 = 6.356 mol C/h.

The **rate constant for faecal excretion** has been estimated previously:

K126 = K29 = 0.114 h^{-1},

and hence, the **pool size of undigested carbohydrates and lipids** is:

C10B = R126/K126 = 6.356/0.114 = 55.756 mol C.

Nitrogen transactions between gut and body tissues

The **exchange of nitrogen between the hind gut and the blood, the N-metabolism in the intestinal wall, and the endogenous protein secretion** are described in the following equations:

```
R37 = K37*(N2B/V2B)          (absorption of NH3/NH4+ from the
                              hind gut, mol N/h)
R38 = R38M*U2/(K38+U2)       (hydrolysis of urea in the hind gut,
                              mol N/h)
R39 = R39M*A12/(K39+A12)     (intestinal protein synthesis,
                              mol N/h)
R40 = R40M*A12/(K40+A12)     (absorption of amino acids, mol N/h)
R41 = R41M*A13/(K41+A13)     (secretion of endogenous protein,
                              mol N/h)
R41M = L41*(R116+R117+R118+KCA*(R22+R23))
                             (mol N/h)
R30 = (1-K31*L31)*R41        (indigestible endogenous protein,
                              mol N/h)
R31 = K31*L31*R41            (digestible endogenous protein,
                              mol N/h)
R42 = K42*A13                (degradation of intestinal protein,
                              mol N/h)
R50 = R50M*A16/(K50+A16)     (uptake of amino acids from the
                              blood, mol N/h)
R56 = K56*(U4/V4-U2/V2B)     (uptake of urea from the blood,
                              mol N/h)
```

It is assumed that the **rate constant for NH_3/NH_4^+ absorption from the hind gut** (K37) is equal to the rate constant for the corresponding process in the rumen (R16):

K37 = K16 = 18.154 l/h.

The volume of digesta in the hind gut is 14.1 l as stated previously, and its dry matter content is estimated as 14% (Phillipson 1970, Hvelplund 1984b). The **fluid volume in the hind gut** is therefore:

V2B = 14.1*0.86 = 12.1 l,

and the simulated rate of **absorption of NH_3/NH_4^+ from the hind gut** is calculated as:

R37 = 18.154*(0.262/12.1) = 0.393 mol N/h.

The rate of **urea hydrolysis** is found by balancing the pool of NH_3/NH_4^+ in the hind gut (N2B):

R38 = R36+R37-R28 = 0.142+0.393-0.364 = 0.171 mol N/h,

and the **maximal capacity of urea hydrolysis** is assumed to be - as in the rumen - 1 g per l per h (Jones 1967 c.f. Owens & Bergen 1983):

R38M = 1*12.1*2/60.1 = 0.403 mol N/h.

The rate of **urea uptake from the blood** equals the rate of urea hydrolysis:

R56 = R38 = 0.171 mol N/h,

and the **rate constant for urea uptake in the intestines** is assumed to be equal to the rate constant for urea uptake in the rumen:

K56 = K55 = 16.765 l/h.

Hence, the **pool size of urea in the intestinal digesta** can be calculated as:

U2 = (U4/V4-R56/K56)*V2B = (2.1/150-0.171/16.765)*12.1 =
0.0462 mol N,

and finally the **affinity constant for urea hydrolysis** is derived as:

K38 = 0.0629 mol N.

Lobley et al. (1980) have measured the rates of protein synthesis in individual tissues of a dry cow. In calculating the fractional rate of synthesis they considered either the extracellular or the intracellular free amino acid pool as the precursor pool for tissue protein synthesis. This resulted in two estimates of protein synthesis rate for each tissue. For the gastro-intestinal tract the estimates were 714 g protein/d and 1421 g protein/d. In the present model the simulated rate of **protein synthesis in the intestinal wall** (R39) is taken as the mean of these two estimates:

R39 = 1068 g protein/d = 0.508 mol N/h,

and the **maximal rate of protein synthesis** is taken as the largest estimated value:

R39M = 1421 g protein/d = 0.676 mol N/h.

The pool size of free intracellular amino acids in the intestinal wall (A12) can be estimated from the concentration gradient, Kg = (intestinal wall amino acid conc.)/(intestinal lumen amino acid conc.) = 1.4 (Rothschild & Reichl 1983). The **amino acid concentration in the lumen** can be expressed as:

(A7+A11)/V2A = (0.863+0.287)/21.3 = 0.054 mol N/l,

and the **intracellular amino acid concentration** is:

A12/VD = A12/12.3 mol N/l.

Hence, the **intracellular pool size of amino acids in the intestinal tissue** is calculated as:

A12 = 1.4*0.054*12.3 = 0.930 mol N,

and the **affinity constant for intestinal protein synthesis** will be:

K39 = 0.3076 mol N.

The simulated rate of **endogenous protein secretion** to the intestinal lumen (R41) has been estimated earlier as 0.379 mol N/h. The maximal rate (R41M) is assumed to be proportional to the amount of organic matter entering the small intestine, which is:
R116+R117+R118+KCA*(R22+R23) = 14.592 mol C/h. The actual value of the **maximal protein secretion rate** is taken from Danfær (1979):

R41M = 188 g N/d = 0.559 mol N/h,

and the **proportionality factor** is accordingly:

L41 = R41/14.592 = 0.559/14.592 = 0.0383 mol N/mol C.

The **protein mass in the intestinal wall** is estimated by Lobley et al. (1980):

A13 = 4900 g protein = 56.0 mol N,

and the **affinity constant for endogenous protein secretion** will be:

K41 = 26.622 mol N.

The partition of **indigestible** (R30) **and digestible** (R31) **endogenous protein** can now be made:

R30 = R32 = 0.018 mol N/h
R31 = R41-R30 = 0.379-0.018 = 0.361 mol N/h.

The **proportion of digestible amino acids** in the endogenous protein secreted is:

K31*L31 = R31/R41 = 0.361/0.379 = 0.9518,

and the **fraction of amino acids** (K31) is assumed to be equal to the **digestibility** (L31) of these amino acids:

K31 = L31 = 0.9756.

According to Waterlow et al. (1978a) breakdown of tissue protein is most likely a constant fractional rate process. Therefore the rate of protein degradation in the intestinal wall is qualitatively defined as such: R42 = K42*A13. Quantitatively, the rate of **intestinal protein breakdown** is equal to the rate of protein synthesis less the rate of protein secretion:

R42 = R39-R41 = 0.508-0.379 = 0.129 mol N/h.

Hence, the **rate constant for intestinal protein degradation** is calculated as:

K42 = R42/A13 = 0.129/56.0 = 0.0023 h^{-1}.

The simulated rate of **amino acid absorption** (R40) is assumed to be equal to the rates of amino acid uptake from the lumen:

R40 = R27+R34 = 0.809+0.292 = 1.101 mol N/h.

The **maximal rate of absorption** equals the maximal rate of intestinal amino acid uptake:

R40M = R27M = 6.98 mol N/h,

and the **affinity constant for amino acid absorption** is then estimated as:

K40 = 4.9666 mol N.

The simulated rate of **amino acid uptake in the intestinal tissue from the blood** (R50) is derived by balancing the intracellular pool of free amino acids (A12):

R50 = R39+R40-(R27+R34+R42) = 1.609-1.230 = 0.379 mol N/h.

The concentration of amino acids in the extracellular fluid is taken as 2.4 mmol/l which is equivalent to 3.36 mmol N/l (Bickerstaffe et al. 1974, Hidiroglou & Veira 1982, Rulquin 1983). The **extracellular pool size of amino acids** is therefore:

A16 = V4*3.36/1000 = 150*0.00336 = 0.504 mol N.

The **maximal capacity for amino acid transmembrane passage** is previously estimated:

R50M = R27M = R34M = R40M = 6.98 mol N/h,

and the **affinity constant for amino acid uptake from the blood** can finally be derived as:

K50 = 8.7832 mol N.

Faecal energy content

At the end of the intestinal compartments subroutine the **energy content in the faeces** is calculated by the following equations (see figure 2.4):

```
CE = R119*((RCE103+RCE107+RCE110)/R116-L119)
                                (undigested cell wall carbohydrates,
                                 mol C/h)
ECE126 = (CE/LCE)*CCE           (energy in faecal cell wall
                                 carbohydrates, MJ/h)
ELI126 = (R119*(1-L119)-CE+R122)*CFA/16
                                (energy in faecal fatty acids, MJ/h)
ESU126 = (R120*(1-L120))*CGLU/6
                                (energy in faecal glucose, MJ/h)
EKA126 = (R127*(1-K127A)/KCA)*CKA/LC
                                (energy in faecal keto acids, MJ/h)
EBC126 = PRBC2*CBC/6            (energy in faecal BCFA, MJ/h)
EPR29  = R29*CAA/LC             (energy in faecal protein, MJ/h)

RFE = ECE126+ELI126+ESU126+EKA126+EBC126+EPR29
                                (faecal energy, MJ/h)
```

The parameters, LCE = 37.037 mol C/kg cell wall carbohydrates and LC = 11.423 mol N/kg protein, are given in the previous section (3.3.1) together with the value for heat of combustion of cell wall carbohydrates, CCE = 18.8 MJ/kg. The other values for heat of combustion are taken from Livesey (1984): CFA = 10.027 MJ/mol fatty acid (C16), CGLU = 2.805 MJ/mol glucose, CKA = 19.4 MJ/kg metabolized protein, CBC = 3.497 MJ/mol branched-chain fatty acid (C6), and CAA = 23.4 MJ/kg protein.

By means of these equations the **outflow rate of faecal energy** is calculated as:

RFE = 4.114 MJ/h = 98.724 MJ/d.

3.3.3 The liver and extracellular fluid compartments

The diagram in figure 2.5 shows the state variables and flow of nutrients in the liver and the extracellular fluid. Numerical values and dimensions of state variables and equation parameters are given in Appendix 7.

Inputs of nutrients to the liver and extracellular fluid compartments from the digestive tract compartments are glucose (R130), triglycerides in chylomicrons (R132), propionate (R133), butyrate (R134), acetate and 3-OH-butyrate (R135), NH_3/NH_4^+ (R16+R35+R37) and amino acids (R40). Nutrient inputs to the extracellular fluid compartment from the peripheral tissue compartments are lactate (R189), free fatty acids (R194), glycerol (R199), and amino acids (R58+R61+R64).

Carbon transactions

The partitioning of nutrients between different tissues and the metabolism of nutrients within the tissues are largely affected by the metabolic hormones: insulin, glucagon, growth hormone, and thyroxine (Hart et al. 1978, Hart et al. 1979, Thilsted 1985a&b). In order to include hormonal regulation in the model simulation the concentrations of growth hormone, glucagon and insulin in the blood plasma are defined in the following equations taken from Herbein et al. (1985):

```
GH = 16.7+0.04607*M-0.00964*B-0.00567*D
                                  (conc. of growth hormone, ng/ml)
GLUCA = ALPHA+0.00514*M-0.00173*B+1.7E-6*B**2
        +6.6E-4*D-1.2E-6*D**2 (conc. of glucagon, ng/ml)
INSUL = BETA-0.01106*M+6.7E-4*B+0.00134*D-3.0E-6*D**2
                                  (conc. of insulin, ng/ml)
RATIO = GLUCA/INSUL
```

The parameters ALPHA and BETA have the numerical values 0.910 and 0.419, respectively, in the data of Herbein et al. (1985). M is the daily milk production (kg), B is the body weight of the cow (kg), and D is days (d) after parturition. In the present model ALPHA and BETA are not constants, but are dependent on absorption rates of propionate (R133) and amino acids (R40), and on the mass of the extracellular glucose pool (C24) (Bassett 1975, Brockman 1978b, Trenkle 1978, Lomax et al. (1979):

```
ALPHA = 0.793*R133/(2.2355+R133)+0.45 (ng/ml)
BETA = 0.86871*(R133+KCA*R40)/(15.0+R133+KCA*R40)+0.05*C24
                                  (ng/ml)
R133 = RPR111+RPR124              (absorption of propionate,
                                   mol C/h)
```

The estimates of the constant values (0.793, 2.2355 etc.) in these equations are derived to give ALPHA = 0.910 and BETA = 0.419 for average values of R133, R40 and C24 during the simulation. KCA, the ratio between C and N in amino acids, is 3.8 mol C/mol N as previously estimated. In order to have independent input to the model, the values of M (kg milk) and B (kg body weight) are those from Herbein et al. (1985) coherent with the actual value of D (days after parturition) which can be varied from 16 to 286.

Ninety per cent (K134=0.10) of the butyrate produced in rumen and hind gut fermentations is assumed to be oxidized to 3-OH-butyrate during absorption (Kronfeld & Van Soest 1976). The remaining butyrate is taken up by the liver, where it is oxidized to CO_2. The absorbed acetate and 3-OH-butyrate are not metabolized in the liver, but pass to the peripheral circulation (Annison 1976, Baird 1981, Bell 1981, Giesecke 1983):

```
R134 = K134*(RBU111+RBU124)  (uptake of butyrate, mol C/h)
R135 = (1-K134)*(RBU111+RBU124)+RAC111+RAC124
                             (passage of acetate and
                              3-OH-butyrate, mol C/h)
R138 = R134                  (oxidation of butyrate, mol C/h)
```

The production of glucose and the oxidations of propionate and keto acids are described in the following equations:

```
R136 = R136M*C14/(K136+C14)  (gluconeogenesis from
                              propionate, mol C/h)
R136M = L136+M136*RATIO      (mol C/h)
R137 = R137M*C14/(K137+C14)  (oxidation of propionate,
                              mol C/h)
R139 = R139M*C16/(K139+C16)  (outflow of glucose, mol C/h)
R142 = R142M*C17/(K142+C17)  (gluconeogenesis from keto acids,
                              mol C/h)
R142M = L142+M142*RATIO      (mol C/h)
R143 = R143M*C17/(K143+C17)  (oxidation of keto acids, mol C/h)
R144 = R144M*C18/(K144+C18)  (gluconeogenesis from glycerol and
                              lactate, mol C/h)
R144M = L144+M144*RATIO      (mol C/h)
```

The rates of glucose synthesis (R136+R142+R144) and glucose secretion from the liver (R139) are suppressed by a high plasma glucose concentration (Thompson et al. 1975, Baird 1981). In the model the affinity constant for glucose secretion (K139) is regulated by the size of the extracellular glucose pool (C24), so that an increase or decrease, respectively, in C24 to and beyond a certain limit (C24MX or C24MN) will increase or decrease K139. An increase in K139 will decrease R139 and in turn increase the intracellular glucose pool in the liver (C16). In the model C16 will regulate the affinity constants for gluconeogenesis (K136, K142, K144), so that an increase or decrease, respectively, in C16 to and beyond a certain limit (C16MX or C16MN) will increase or decrease the affinity constants. This will in turn decrease or increase the rate of gluconeogenesis. In this way a high plasma glucose concentration (C24$\geq$C24MX) will inhibit the rates of gluconeogenesis (R136, R142 and R144).

In order to maintain the liver pool sizes of propionate (C14) and keto acids (C17) without too much fluctuation during the modelling period, the affinity constants of propionate oxidation (K137) and of keto acid oxidation (K143) are regulated by the current values of C14 and C17, respectively. The mathematical formulations of all these regulations are shown in Appendix 2 (subroutine REGUL3).

The parameter values governing the rate of **gluconeogenesis from propionate** are derived as follows:

1) The total glucose flux rate is: R130+R139 = 3.568 mol C/h (Danfær 1983b)

2) The rate of glucose output from the liver is then: R139 = 3.568-R130 = 3.568-0.137 = 3.431 mol C/h

3) The contribution from propionate is 65.7% (Danfær 1983b): R136 = 3.431*0.657 = 2.253 mol C/h

4) The intracellular concentration of propionate is 1.15 mmol/l (Ricks & Cook 1981)

5) The liver weight is 8.6 kg (Smith & Baldwin 1974, Lobley et al. 1980, Smith et al. 1982, Butler-Hogg et al. 1985), and the water content is 70% (Huber et al. 1984). The volume of liver fluid is then: V3 = 8.6*0.70 = 6.0 l

6) Hence, the intracellular propionate pool is: C14 = 1.15*3*6.0/1000 = 0.021 mol C

7) The affinity constant of the process is 1.8 mmol/l (Mesbah & Baldwin 1983): K136 = 1.8*3*6.0/1000 = 0.032 mol C

8) From this the maximal rate is calculated: R136M = 5.687 mol C/h

9) The maximal capacity (R136M) increases with an increased ratio of glucagon to insulin (Brockman 1978a, Kraus-Friedmann 1984)

10) The extracellular concentration of glucose is 3.0 mmol/l (Manns 1972, Palmquist & Conrad 1978, Dale et al. 1979, Horber et al. 1980, Manston et al. 1981, Kunz & Blum 1981): C24 = 3.0*6*150/1000 = 2.70 mol C

11) The actual stage of lactation (D) is estimated as 44 days post partum on the basis of the energy concentration of the ration and the feed intake of the model cow (Kristensen 1983b). The corresponding values of M (milk yield), and B (body weight) are 29.7 kg and 561 kg, respectively (Herbein et al. 1985)

12) The concentrations of glucagon and insulin can now be calculated: GLUCA = 0.910-0.256 = 0.654 ng/ml, and INSUL = 0.419+0.101 = 0.520 ng/ml. RATIO is then: 0.654/0.520 = 1.258

13) The independent part (L136) of R136M is assumed to make up 70 % of the maximal rate: L136 = 5.687*0.70 = 3.981 mol C/h. The dependent part (M136*RATIO) is then: R136M-L136 = 1.706 mol C/h, and M136 = 1.706/1.258 = 1.356 mol C/h.

Propionate is metabolized in the liver by 2 pathways: gluconeogenesis and oxidation (Wilson et al. 1983). The rate of **oxidation** is therefore:

R137 = R133-R136 = 3.074-2.253 = 0.821 mol C/h.

Data from Aiello et al. (1984) indicate that the **affinity constant for propionate oxidation** (K137) is lower than the affinity constant for propionate conversion into glucose (K136):

K137 = K136*0.25 = 0.032*0.25 = 0.008 mol C.

The **maximal rate of oxidation** is then calculated:

R137M = 1.133 mol C/h.

The process of **glucose outflow from the liver** (R139) is assumed to be performed at 60% of its **maximal capacity:**

R139M = R139/0.60 = 3.431/0.60 = 5.718 mol C/h.

The **intracellular pool of free glucose** (exclusive glycogen) in the liver can be estimated as 26 g (Bergman 1971, Reid et al. 1980, Baird 1981):

C16 = 26*6/180.2 = 0.866 mol C.

The **affinity constant** (K139) is then derived:

K139 = 0.5772 mol C.

The rate of gluconeogenesis from glycerol and lactate (R144) is 0.500 mol C/h (Danfær 1983b). The rate of **gluconeogenesis from amino acids** is then found by difference:

R142 = R139-(R136+R144) = 3.431-2.753 = 0.678 mol C/h.

The substrate **pool of keto acids** (C17) is estimated as 2.3 mmol C per kg liver weight (Baird 1981, Kolb 1981):

C17 = 2.3*8.6/1000 = 0.02 mol C.

The **maximal rate of gluconeogenesis from amino acids** (R142M) is derived from the highest contribution of amino acid-C to glucose-C reported in the literature (Black et al. 1968):

R142M = 2.260 mol C/h.

It follows from this, that the value of R142 is only 30% of the maximal capacity (R142M). The **affinity constant** is then calculated:

K142 = 0.0467 mol C.

The maximal capacity of gluconeogenesis from amino acids (R142M) is increased by an increase in the ratio of glucagon to insulin concentrations (RATIO), and it is increased even more than is the capacity of gluconeogenesis from propionate, i.e. M142>M136 (Brockman 1978a, Brockman 1979, Brockman & Greer 1980). The independent part of R142M is assumed to be:

L142 = 0.150 mol C/h,

and the dependent part is derived as:

M142 = (R142M-L142)/RATIO = (2.260-0.150)/1.258
= 1.677 mol C/h.

The rate of **keto acid oxidation** (R143) is found by balancing the pool of keto acids (C17): R143 = R140-(R141+R142). The rate of net deamination of amino acids (R140-R141) is 1.108 mol C/h (see later), and

R143 = 1.108-0.678 = 0.430 mol C/h,

which is supposed to be 50% of the **maximal rate:**

R143M = 0.860 mol C/h.

The **affinity constant** is then:

K143 = 0.02 mol C.

The parameters used to describe the rate of **glucose synthesis from glycerol and lactate** (R144) are estimated as follows:

1) R144 = 0.500 mol C/h (Danfær 1983b)

2) The substrate pool (C18) consists of 2.6 g glycerol and 6.2 mmol lactate (Reid et al. 1980, Baird 1981):
C18 = 2.6*3/92.1+6.2*3/1000 = 0.085+0.018 = 0.103 mol C

3) The affinity constant for lactate is 2 mmol/l (Mesbah & Baldwin 1983): 2*3*6.0/1000 = 0.036 mol C

4) The rate of lactate conversion into glucose is estimated as 0.125 mol C/h (Danfær 1983b), and the maximal rate is calculated to be 0.375 mol C/h

5) The ratio R144/R144M is assumed to be equal to the corresponding ratio for lactate conversion alone: R144/R144M = 0.125/0.375 = 0.333. R144M is then: 0.500*3 = 1.500 mol C/h

6) L144 is assumed to be 0.15 mol C/h, and M144 is derived as: (1.500-0.15)/RATIO = 1.350/1.258 = 1.073 mol C/h

7) The affinity constant (K144) is finally estimated as 0.206 mol C.

The following equations describe the lipid metabolism in the liver:

```
R147 = R147M*C19/(K147+C19)   (liver fat synthesis, mol C/h)
R148 = R148M*C19/(K148+C19)   (lipoprotein synthesis, mol C/h)
R145 = K145*R147              (esterification of liver fat,
                               mol C/h)
R146 = K146*R148              (esterification of lipoproteins,
                               mol C/h)
R149 = R149M*C19/(K149+C19)   (acetate and ketone body
                               synthesis, mol C/h)
R149M = L149+M149*RATIO       (mol C/h)
R150 = R150M*C19/(K150+C19)   (fatty acid oxidation, mol C/h)
R150M = L150-M150*RATIO       (mol C/h)
R152 = R152M*C20/(K152+C20)   (liver fat breakdown into fatty
                               acids, mol C/h)
R151 = K151*R152              (liver fat breakdown into
                               glycerol, mol C/h)
R153 = R153M*C21/(K153+C21)   (outflow of lipoproteins, mol C/h)
R154 = K154*C22               (outflow of acetate and ketone
                               bodies, mol C/h)
```

The parameter values concerned with **lipid synthesis in the liver** are estimated as shown below:

1) The extracellular concentration of free fatty acids is 0.47 mmol/l (Dale et al. 1979, Kosak 1980, Blum et al. 1983, Doreau 1983, Gibson 1983, Reid & Treacher 1983) equivalent to 8.27 mmol C/l as the average chain length of free fatty acids in the blood is 17.6 carbon atoms (Husveth et al. 1982)

2) The intracellular concentration of free fatty acids is presumed to be lower than the extracellular concentration as fatty acids are taken up by the liver along a concentration gradient (Bell 1981, Madsen 1983b, Zammit 1984). Accordingly, the intracellular concentration (C19/V3) is assumed to be 5.0 mmol C/l, and the pool size of free fatty acids in the liver is: C19 = 5*6.0/1000 = 0.030 mol C

3) According to Reid & Roberts (1983) the content of liver fat is decreased from 14% to 2.5% of the liver weight during the period 4 to 8 weeks after calving. This will result in an average decrease in the pool of liver fat of 35 g/d equivalent to 0.043 mol triglyceride/d (tripalmitin) = 2.211 mol C/d

4) The rate of decrease in liver fat on a fatty acid basis (R152-R147) can be calculated as: 2.211*48/(51*24) = 0.0867 mol C/h. The rate of lipolysis (R152) is assumed to be 4 times higher than the rate of fat synthesis (R147): R147 = 0.0867/3 = 0.0289 mol C/h, and R152 = 0.0289*4 = 0.116 mol C/h

5) The maximal rate of fat synthesis (R147M) is assumed to be one order of magnitude higher than R147, i.e. R147M = 0.0289*10 = 0.289 mol C/h. Reid & Roberts (1983) have re-

ported a rate of liver fat synthesis equivalent to 0.213 mol C/h around parturition (-1 to +1 weeks post partum)

6) The affinity constant is then estimated: K147 = 0.270 mol C

7) The rate of lipoprotein synthesis is 1.3 mol fatty acids (C_{16}) per day (Danfær 1983b): R148 = 1.3*16/24 = 0.867 mol C/h

8) According to Zammit (1984) the affinity constant (K148) should be lower than the substrate pool (C19), and is assumed here to be 25% of C19: K148 = 0.03*0.25 = 0.0075 mol C

9) The maximal rate of lipoprotein synthesis is then estimated: R148M = 1.084 mol C/h

10) The factor for esterification of fatty acids is: K145 = K146 = K151 = 3/(3*16) = 0.0625 mol C/mol C.

Parameters in the equations of **acetate and ketone body syntheses, fatty acid oxidation, and lipolysis** are estimated as follows:

1) The rate of ketogenesis is 2.0 mol ketone bodies/d in the static model (Danfær 1983b). The magnitude of endogenous acetate production in the liver can be estimated as 5% of the absorbed acetate (Bergman & Wolf 1971 c.f. Brockman & Laarveld 1985): 0.05*(RAC111+RAC124) = 0.05*4.824 = 0.241 mol C/h. Then: R149 = (2.0*4)/24+0.241 = 0.575 mol C/h

2) According to Zammit (1984) the affinity constant (K149) is larger than the substrate pool size (C19 = 0.030 mol C): K149 = 0.10 mol C

3) The maximal rate, which is increased by glucagon and decreased by insulin (Brockman 1979, Brockman & Laarveld 1985), is then calculated: R149M = 2.492 mol C/h

4) The dependent part of R149M (M149) is arbitrarily estimated as 1.0 mol C/h, and the independent part (L149) is consequently: 2.492-1.0*1.258 = 1.234 mol C/h

5) The rate of fatty acid oxidation (R150) is assumed to be inversely related to the rate of gluconeogenesis because of the consumption of oxaloacetate in the gluconeogenic pathway (Baird 1977, Aiello et al. 1984). The maximal rate (R150M) is therefore reduced when the glucagon/insulin ratio is high

6) R150M is assumed to be 0.0 mol C/h when RATIO = 1.35, and 0.67 mol C/h when RATIO = 0.85. Solving these two equations gives: M150 = 1.34 mol C/h, and L150 = 1.809 mol C/h. For the actual value of RATIO (= 1.258), R150M = 0.123 mol C/h

7) According to Zammit (1984) the hepatic priority for fatty acid oxidation is lower than for lipoprotein synthesis, but higher than for ketogenesis: K148 < K150 < K149. The value of the affinity constant for fatty acid oxidation is chosen as: K150 = 0.02 mol C, and the rate of oxidation can then be calculated: R150 = 0.074 mol C/h

8) The content of total lipid in the liver 6 weeks postpartum can be estimated as 8% of the liver weight (Reid & Roberts 1983), i.e. 8.6*0.08 = 0.7 kg

9) The liver content of triglyceride is 45% of total lipid (Gaal et al. 1983 a&b, Herdt et al. 1983), i.e. C20+C21 = 0.45*700 = 315 g triglyceride. The pool of free fatty acids (C19) is: 0.03*256.4/16 = 0.5 g, and the mass of cholesterol, phospholipids etc. in lipoproteins is: 700-315-0.5 = 385 g

10) From the amount and composition of serum lipoproteins (VLDL and LDL) in cows it can be calculated that triglycerides make up 17.3% of total lipid in lipoproteins (Palmquist 1976). Hence, the pool of triglycerides in lipoproteins is: C21 = (385/(1-0.173))*0.173 = 80.5 g, equivalent to 5.1 mol C, and the pool of triglycerides in depot fat is: C20 = 315-80.5 = 234.5 g, equivalent to 14.8 mol C

11) The rate of lipolysis into fatty acids (R152) has been estimated earlier as 0.116 mol C/h, which is assumed to be 90% of the maximal rate: R152M = 0.116/0.90 = 0.129 mol C/h

12) The affinity constant is then estimated: K152 = 1.659 mol C

13) The rate of glycerol release in lipolysis is: R151 = 0.116*0.0625 = 0.0073 mol C/h.

The rate of **lipoprotein secretion** (R153) is equal to the rate of lipoprotein formation (R146+R148):

R153 = R148*(1+K146) = 0.867*1.0625 = 0.921 mol C/h.

The **maximal rate of lipoprotein secretion** is equal to the maximal rate of lipoprotein formation:

R153M = R148M*1.0625 = 1.084*1.0625 = 1.152 mol C/h.

The **affinity constant** is then estimated:

K153 = 1.279 mol C.

The rate of **acetate and ketone body secretion** is equal to the rate of acetate and ketone body synthesis:

R154 = R149 = 0.575 mol C/h.

The concentration of ketone bodies in the liver is 0.6 mmol/kg (Baird 1981), and the pool size of ketone bodies is therefore: 0.6*8.6*4/1000 = 0.021 mol C. It is assumed that the pool sizes of ketone bodies and endogenous acetate in the liver are in proportion to their respective rates of formation. The **pool of ketone bodies plus acetate** is calculated accordingly:

C22 = (0.021/(2.0*4))*(2.0*4+2.9*2) = 0.036 mol C.

Finally, the **diffusion constant** is derived:

K154 = R154/C22 = 0.575/0.036 = 15.97 h^{-1}.

The rates of cellular uptake of acetate plus ketone bodies and glucose in peripheral tissues are described by the following equations:

R156 = K156*(C23/V4)	(uptake of acetate and ketone bodies in the mammary gland, mol C/h)
K156 = L156+M156*GH	(l/h)
R157 = K157*(C23/V4)	(uptake of acetate and ketone bodies in muscle tissue, mol C/h)
R158 = K158*(C23/V4)	(uptake of acetate and ketone bodies in adipose tissue, mol C/h)
K158 = L158+M158*INSUL	(l/h)
R159 = K159*(C23/V4)	(uptake of acetate and ketone bodies in other tissues, mol C/h)
R160 = R160M*C24/(K160+C24)	(uptake of glucose in the mammary gland, mol C/h)
R160M = L160+M160*GH	(mol C/h)

```
R161 = R161M*C24/(K161+C24)  (uptake of glucose in muscle
                              tissue, mol C/h)
R161M = L161+M161*INSUL      (mol C/h)
R162 = R162M*C24/(K162+C24)  (uptake of glucose in adipose
                              tissue, mol C/h)
R162M = L162+M162*INSUL      (mol C/h)
R163 = R163M*C24/(K163+C24)  (uptake of glucose in other
                              tissues, mol C/h)
```

Daily injections of growth hormone in dairy cows for about 10 days result in increased milk yield, unchanged or slightly decreased feed intake, and decreased energy balance in body tissues (Peel et al. 1981 a&b, Tyrrell et al. 1982). This strongly indicates that growth hormone directly or indirectly alters the partitioning of nutrients in favour of the mammary gland - maybe by increasing the rate of mammary blood flow (Hart et al. 1980, Mepham et al. 1984, Davis et al. 1988). Insulin does not affect the rate of nutrient uptake in the mammary gland (Laarveld et al. 1985). However, insulin does increase the uptake and utilization of acetate and glucose in adipose tissue (Khachadurian et al. 1966, Yang & Baldwin 1973b, Jarrett et al. 1974, Vernon 1986). Glucose uptake in muscle tissue is also stimulated by insulin (Jarrett et al. 1974, Madsen 1983a, Vernon 1986). The effect on glucose uptake is accomplished by an increase in V_{max} for glucose transport without a change in the K_m value (Conover et al. 1975, Czech 1975).

In the model the rates of nutrient uptake into the mammary gland are therefore related to the plasma concentration of growth hormone (GH). The concentration of insulin (INSUL) affects the rate constant for acetate and ketone body uptake in adipose tissue (K158), and also the maximal rates of glucose uptake in muscle (R161M) and adipose tissue (R162M).

The parameter values of the equations describing **tissue uptake of acetate and ketone bodies** are estimated as shown below:

1) The partition of nutrients between the mammary gland, muscle tissue, adipose tissue, and other tissues is adopted from the static model (Danfær 1983b). The rate of acetate and ketone body uptake in the mammary gland is accordingly: R156 = (R135+R154)*77.04/158.44 = 7.037*0.486 = 3.422 mol C/h

2) The extracellular concentration of acetate and ketone bodies (C23/V4) is 0.0058 mol C/l (see subsection 3.3.2), and the rate constant is found as: K156 = 3.422/0.0058 = 590.0 l/h

3) The concentration of growth hormone is:
GH = 16.7+0.04607*29.7-0.00964*561-0.00567*44 = 12.411 ng/ml

4) The independent part (L156) of the rate constant is assumed to be 0.0 l/h, and the part dependent on growth hormone concentration is then: M156 = K156/GH = 590.0/12.411 = 47.538 $l^2/(h*\mu g)$

5) The rate of acetate and ketone body uptake in muscle tissue is: R157 = (R135+R154)*13.0/158.44 = 7.037*0.082 = 0.577 mol C/h, and the rate constant will be: K157 = 0.577/0.0058 = 99.48 l/h

6) The rate of acetate and ketone body uptake in adipose tissue is calculated as: R158 = (R135+R154)*31.0/158.44 = 7.037*0.196 = 1.377 mol C/h, and K158 = 1.377/0.0058 = 237.4 l/h

7) The independent part (L158) of the rate constant is assumed to be 0.0 l/h, and the part dependent on insulin concentra-

tion is calculated as: M158 = K158/INSUL = 237.4/0.520 = 456.5 $l^2/(h*\mu g)$

8) The rate of acetate and ketone body uptake in other tissues is: R159 = (R135+R154)*37.40/158.44-R155 = 7.037*0.236-0.642 = 1.019 mol C/h, and the rate constant is derived as: K159 = 1.019/0.0058 = 175.7 l/h.

The parameters concerned with the **tissue uptake of glucose** are partly estimated on the assumption that the partition between tissues is as in the static model:

1) The rate of glucose uptake in the mammary gland is: R160 = (R130+R139)*11.42/14.26 = 3.5675*0.801 = 2.857 mol C/h

2) The rate of glucose uptake is assumed to be performed at 70% of the maximal rate: R160M = 2.857/0.70 = 4.081 mol C/h

3) The independent part (L160) of the maximal rate is assumed to be 0.0 mol C/h, and the part dependent on growth hormone concentration is: M160 = R160M/GH = 4.081/12.411 = 0.3288 mol C*l/(h*µg)

4) The extracellular glucose pool size (C24) is estimated earlier as 2.70 mol C, and the affinity constant can be calculated: K160 = 1.1567 mol C

5) The rate of glucose uptake in other tissues: R163 = (R130+R139)*0.34/14.26 = 3.5675*0.024 = 0.086 mol C/h. This is assumed to be 65% of the maximal rate: R163M = 0.086/0.65 = 0.132 mol C/h

6) The affinity constant is then: K163 = 1.444 mol C

7) The rate of glucose uptake in muscle tissue is estimated in the following subsection 3.3.4: R161 = 0.434 mol C/h, and it is assumed to occur at 60% of its maximal rate: R161M = 0.434/0.60 = 0.724 mol C/h

8) L161, the independent part of R161M, is assumed to be 0.0 mol C/h, and the part dependent on insulin concentration is: M161 = R161M/INSUL = 0.724/0.520 = 1.392 mol C*l/(h*µg)

9) The affinity constant is then: K161 = 1.799 mol C

10) The rate of glucose uptake in adipose tissue is calculated by difference: R162 = (R130+R139)-(R160+R161+R163) = 3.568-3.377 = 0.191 mol C/h, and the maximal rate is assumed to be 2 times as high: R162M = 0.382 mol C/h

11) The independent part of R162M (L162) is assumed to be 0.0 mol C/h, and M162 is consequently: R162M/INSUL = 0.382/0.520 = 0.7346 mol C*l/(h*µg)

12) The affinity constant is equal to the substrate pool size: K162 = 2.70 mol C.

The rates of glycerol plus lactate and lipid uptake in the liver from the peripheral blood are described in the following equations:

R164 = R164M*C25/(K164+C25)	(uptake of glycerol and lactate, mol C/h)
R165 = K165*C26/V4	(uptake of free fatty acids, mol C/h)
K165 = L165-M165*INSUL	(l/h)
R169 = R169M*C27/(K169+C27)	(uptake of fatty acids from chylomicrons, mol C/h)

R168 = K168*R169 (uptake of glycerol from chylomicrons, mol C/h)

The liver takes up 25% of absorbed **fatty acids from chylomicrons** (Danfær 1983b), and this uptake is assumed to be performed at 75% of its **maximal rate:**

R169 = R123*0.25 = 1.942*0.25 = 0.485 mol C/h,
R169M = R169/0.75 = 0.485/0.75 = 0.647 mol C/h.

Data from Palmquist (1976), Holter et al. (1982), and Herdt et al. (1983) have been used to estimate the plasma concentrations of **triglycerides in chylomicrons** (C27/V4 = 0.048 mmol/l) and **in lipoproteins** (C28/V4 = 0.095 mmol/l). The respective **plasma pool sizes** are calculated as follows:

C27 = 0.048*51*150/1000 = 0.367 mol C,
C28 = 0.095*51*150/1000 = 0.727 mol C.

The **affinity constant for uptake of fatty acids from chylomicrons** (by lipoprotein lipase) is derived:

K169 = 0.123 mol C.

The rate of **glycerol uptake from triglycerides in chylomicrons** is:

R168 = K168*R169 = 0.0625*0.485 = 0.030 mol C/h.

The rate of **uptake of free glycerol and lactate** (R164) can be calculated by balancing the pool of glycerol and lactate in the liver (C18):

R164 = R144+R145+R146-(R151+R168)
= 0.500+0.0018+0.054-(0.0073+0.030) = 0.518 mol C/h.

The **plasma concentrations of glycerol and lactate** are estimated as 0.035 mmol/l and 0.55 mmol/l, respectively (Treacher et al. 1976, Bines et al. 1983, Lomax & Baird 1983, Rulquin 1983):

C25 = (0.035+0.55)*3*150/1000 = 0.263 mol C.

The **maximal rate** (R164M) and the **affinity constant** (K164) can now be calculated under the assumption that the actual rate of uptake (R164) is performed at 60% of the maximal capacity:

R164M = R164/0.60 = 0.518/0.60 = 0.864 mol C/h,
K164 = 0.175 mol C.

In the same way the rate of **uptake of free fatty acids** (R165) can be found by balancing the pool of free fatty acids in the liver (C19):

R165 = R147+R148+R149+R150-(R152+R169) =
0.0289+0.867+0.575+0.074-(0.116+0.485) = 0.943 mol C/h.

The **plasma concentration of free fatty acids** (C26/V4) is 0.00827 mol C/l as previously estimated:

C26 = 0.00827*V4 = 0.00827*150 = 1.241 mol C.

The uptake of free fatty acids in the liver is decreased by insulin (Brockman & Laarveld 1985). Hence, the value of the rate constant (K165) depends on the concentration of insulin (INSUL). The **rate constant** can be calculated from the rate of uptake and the plasma concentration:

K165 = R165/(C26/V4) = 0.943/0.00827 = 114.082 l/h.

The independent part of the rate constant (L165) is assumed to be 150.0 l/h, and consequently the dependent part will be:

$$M165 = (L165-K165)/INSUL = 35.918/0.520 = 69.073\ l^2/(h*\mu g).$$

The rates of lipid uptake in the peripheral tissues are described by the equations listed below:

```
R166 = K166*C26/V4                  (uptake of free fatty acids in
                                     muscle tissue, mol C/h)
R167 = K167*C26/V4                  (uptake of free fatty acids in
                                     other tissues, mol C/h)
R170A = R170AM*C27/(K170A+C27)      (uptake of fatty acids +
                                     glycerol from chylomicrons in
                                     the mammary gland, mol C/h)
R170AM = L170A-M170A*INSUL          (mol C/h)
R170B = R170BM*C27/(K170B+C27)      (uptake of fatty acids +
                                     glycerol from chylomicrons
                                     in adipose tissue, mol C/h)
R170BM = EXP(M170B*INSUL)-L170B     (mol C/h)
R171A = R171AM*C28/(K171A+C28)      (uptake of fatty acids +
                                     glycerol from lipoproteins
                                     in the mammary gland, mol C/h)
R171AM = L171A-M171A*INSUL          (mol C/h)
R171B = R171BM*C28/(K171B+C28)      (uptake of fatty acids +
                                     glycerol from lipoproteins
                                     in adipose tissue, mol C/h)
R171BM = EXP(M171B*INSUL)-L171B     (mol C/h)
R172 = R170A+R171A                  (uptake of fatty acids +
                                     glycerol in the mammary gland,
                                     mol C/h)
R172A = R172/(1+K172)               (uptake of fatty acids in the
                                     mammary gland, mol C/h)
```

R172B = K172*R172A (uptake of glycerol in the mammary gland, mol C/h)

R173 = R170B+R171B (uptake of fatty acids + glycerol in adipose tissue, mol C/h)

R173A = R173/(1+K173) (uptake of fatty acids in adipose tissue, mol C/h)

R173B = K173*R173A (uptake of glycerol in adipose tissue, mol C/h)

In the static model the **uptake of free fatty acids in extra-hepatic tissues** is 16.0 mol C/d. It is assumed here that 75% of this amount is taken up by muscle tissues, and that the rest is taken up by tissues other than adipose tissue and the mammary gland:

R166 = 0.75*16.0/24 = 0.500 mol C/h, and
R167 = 0.25*16.0/24 = 0.167 mol C/h.

The **rate constants** are:

K166 = R166/(C26/V4) = 0.500/0.00827 = 60.459 l/h, and
K167 = R167/(C26/V4) = 0.167/0.00827 = 20.153 l/h.

The amount of **triglycerides in chylomicrons available for extra-hepatic tissues** is derived by balancing the plasma pool (C27):

R170A+R170B = R132-(R168+R169) =
2.063-(0.030+0.485) = 1.548 mol C/h.

The amount of **triglycerides in lipoproteins available for extra-hepatic tissues** is equal to that synthesized in the liver:

R171A+R171B = R153 = 0.921 mol C/h.

In early lactation the activity of lipoprotein lipase (LPL) in the mammary gland is approximately six times higher than the activity of LPL in adipose tissue from first-calving heifers (Shirley et al. 1973). This difference in activity of the two types of LPL is probably greater in mature multiparous cows, and it is assumed here that the rate of fatty acid uptake in the mammary gland is seven times higher than the rate of adipose tissue uptake:

R170B = (R170A+R170B)/8 = 1.548/8 = 0.193 mol C/h,
R170A = R170B*7 = 0.193*7 = 1.354 mol C/h,
R171B = (R171A+R171B)/8 = 0.921/8 = 0.115 mol C/h, and
R171A = R171B*7 = 0.115*7 = 0.806 mol C/h.

Before parturition the activity of adipose tissue LPL is much higher than that of mammary LPL (Shirley et al. 1973). From parturition until around peak lactation the activity of adipose LPL decreases and thereafter increases with progressing lactation (Shirley et al. 1973, Vernon 1980, McNamara et al. 1987). These changes in adipose LPL activity can be explained by the almost parallel changes in plasma insulin concentration (Hart et al. 1978, Herbein et al. 1985, Thilsted 1985b), as the activity of adipose LPL is stimulated by insulin (Shirley et al. 1972, Emery 1979, Vernon 1980, Vernon 1986). Mammary LPL is not stimulated (Shirley et al. 1972), but on the contrary seems to be inhibited by insulin. This is indicated by the findings that the activity of mammary LPL is lower on low roughage-high grain rations compared to normal rations, whereas the opposite is the case for the activity of adipose LPL (Benson et al. 1972, Emery 1973, Tanaka & Ohtani 1986). Feeding low roughage-high grain rations to dairy cows will normally increase the plasma insulin concentration (Jenny et al. 1974, Sutton et al. 1983, Agergaard et al. 1988).

Based on these considerations the maximal rates of fatty acid and

glycerol uptake in the mammary gland (R170AM and R171AM) are decreased, and the maximal rates of adipose tissue uptake (R170BM and R171BM) are increased by an increase in insulin concentration (INSUL).

The rates of **mammary uptake** are assumed to be performed at 75% of the **maximal capacities:**

R170AM = R170A/0.75 = 1.354/0.75 = 1.805 mol C/h,
R171AM = R171A/0.75 = 0.806/0.75 = 1.074 mol C/h.

The value of INSUL will be approximately 0.8 ng/ml in late lactation, when milk fat production is only about 60% of that in early lactation. Assuming then that R170AM = 1.805*0.60 = 1.1 mol C/h when INSUL = 0.8 ng/ml, and having that R170AM = 1.805 mol C/h when INSUL = 0.520 ng/ml, the remaining parameters can be estimated:

M170A = (1.805-1.1)/(0.8-0.520) = 2.518 mol C*l/(h*µg),
L170A = 1.805+2.518*0.520 = 3.114 mol C/h.

In the same way it can be argued, that R171AM = 1.074*0.60 = 0.64 mol C/h when INSUL = 0.8, and the parameter estimation will be:

M171A = (1.074-0.64)/(0.8-0.520) = 1.550 mol C*l/(h*µg),
L171A = 1.074+1.550*0.520 = 1.880 mol C/h.

The plasma pool sizes of triglycerides are estimated previously (C27 = 0.367 mol C, C28 = 0.727 mol C), and the **affinity constants for mammary uptake of fatty acids and glycerol** can be calculated:

K170A = 0.122 mol C, and
K171A = 0.242 mol C.

The rates of **fatty acid and glycerol uptake in adipose tissue** are assumed to be performed at 50% of their **maximal capacities:**

R170BM = R170B/0.50 = 0.193/0.50 = 0.387 mol C/h,
R171BM = R171B/0.50 = 0.115/0.50 = 0.230 mol C/h.

It is further assumed that the maximal rates of uptake are increased three times in late lactation. Hence, when INSUL = 0.8, R170BM = 0.387*3 = 1.16 mol C/h, and R171BM = 0.230*3 = 0.69 mol C/h. The parameters describing the dependence on insulin concentration is then estimated by a graphical method:

(0.387+L170B)**(0.8/0.520)-L170B = 1.16 mol C/h,
L170B = 1.503 mol C/h,
M170B = ln(0.387+1.503)/0.520 = 1.224 ml/ng,
(0.230+L171B)**(0.8/0.520)-L171B = 0.69 mol C/h,
L171B = 1.369 mol C/h,
M171B = ln(0.230+1.369)/0.520 = 0.903 ml/ng.

Finally, the **affinity constants** are derived:

K170B = 0.369 mol C, and
K171B = 0.727 mol C.

The rates of **fatty acid** (R172A) and **glycerol** (R172B) **uptake in the mammary gland** are easily calculated:

R172A = (R170A+R171A)/(1+K172) = 2.160/1.0625 = 2.033 mol C/h,
R172B = K172*R172A = 0.0625*2.033 = 0.127 mol C/h,

and in the **adipose tissue:**

R173A = (R170B+R171B)/(1+K173) = 0.308/1.0625 = 0.290 mol C/h,
R173B = K173*R173A = 0.0625*0.290 = 0.018 mol C/h.

The flow of N-free nutrients from the peripheral tissues to the extracellular fluid compartment is described in the following equations:

R189 = K189*C38	(outflow of lactate from muscle tissue, mol C/h)
R194 = K194*C41	(outflow of fatty acids from adipose tissue, mol C/h)
R199 = K199*C44	(outflow of glycerol from adipose tissue, mol C/h)

These flow rates can be estimated by balancing the extracellular pools of glycerol + lactate (C25) and free fatty acids (C26):

R189+R199 = R164 = 0.518 mol C/h,
R194 = R165+R166+R167 = 0.943+0.500+0.167 = 1.610 mol C/h.

The rate of **glycerol release from adipose tissue** is estimated in subsection 3.3.4:

R199 = 0.109 mol C/h,

and the rate of **lactate release from muscle tissue** is therefore:

R189 = 0.518-0.109 = 0.409 mol C/h.

The sizes of the **intracellular nutrient pools** are estimated in the succeeding subsection 3.3.4: C38 = 3.270 mol C (muscle lactate), C41 = 3.04 mol C (adipose free fatty acids), and C44 = 0.046 mol C (adipose glycerol). The **rate constants** for the 3 processes are, respectively:

$K189 = R189/C38 = 0.409/3.270 = 0.1252\ h^{-1}$

K194 = R194/C41 = 1.610/3.04 = 0.5296 h^{-1}, and
K199 = R199/C44 = 0.109/0.046 = 2.370 h^{-1}.

Nitrogen transactions

The metabolism of amino acids and protein in the liver is simulated according to the following rate equations:

```
R43 = R43M*A14/(K43+A14)      (liver protein synthesis, mol N/h)
R44 = R44M*A14/(K44+A14)      (outflow of amino acids, mol N/h)
R45 = R45M*A14/(K45+A14)      (amino acid deamination, mol N/h)
R45M = L45+M45*RATIO          (mol N/h)
R46 = K46*A15                 (liver protein breakdown, mol N/h)
K46 = L46*EXP(M46*RATIO)      (h-1)
R47 = R47M*N3/(K47+N3)        (amino acid synthesis, mol N/h)
R140 = KCA*R45                (keto acids produced by amino acid
                               deamination, mol C/h)
R141 = KCA*R47                (keto acids used in amino acid
                               synthesis, mol C/h)
```

As an average during the day the rate of **liver protein synthesis** is assumed to be equal to the rate of **liver protein breakdown** (Waterlow et al. 1978d), i.e. R43 = R46. According to the static model the turnover rate of the liver protein pool is 20% per day, and the **mass of the protein pool** is 20% of the liver weight (Lobley et al. 1980):

K46 = 0.20/24 = 0.0083 h^{-1},
A15 = 8.6*0.20 = 1.72 kg protein,
A15 =1.72*1000/(6.25*14.01) = 19.643 mol N,
R46 = 0.0083*19.643 = 0.164 mol N/h, and
R43 = 0.164 mol N/h.

The intracellular concentrations of 4 amino acids are determined in cow liver (Baird 1972, c.f. Kolb 1981), but the **total concentration of free amino acids in the liver** is assumed here to be 26 mmol/l as found in rats (Waterlow et al. 1978b):

A14 = 26*6.0*1.3/1000 = 0.203 mol N.

The K_m values for amino acyl t-RNA synthetases are very low compared to the intracellular amino acid concentrations, and these enzymes will therefore be almost saturated with their substrates under normal conditions (Lindsay 1980). This means that protein synthesis will occur at a rate near the **maximal capacity:**

R43M = R43/0.95 = 0.172 mol N/h.

The **affinity constant** is then calculated:

K43 = 0.0099 mol N.

As stated in subsection 3.3.2 protein breakdown is described as a process of constant fractional rate (Waterlow et al. 1978a). However, the rate of protein breakdown in the liver is stimulated by glucagon and inhibited by insulin (Ballard & Gunn 1982), and the rate constant (K46) is therefore increased with an increasing ratio of glucagon to insulin (RATIO).

The liver protein mass is regulated between meals by a change in the rate of protein breakdown and not in the rate of protein synthesis (Garlick et al. 1973). In order to simulate this kind of regulation it is assumed that the rate constant (K46) will vary from 10% per day to 40% per day, when RATIO varies from 0.85 to 1.35 (Ballard & Gunn 1982). Based on this assumption the parameters (L46 and M46) can be estimated by linear regression: lnK46 = lnL46+M46*RATIO:

$L46 = 0.0005\ h^{-1}$

$M46 = (\ln K46 - \ln L46)/RATIO = 2.233.$

From the work of Oldham et al. (1980b) the total flux rate of amino acids (absorption + body protein turnover) can be estimated as 28 mol/d (Riis 1983a) equivalent to 36.2 mol N/d. The absorption rate (R40) is 1.101 mol N/h = 26.4 mol N/d (see subsection 3.3.2), and the contribution from **body protein degradation** (R54) is calculated by difference:

R54 = total flux - absorption = 36.2-26.4 = 9.8 mol N/d.

The rate of net protein mobilization is taken from the static model (Danfær 1983b): 0.53 mol amino acids/d equivalent to 0.7 mol N/d, and the rate of **protein synthesis in muscle and other tissues** (R62+R65) is calculated by difference:

R62+R65 = 9.8-0.7 = 9.1 mol N/d.

The rate of intestinal amino acid uptake (R50) is 0.379 mol N/h = 9.1 mol N/d (see subsection 3.3.2), and the rate of amino acid uptake in the mammary gland (R51) is 11.0 mol N/d (see later). The uptake in muscle (R52) and other tissues (R53) is taken to be equal to the rate of protein synthesis in these tissues (R62+R65). The **amino acid output from the liver** (R44) is then calculated by summation:

R44 = R50+R51+R52+R53 = 9.1+11.0+9.1 = 29.2 mol N/d
= 1.217 mol N/h,

and this is assumed to be performed at 25% of its **maximal rate:**

R44M = R44/0.25 = 1.217/0.25 = 4.867 mol N/h.

The **affinity constant** for amino acid transport out of the liver cells is then derived:

K44 = 0.609 mol N.

The net catabolism of amino acids is the difference between **amino acid deamination** (R45) and **amino acid synthesis** (R47), which is calculated as the difference between the total amino acid flux rate (36.2 mol N/d) and the rate of amino acid outflow from the liver (R44 = 29.2 mol N/d):

R45-R47 = 36.2-29.2 = 7.0 mol N/d = 0.292 mol N/h.

It is assumed that 15% of the catabolized amino acid-N is resynthesized into new amino acids: R47 = 0.15*R45. Solving for R45 and R47 gives:

R45 = 0.292/(1-0.15) = 0.343 mol N/h
R47 = 0.15*0.343 = 0.051 mol N/h.

The **Michaelis-Menten constants for enzymes initiating catabolism of amino acids** are of the same order as the concentration of amino acids in blood plasma (Krebs 1972 c.f. Lindsay 1980), which is: A16/V4 = 0.504/150 = 0.00336 mol N/l (see subsection 3.3.2). According to this : K45/V3 = A16/V4, and

K45 = V3*A16/V4 = 6.0*0.00336 = 0.0202 mol N.

The **maximal rate** can now be calculated:

R45M = 0.377 mol N/h.

The capacity of amino acid catabolism increases at the onset of lactation (Riis 1983a), and this increase could be related to the

increased ratio of glucagon to insulin. The independent part (L45) of the maximal rate equation is assumed to be 0.0 mol N/h, and consequently the dependent part will be:

M45 = (R45M-L45)/RATIO = 0.377/1.258 = 0.300 mol N/h.

The **maximal rate of amino acid synthesis** (R47M) is estimated as:

R47M = R47/0.65 = 0.051/0.65 = 0.079 mol N/h.

The intracellular concentration of NH_3/NH_4^+ in the liver is not higher than the concentration in blood plasma, which is 0.00015 mol N/l (Holter et al. 1982). Therefore, the **mass of the NH_3/NH_4^+ pool in the liver** is taken to be:

N3 = 0.0001*6.0 = 0.0006 mol N,

and the **affinity constant** is in turn calculated as:

K47 = 0.00032 mol N.

The rates of **keto acid production** (R140) and **keto acid utilization** in amino acid synthesis (R141) are calculated in proportion to R45 and R47:

R140 = 3.8*0.343 = 1.304 mol C/h, and
R141 = 3.8*0.051 = 0.196 mol C/h.

The rates of urea synthesis and excretion are described as follows:

```
R48 = R48M*N3/(K48+N3)        (urea synthesis, mol N/h)
R49 = K49*(U3/V3)             (outflow of urea, mol N/h)
R57 = K57*(U4/V4)             (urinary excretion of urea, mol N/h)
```

The rate of **urea synthesis** is found by balancing the pool of liver NH_3/NH_4^+ (N3):

```
R48 = R16+R35+R37+R45-R47 =
      0.228+0.104+0.393+0.343-0.051 = 1.017 mol N/h.
```

The **maximal hepatic utilization of NH_3/NH_4^+** is estimated to be 2.6 mmol/min per kg wet liver weight in non-lactating cows (Symonds et al. 1981). It is assumed here that this capacity is increased 10% during lactation:

```
R48M = 1.10*2.6*60*8.6/1000 = 1.476 mol N/h,
```

and the **affinity constant** is then:

```
K48 = 0.00027 mol N.
```

In order to prevent the liver NH_3/NH_4^+ pool exceeding some toxic level the numerical value of the affinity constant for urea synthesis (K48) is regulated by the current value of N3 (see subroutine REGUL 3, Appendix 2).

The rate of **urea diffusion from liver cells** to blood is equal to the rate of urea synthesis:

```
R49 = R48 = 1.017 mol N/h,
```

and the **rate constant** (K49) for the process is assumed to be equal to the rate constants for the diffusions of urea from blood into

the digestive tract:

K49 = K55 = K56 = 16.765 l/h.

The concentration of urea in the liver cells can then be calculated as:

U3/V3 = R49/K49 = 0.0606 mol N/l,

which turns out to be higher than the urea concentration in the blood plasma (U4/V4 = 0.014 mol N/l, see subsection 3.3.1). The **pool size of liver urea** is now easily derived:

U3 = 0.0606*V3 = 0.0606*6.0 = 0.364 mol N.

The rate of **urea excretion in the urine** (R57) is found as the difference between total urea flux rate (R49) and the rate of urea uptake in the rumen (R55) and in the lower gut (R56):

R57 = R49-(R55+R56) = 1.017-0.355 = 0.662 mol N/h.

The **rate constant** is calculated from the blood plasma concentration:

K57 = R57/(U4/V4) = 0.662/0.014 = 47.256 l/h.

Amino acid uptakes from blood into peripheral tissues and liver are described by the equations listed below:

R51 = R51M*A16/(K51+A16)	(uptake of amino acids in the mammary gland, mol N/h)
R51M = L51+M51*GH	(mol N/h)

```
R52 = R52M*A16/(K52+A16)      (uptake of amino acids in muscle
                               tissue, mol N/h)
R52M = L52+M52*INSUL          (mol N/h)
R53 = R53M*A16/(K53+A16)      (uptake of amino acids in other
                               tissues, mol N/h)
R54 = R54M*A17/(K54+A17)      (uptake of amino acids in the
                               liver, mol N/h)
R54M = L54+M54*RATIO          (mol N/h)
```

The **mammary uptake of amino acids** in the static model is 8.5 mol/d equivalent to 11.0 mol N/d (Danfær 1983b). Therefore:

R51 = 11.0/24 = 0.458 mol N/h.

Based on an average extraction rate of amino acids from arterial blood into the mammary gland of 30% (Mepham et al. 1982) and variations in amino acid concentrations in the mammary vein (Bickerstaffe et al. 1974, Clark et al. 1977, Peeters et al. 1979) the **maximal rate of amino acid uptake** is estimated as:

R51M = R51/0.63 = 0.458/0.63 = 0.727 mol N/h.

As stated previously the rates of nutrient uptake in the mammary gland are related to growth hormone concentration (GH). The independent part (L51) of the maximal rate is assigned as 0.0 mol N/h, and the dependent part is calculated accordingly:

M51 = (R51M-L51)/GH = 0.727/12.411 = 0.059 mol N*l/(h*µg).

The **affinity constant** is then found as:

K51 = 0.2954 mol N.

The mass of total body protein can be estimated as 13.2% of the live weight (Lobley et al. 1980, Riis 1983b): 600*0.132 = 79.2 kg. The mass of **muscle tissue protein** (A21) makes up 50-60% of total body protein (Riis 1983b):

A21 = 79.2*0.55 = 43.6 kg protein, equivalent to
43.6*1000/(6.25*14.01) = 498 mol N.

The rate of **amino acid uptake in muscle tissue** (R52) is taken as equal to the rate of **muscle protein synthesis** (R62). This rate is calculated as the muscle protein mass (A21) multiplied by the fractional rate of muscle protein synthesis, which is in the order of 0.9% per d in mature cows (Lobley et al. 1980):

R52 = R62 = 498*0.9/(100*24) = 0.187 mol N/h.

Insulin stimulates amino acid uptake in muscle tissue (Riis 1983a) by increasing the maximal rate of transport (R52M) without affecting the affinity constant (Waterlow et al. 1978b). The **maximal rate of uptake** is estimated as:

R52M = R52/0.55 = 0.187/0.55 = 0.340 mol N/h,

and the insulin dependent part of R52M is:

M52 = (R52M-L52)/INSUL = 0.340/0.520 = 0.653 mol N*l/(h*µg),

as the independent part (L52) is assumed to be 0.0 mol N/h. The **affinity constant** is now derived:

K52 = 0.4124 mol N.

The total **amino acid uptake in** muscle and **other tissues** has been estimated previously (R52+R53 = 9.1 mol N/d), hence:

R53 = 9.1/24-R52 = 0.379-0.187 = 0.192 mol N/h,

which is assumed to be 60% of the **maximal rate of uptake:**

R53M = 0.192/0.60 = 0.321 mol N/h,

and the **affinity constant** is:

K53 = 0.336 mol N.

The rate of **amino acid uptake into the liver** via the hepatic artery (R54) is 9.8 mol N/d (see above):

R54 = 9.8/24 = 0.408 mol N/h.

The **substrate pool** (A17) is in fact identical to the pool of **amino acids in the extracellular fluid** (A16), but is given a separate label in the model to indicate that amino acids are released from the liver to venous blood and taken up by the liver from arterial blood:

A17 = A16 = 0.504 mol N.

Glucagon stimulates while insulin, if anything, inhibits the amino acid uptake in the liver (Bergman & Heitmann 1978, Brockman 1978b, Riis 1983a, Kraus-Friedmann 1984, Brockman 1985). Therefore, in the model the ratio between these two hormones affects the **maximal rate of amino acid uptake** (R54M), which is taken as equal to the maximal rate of amino acid outflow (R44M) from the liver (Waterlow et al. 1978b):

R54M = R44M = 4.867 mol N/h.

The independent part (L54) of the maximal rate is assumed to be

0.0 mol N/h, and the dependent part is then found as:

M54 = (R54M-L54)/RATIO = 4.867/1.258 = 3.869 mol N/h.

Finally the **affinity constant** is calculated:

K54 = 5.503 mol N.

The last three equations in the liver and extracellular fluid compartment describe **the release of amino acids from the peripheral tissue compartment:**

R58 = R58M*A18/(K58+A18)	(outflow of amino acids from the mammary gland, mol N/h)
R61 = R61M*A20/(K61+A20)	(outflow of amino acids from muscle tissue, mol N/h)
R64 = R64M*A22/(K64+A22)	(outflow of amino acids from other tissues, mol N/h)

The **amino acid flow from the peripheral tissues** is taken up by the liver (balancing the A17 pool):

R58+R61+R64 = R54 = 0.408 mol N/h.

The secretion of amino acid carbon and nitrogen in milk protein is closely balanced by the mammary uptake of amino acid carbon and nitrogen (Clark et al. 1978), which means that the spillover or outflow from the mammary gland is almost zero:

R58 = 0.0 mol N/h,
R61+R64 = 0.408 mol N/h.

The rates of net mobilization of protein from the muscle tissue compartment (R63-R62) and from the compartment of other tissues (R66-R65) are related to the protein masses in these compartments. Total protein mass is estimated as 79.2 kg equivalent to 904 mol N. The muscle protein pool (A21) is 498 mol N, and the **protein pool size in other tissues** (A23) is calculated by difference:

A23 = 904-A13(intestinal tissue protein)-A15(liver protein)-A21
= 904-56-20-498 = 330 mol N.

As stated previously the total mobilization of body protein is 0.7 mol N/d:

(R63-R62)+(R66-R65) = 0.7/24 = 0.029 mol N/h,

and this is equivalent to the difference between amino acid outflow and amino acid uptake in the two compartments:

(R61-R52)+(R64-R53) = R61+R64-(R52+R53)
= 0.408-(0.187+0.192) = 0.029 mol N/h.

Relating the net mobilization to the protein mass gives:

R61-R52 = 498*0.029/(498+330) = 0.018 mol N/h,
R64-R53 = 330*0.029/(498+330) = 0.011 mol N/h,
R61 = R52+0.018 = 0.187+0.018 = 0.205 mol N/h,
R64 = R53+0.011 = 0.192+0.011 = 0.203 mol N/h.

The intracellular concentration of free amino acids is higher than the extracellular concentration. In muscle cells the concentration is 21 mmol/l (Waterlow et al. 1978b) or 15 mmol/kg wet weight (Reich & Sel'kov 1981). As muscle tissue contains 20% protein (Harper 1973, Riis 1983b) the muscle tissue mass is: 43.6/0.20 = 218 kg, and the size of the **free amino acid pool** is:

A20 = 218*15/1000 = 3.27 mol amino acids
equivalent to 4.251 mol N.

The **maximal rate of amino acid outflow from muscle tissue** is estimated as:

R61M = R61/0.60 = 0.205/0.60 = 0.342 mol N/h,

and the **affinity constant** is derived as:

K61 = 2.834 mol N.

The ratio between the pools of **intracellular free amino acids** and protein-bound amino acids is assumed to be equal in muscle tissue and in **other tissues:**

A22 = A23*A20/A21 = 330*4.251/498 = 2.817 mol N.

The **maximal rate of amino acid outflow from other tissues** is (as in muscle tissue):

R64M = R64/0.60 = 0.203/0.60 = 0.339 mol N/h,

and finally the **affinity constant** can be estimated:

K64 = 1.878 mol N.

The rates of protein synthesis in muscle tissue (R62) and in other tissues (R65) are as estimated previously:

R62+R65 = 9.1/24 = 0.379 mol N/h.

Total protein synthesis in the body can be calculated by summa-

tion: R39(intestinal tissue)+R43(liver)+R62+R65 = 0.508+0.164+0.379 = 1.051 mol N/h equivalent to 2.21 kg protein/d. In the study of Lobley et al. (1980) estimates of whole body protein synthesis in a mature cow ranged from 2.0 to 2.9 kg protein/d depending on whether leucine or tyrosine, respectively, was used as a tracer amino acid. As the true value is probably lower than the average of the two estimates because of a substantial oxidation of tyrosine (Lobley et al. 1980) the rate of total protein synthesis in the model seems to be in good agreement with an in vivo situation.

3.3.4 The mammary gland and body tissue compartments

The state variables and flow of nutrients in the mammary gland, in muscle tissue, in adipose tissue and in other tissues are depicted in figure 2.6. Numerical values and dimensions of the state variables and equation parameters are listed in Appendix 8.

The mammary gland

Nutrient inputs to the mammary gland compartment from the extracellular fluid compartment are acetate and ketone bodies (R156), glucose (R160), fatty acids (R172A), glycerol (R172B), and amino acids (R51).

The weight of the udder is estimated as 22 kg (Smith & Baldwin 1974, Harrison et al. 1983, Butler-Hogg et al. 1985). The mammary parenchyma constitutes about 90% of the organ weight in early lactation (Sejrsen 1987), and 75% of the paranchyma is water (Swanson & Poffenbarger 1979). The volume of **"metabolic" water in the mammary gland** is therefore:

V5 = 22*0.90*0.75 = 14.85 l.

In fact this volume is an overestimation of the true metabolic water pool, as the intracellular water is only 30% of total tissue water (Baumrucker 1984).

Carbon transactions

The following equations describe the metabolism of acetate and 3-OH-butyrate, glucose and lipids:

R174 = R174M*C29/(K174+C29)	(fatty acid synthesis from acetate and ketone bodies, mol C/h)
R175 = R175M*C29/(K175+C29)	(oxidation of acetate and ketone bodies, mol C/h)
R177 = R177M*C30/(K177+C30)	(milk lactose synthesis, mol C/h)
R178 = R178M*C30/(K178+C30)	(oxidation of glucose, mol C/h)
R179 = R179M*C31/(K179+C31)	(milk fat synthesis, mol C/h)
R180 = R180M*C31/(K180+C31)	(oxidation of fatty acids, mol C/h)
R181 = L179*R179	(esterification of milk fat, mol C/h)
R176 = R181-R172B	(glycerol synthesis, mol C/h)
R182 = K182*C33	(milk lactose secretion, mol C/h)
R183 = K183*C34	(milk fat secretion, mol C/h)

The rate of milk fat production is 1200 g/d in the static model (Danfær 1983b). The composition of this milk fat is assumed to be as reported by Palmquist & Conrad (1978). The proportion of fatty

acids synthesized in the mammary gland is taken to be the fatty acids having carbon chains from C_4 to C_{14} in addition to half of the C_{16} acids (Bauman & Davis 1974, King et al. 1985).

According to this 1200 g milk fat contain 1138.7 g fatty acids of which 445.3 g are synthesized de novo (mol.w. = 192, 11.4 mol C/mol FA), and 693.4 g are taken up from the blood (mol.w. = 276, 17.5 mol C/mol FA). The rates of **milk fatty acid synthesis** (R174) and **total milk fatty acid production** (R179) can now be estimated:

R174 = 445.3*11.4/(192*24) = 1.102 mol C/h
R179 = 693.4*17.5/(276*24)+R174
= 1.832+1.102 = 2.934 mol C/h.

The physiological concentrations of acetate and 3-OH-butyrate in the mammary gland are taken as 3mM and 1mM, respectively (Forsberg et al. 1985b). The K_m value for acetate conversion into fatty acids is estimated by Forsberg et al. (1984) as 1.22 mM, and the **affinity constant for fatty acid synthesis** from acetate and ketone bodies is derived as:

K174 = 14.85*1.22*(3*2+1*4)/(3*1000) = 0.0604 mol C.

The intracellular **pool size of acetate and ketone bodies** is calculated as:

C29 = 14.85*(3*2+1*4)/1000 = 0.1485 mol C,

which is a little higher than the 0.09 mol C stated by Waghorn & Baldwin (1984). The **maximal rate of fatty acid synthesis** is then:

R174M = 1.550 mol C/h.

The rate of **acetate and ketone body oxidation** is found by balancing the substrate pool (C29):

R175 = R156-R174 = 3.422-1.102 = 2.320 mol C/h.

The K_m value for acetate oxidation in mammary tissue is estimated by Forsberg et al. (1984) as 1.79 mM. From this the **affinity constant for oxidation of acetate and ketone bodies** can be calculated as:

K175 = 14.85*1.79*(3*2+1*4)/(3*1000) = 0.0886 mol C,

and the **maximal rate of oxidation** is found as:

R175M = 3.704 mol C/h.

In the static model the rate of **lactose synthesis** is 1440 g/d equivalent to 4.21 mol/d:

R177 = 4.21*12/24 = 2.105 mol C/h.

As the intracellular concentration of glucose is 2 mM according to Forsberg et al. (1985b), the mass of the **glucose pool** can be derived as:

C30 = 14.85*2*6/1000 = 0.1782 mol C,

which is of the same magnitude as reported by Baldwin & Yang (1974) and by Waghorn & Baldwin (1984). The **affinity constant for lactose synthesis** is derived from a K_m value of 3.45 mM estimated by Forsberg et al. (1985a):

K177 = 14.85*3.45*6/1000 = 0.3074 mol C,

and the **maximal rate of lactose synthesis** is:

R177M = 5.736 mol C/h.

The rate of fatty acid esterification into milk fat is: 445.3/192+693.4/276 = 4.832 mol FA/d. Hence, the rate of **glycerol incorporation into milk fat** is:

R181 = 4.832/3 = 1.611 mol glycerol/d, equivalent to
1.611*3/24 = 0.201 mol C/h,

and the **factor for esterification:**

L179 = R181/R179 = 0.201/2.934 = 0.06863 mol C/mol C.

The intracellular pool of glycerol (C32) originates partly from glycerol taken up from blood lipids (R172B) and partly from **glycerol synthesized from glucose** in the mammary tissue (R176) (Bauman & Davis 1974):

R181 = R172B+R176,
R176 = 0.201-0.127 = 0.074 mol C/h.

The estimated rate of glycerol synthesis (R176) is close to a value (0.07 mol C/h) given by Baldwin & Yang (1974).

The rate of **glucose oxidation** (R178) is found by balancing the glucose pool (C30):

R178 = R160-R176-R177 = 2.857-0.074-2.105 = 0.678 mol C/h.

The K_m **value for glucose oxidation** through the pentose-P pathway

is low (1.07 mM) compared to the K_m value for lactose synthesis (Forsberg et al. 1985a):

K178 = 14.85*1.07*6/1000 = 0.0953 mol C.

The **maximal rate of glucose oxidation** is then derived:

R178M = 1.040 mol C/h.

Normally, there is no net uptake of free fatty acids in the mammary tissue (Bickerstaffe et al. 1974, Schultz 1974). But in ketotic and in fasted cows having very high concentrations of free fatty acids in the blood a significant uptake in the mammary gland has been observed (Schwalm et al. 1969, Annison 1983, Hawke & Taylor 1983). As free fatty acids are taken up in other tissues along a concentration gradient (Bell 1981, Madsen 1983c) it can be suggested that the **intracellular concentration of free fatty acids** in mammary tissue is about the same as the concentration in blood plasma:

C31/V5 = C26/V4 = 1.241/150 = 0.0083 mol C/l.

From this the calculation of the **intracellular pool size** is straightforward:

C31 = 0.0083*14.85 = 0.123 mol C.

In the model it is assumed that the fatty acids synthesized de novo and the preformed fatty acids taken up from blood triglycerides share a common intracellular pool (C31). The average fatty acid chain length in this pool can be estimated as 14 carbon atoms, and the pool size will then be: 1000*0.123/14 = 8.8 mmol fatty acids, which is about 50% higher than the intracellular pool size of long chain fatty acids given by Waghorn & Baldwin (1984).

Esterification of fatty acids is probably a process close to equilibrium with a relatively high V_{max} (Baldwin & Yang 1974). The rate of **triglyceride synthesis** (R179) is assumed here to be performed at 35% of its **maximal rate:**

R179M = R179/0.35 = 2.934/0.35 = 8.382 mol C/h.

The **affinity constant** is then found as:

K179 = 0.2284 mol C.

The rate of **fatty acid oxidation** (R180) is found by balancing the free fatty acid pool in the tissue (C31):

R180 = R172A+R174-R179 = 0.201 mol C/h.

Although the capacity for fatty acid transport across the mitochondrial membrane and for fatty acid oxidation seems to be high in mammary tissue (Crabtree et al. 1981) the usage of fatty acids for oxidation has a low priority compared to fat synthesis (Davis & Bauman 1974): K180>K179. Crabtree et al. (1981) has estimated the activity of carnitine palmitoyltransferase in cow mammary tissue as 0.36 mmol per min. per kg wet weight. This value is adapted in the model for estimation of the **maximal rate of fatty acid oxidation:**

R180M = 0.36*16*60*22*0.90/1000 = 6.843 mol C/h,

and the corresponding **affinity constant:**

K180 = 4.065 mol C

is much higher than the affinity constant for fat synthesis (K179).

The rate of **lactose secretion** is equal to the rate of lactose synthesis:

R182 = R177 = 2.105 mol C/h.

The **content of lactose** in Golgi vacuoles and secretory vesicles of the alveolar cells is represented by the state variable C33. The concentration of lactose in the secretory vesicles is considered to be the same as the concentration in milk (Holt 1983), which according to the static model is 48 g/kg, equivalent to 1.7 mol C/l. The fractional volume of secretory vesicles in lactating mammary tissue can be estimated as 2-5% of the alveolar cell volume (Hollmann 1974, Larson 1979). It is assumed here that the secretory vesicles make up 3% of the parenchyma:

C33 = 22*0.90*0.03*1.7 = 1.01 mol C.

The **rate constant for lactose secretion** is:

K182 = R182/C33 = 2.105/1.01 = 2.084 h^{-1}.

The rate of **milk fat secretion** is calculated as:

R183 = R179+R181 = 2.934+0.201 = 3.135 mol C/h.

The state variable C34 represents **lipid droplets** in the secretory tissue. It can be estimated that the volume of these particles accounts for 7-10% of the cell volume (Hollmann 1974, Larson 1979). It is assumed here that the lipid droplets make up 5% of the parenchyma, and that the density of milk fat is 0.9 g/ml (Jensen 1964):

C34 = 22*0.9*0.05*0.9*1000 = 891 g fat, equivalent to
891*3.135*24/1200 = 55.866 mol C.

The **rate constant for milk fat secretion** is found as:

$$K183 = R183/C34 = 3.135/55.866 = 0.056\ h^{-1}.$$

Nitrogen transactions

The rates of **milk protein synthesis and secretion** are described as follows:

```
R59 = R59M*A18/(K59+A18)      (milk protein synthesis, mol N/h)
R60 = K60*A19                 (milk protein secretion, mol N/h)
```

The **rate of protein synthesis** (R59) is equal to the rate of amino acid uptake (R51) as the outflow of amino acids from the gland (R58) is considered to be negligible (Clark et al. 1978):

$$R59 = R51 = 0.458 \text{ mol N/h}.$$

From the papers of Clark et al. (1980), Baumrucker (1984), and Waghorn & Baldwin (1984) the intracellular concentration of free amino acids is estimated to be 30 mmol/l. The average molecular weight of protein bound amino acids in milk protein is 116 (Jenness 1982, Swaisgood 1982), and the protein: nitrogen ratio is 6.38 (Jenness 1974). From this the **amino acid pool** size can be calculated:

$$A18 = 30*116*14.85/(6.38*14.01*1000) = 0.578 \text{ mol N}.$$

Although the mechanism of milk protein synthesis and secretion has been described in detail in several reviews (e.g. Larson 1979, Mercier & Gaye 1982), data on the kinetic aspects of these processes are difficult to find in the literature. However, it is as-

sumed here that the **affinity constant for milk protein synthesis** is of the same order as the intracellular amino acid pool:

K59 = A18 = 0.578 mol N.

It follows that the **maximal rate of protein synthesis** is:

R59M = 0.917 mol N/h.

The rate of **milk protein secretion** is equal to the rate of milk protein synthesis:

R60 = R59 = 0.458 mol N/h.

The state variable A19 represents the **content of milk protein** in Golgi vacuoles and secretory vesicles, the volume of which is 0.594 l as estimated previously. The concentration of protein in these vesicles is assumed to be equal to the concentration in milk, which is 34 g/kg (Danfær 1983b) equivalent to 0.39 mol N/l:

A19 = 0.594*0.39 = 0.232 mol N.

Finally, the **rate constant for milk protein secretion** is derived:

K60 = R60/A19 = 0.458/0.232 = 1.976 h^{-1}.

The muscle tissue

The nutrients taken up by the muscle tissue compartment from the extracellular fluid compartment are acetate and ketone bodies (R157), glucose (R161), free fatty acids (R166), and amino acids (R52).

Carbon transactions

The metabolism of energy-yielding nutrients is simulated by the equations below:

```
R184 = R184M*CA20/(K184+CA20)     (ketones produced by amino
                                   acid deamination, mol C/h)
R185 = R185M*C35/(K185+C35)       (oxidation of acetate and
                                   ketone bodies, mol C/h)
R186 = R186M*C36/(K186+C36)       (glycolysis into lactate,
                                   mol C/h)
R187 = R187M*C36/(K187+C36)       (oxidation of glucose, mol C/h)
R188 = R188M*C37/(K188+C37)       (oxidation of fatty acids,
                                   mol C/h)
```

The total production of ATP in muscle tissue is estimated as approximately 200 mol ATP/d (Madsen 1983c, Danfær 1983b). From this and from the oxidation rates of nutrients taken up into the tissue the rate of **amino acid deamination** can be calculated:

R184 = 0.142 mol C/h.

The affinity constant for amino acid catabolism is of the same order as the amino acid concentration in blood plasma (Krebs 1972 c.f. Lindsay 1980):

K184/V6 = KCA*A16/V4 = 3.8*0.504/150 = 0.0128 mol C/l.

The mass of muscle protein (A21) is estimated as 43.6 kg (see subsection 3.3.3), and the protein concentration in the tissue is 20% (Harper 1973, Riis 1983b). The water content in muscle tissue is 71% (Smith & Baldwin 1974), and the **volume of tissue water** is therefore:

V6 = 43.6*0.71/0.20 = 155 l.

Hence, the **affinity constant for amino acid catabolism** is:

K184 = 0.0128*155 = 1.984 mol C.

The intracellular **pool of free amino acids** (A20) is estimated in subsection 3.3.3 as 4.251 mol N. Converted into carbon this is:

CA20 = KCA*A20 = 3.8*4.251 = 16.154 mol C.

Then, the **maximal rate of amino acid deamination** is obtained:

R184M = 0.1594 mol C/h.

The rate of **acetate and ketone body oxidation** (R185) is the sum of tissue uptake (R157) and endogenous production (R184):

R185 = R157+R184 = 0.577+0.142 = 0.719 mol C/h.

The intracellular concentrations of acetate and ketone bodies fall in the range of 1-2 mmol/kg tissue (Reich & Sel'kov 1981), which is about the same as the intracellular concentration in mammary tissue (Forsberg et al. 1985b):

C35/V6 = C29/V5 = 0.01 mol C/l.

Hence, the **pool size of acetate and ketone bodies** in muscle tissue is:

C35 = 0.01*V6 = 0.01*155 = 1.55 mol C.

The maximal capacity of acetyl-CoA synthetase in muscle tissue is 0.1 mmol per min per kg fresh weight (Reich & Sel'kov 1981). This

value is used to estimate the **maximal rate of acetate and ketone body oxidation:**

R185M = 0.1*2*60*43.6/(0.20*1000) = 2.616 mol C/h,

and the **affinity constant** is derived as:

K185 = 4.089 mol C.

The rate of **lactate production from glucose** (R186) is equal to the rate of lactate outflow (R189), which was estimated in the previous subsection 3.3.3:

R186 = R189 = 0.409 mol C/h.

The intracellular concentration of glucose is generally in the millimolar range (Reich & Sel'kov 1981). In muscle tissue it has been estimated as 2mM like in the mammary gland (McVeigh & Tarrant 1982, Forsberg et al. 1985b), and the **mass of the glucose pool** (C36) is therefore:

C36/V6 = 2*6/1000 = 0.012 mol C/l,
C36 = 0.012*155 = 1.860 mol C.

According to Reich & Sel'kov (1981) the maximal capacity of lactate dehydrogenase is very high in muscle tissue and the production of lactate is assumed here to occur at 25% of its **maximal rate:**

R186M = R186/0.25 = 0.409/0.25 = 1.639 mol C/h.

The **affinity constant** for the process in then calculated:

K186 = 5.582 mol C.

Compared to lactate dehydrogenase the maximal capacity of pyruvate dehydrogenase complex is low (Reich & Sel'kov 1981). It is therefore assumed that the rate of **glucose oxidation to CO_2** (R187) is correspondingly low, and that it is occurring near its **maximal rate:**

R187 = 0.025 mol C/h,
R187M = R187/0.90 = 0.028 mol C/h.

The **affinity constant** is calculated as:

K187 = 0.2232 mol C.

The rate of **glucose uptake** in the muscle tissue compartment (R161) is then calculated:

R161 = R186+R187 = 0.434 mol C/h.

The **free fatty acids** taken up from the extracellular fluid (R166), estimated in subsection 3.3.3, are exclusively used for **oxidation:**

R188 = R166 = 0.500 mol C/h.

The intracellular concentration of free fatty acids is taken as 0.1 mmol/kg tissue (Reich & Sel'kov 1981) and the mass of the **free fatty acid pool** is, accordingly:

C37 = 0.1*16*43.6/(0.20*1000) = 0.349 mol C.

The capacity for fatty acid transport across the mitochondrial membrane (carnitine palmitoyltransferase) in muscle tissue is much higher than the maximal activity of acyl-CoA synthetase, which is 0.1 mmol per min per kg fresh weight (Reich & Sel'kov 1981). This

value is used in the model to calculate the **maximal rate of fatty acid oxidation:**

R188M = 0.1*16*60*43.6/(0.20*1000) = 20.928 mol C/h.

The **affinity constant for fatty acid oxidation** can now be derived:

K188 = 14.259 mol C.

Walsh et al. (1981) have measured the concentration of lactate in ovine muscle tissue as 5 mmol/kg. According to this the **pool of muscle lactate** (C38) is estimated as:

C38 = 5*3*43.6/(0.20*1000) = 3.270 mol C,

and the **rate constant for lactate outflow** from muscle tissue is:

K189 = R189/C38 = 0.409/3.270 = 0.1252 h^{-1}

as previously given in subsection 3.3.3.

Nitrogen transactions

The rates of amino acid and protein metabolism are defined as follows:

R62 = R62M*A20/(K62+A20)	(muscle protein synthesis, mol N/h)
R62M = L62+M62*INSUL	(mol N/h)
R63 = K63*A21	(muscle protein breakdown, mol N/h)

The rate of **muscle protein synthesis** and the **free amino acid pool** size (A20) are estimated in the previous subsection 3.3.3:

R62 = 0.187 mol N/h,
A20 = 4.251 mol N.

The K_m values for the initiation of protein synthesis are much lower than the intracellular concentrations of free amino acids (Lindsay 1980). It follows from this that protein synthesis will occur at a rate near the **maximal capacity:**

R62M = R62/0.90 = 0.187/0.90 = 0.208 mol N/h.

Insulin stimulates muscle protein synthesis most likely by increasing V_{max} (Bergman & Heitmann 1978, Waterlow et al. 1978c, Buttery & Vernon 1980, Young 1980, Riis 1983a). Hence, the maximal rate (R62M) is dependent on the plasma insulin concentration (INSUL) in the model. The independent part of R62M is assumed to be zero, and the dependent part is calculated accordingly:

L62 = 0.0 mol N/h,
M62 = R62M/INSUL = 0.208/0.520 = 0.399 mol N*l/(h*µg)

The **affinity constant for muscle protein synthesis** is then obtained:

K62 = 0.4723 mol N.

Net protein mobilization from muscle tissue was calculated in the previous subsection 3.3.3 as 0.018 mol N/h. The rate of **muscle protein breakdown** is estimated as the sum of protein synthesis and mobilization:

R63 = 0.187+0.018 = 0.205 mol N/h.

The mass of muscle protein is previously estimated (A21 = 498 mol N), and the **rate constant for protein breakdown** is derived as:

$$K63 = R63/A21 = 0.205/498 = 4.1*10^{-4}\ h^{-1}.$$

The adipose tissue

Nutrients taken up by the adipose tissue compartment from the extracellular fluid compartment are acetate and ketone bodies (R158), glucose (R162), fatty acids (R173A), and glycerol (R173B).

The intermediary metabolism in this compartment is mainly concerned with **lipid synthesis, lipolysis, and substrate oxidations:**

```
R190 = R190M*C39/(K190+C39)      (fatty acid synthesis from
                                  acetate and ketone bodies,
                                  mol C/h)
R190M = L190+M190*INSUL          (mol C/h)
R191 = R191M*C39/(K191+C39)      (oxidation of acetate and
                                  ketone bodies, mol C/h)
R193 = R193M*C40/(K193+C40)      (oxidation of glucose, mol C/h)
R195 = R195M*C41/(K195+C41)      (body fat synthesis, mol C/h)
R195M = L195+M195*INSUL          (mol C/h)
R196 = K196*R195                 (esterification of body fat,
                                  mol C/h)
R192 = R196                      (glycerol synthesis, mol C/h)
R197 = R197M*C43/(K197+C43)      (body fat breakdown into fatty
                                  acids, mol C/h)
R197M = L197-M197*INSUL          (mol C/h)
R198 = K198*R197                 (body fat breakdown into
                                  glycerol, mol C/h)
```

At peak lactation (5-6 weeks post partum) the total fat content in the cow is 80 g/kg body weight (Butler-Hogg et al. 1985): 80*600/1000 = 48 kg. The fat content in adipose tissue is given as 760 g/kg by Reiser (1975), and the total mass of adipose tissue is consequently calculated as: 48/0.76 = 63.2 kg.

The content of **water in adipose tissue** is estimated from Smith & Baldwin (1974) and from Christie (1981) as 70 g/kg tissue:

V7 = 63.2*70/1000 = 4.42 l.

The intracellular concentration of acetate and ketone bodies is assumed to be 5 times higher than in muscle tissue because of the low water content in adipocytes (Reich & Sel'kov 1981):

C39/V7 = 5*C35/V6 = 5*0.01 = 0.05 mol C/l,

and the **pool size of acetate and ketone bodies** in adipose tissue is then:

C39 = 0.05*V7 = 0.05*4.42 = 0.221 mol C.

The consumption of **acetate and ketone bodies in fatty acid synthesis** is 7.0 and 0.5 mol/d, respectively, in the static model (Danfær 1983b):

R190 = (7.0*2+0.5*4)/24 = 0.667 mol C/h.

The activity of acetyl-CoA synthetase in adipose tissue from lactating cows is 75 nmol per min per g (Vernon 1981). Conversion of this value into terms used in the model gives: 75*2*60*63.2/10^6 = 0.57 mol acetate-C/h, which is almost the same as the corresponding rate in the model (7.0*2/24 = 0.58 mol acetate-C/h).

Acetyl-CoA carboxylase is generally considered to be the rate-limiting enzyme in the fatty acid synthetic pathway (Bauman 1976, Vernon 1981). Estimates of the activity of this enzyme vary from 10 to 90 nmol per min per g tissue (Vernon 1981), and the highest value is used here to calculate the **maximal rate of fatty acid synthesis:**

$90*2*60*63.2/10^6$ = 0.683 mol acetate-C/h,
R190M = 0.683*(7.0*2+0.5*4)/(7.0*2) = 0.780 mol C/h.

Insulin stimulates the activity of acetyl-CoA carboxylase by increasing V_{max} (Yang & Baldwin 1973b, Haystead & Hardie 1986). The independent part of R190M is assumed to be zero (L190 = 0.0 mol C/h), and the dependent part is consequently:

M190 = R190M/INSUL = 0.780/0.520 = 1.500 mol C*l/(h*µg).

Estimation of the **affinity constant for fatty acid synthesis** gives:

K190 = 0.0376 mol C.

The rate of **acetate and ketone body oxidation** is found by balancing the substrate pool (C39):

R191 = R158-R190 = 1.377-0.667 = 0.710 mol C/h.

In isolated bovine adipocytes the apparent K_m value for acetate oxidation is higher than that for acetate conversion into fat (Yang & Baldwin 1973b). From the results of these authors it can be roughly estimated that the **affinity constant for acetate and ketone body oxidation** is 6 times higher than for fatty acid synthesis:

K191 = K190*6 = 0.0376*6 = 0.2256 mol C.

The **maximal rate of oxidation** is then calculated as:

R191M = 1.435 mol C/h.

The estimation of the rate of **fatty acid esterification** (R195, R196) is based on reported enzymatic activities in cow adipose tissue (Yousef et al. 1969, Baldwin & Smith 1971, Benson & Emery 1971, Benson et al. 1972, Baldwin et al. 1973, Shirley et al. 1973), which range from 0.2 to 28.8 nmol fatty acids per min per g tissue. Considering the actual stage of lactation of the model cow a value of 13.2 nmol per min per g is chosen:

R195 = 13.2*16*60*63.2/10^6 = 0.800 mol C/h,
R196 = K196*R195 = 0.0625*0.800 = 0.050 mol C/h.

The concentration of **intracellular free fatty acids** (C41/V7) is estimated as 3 mmol fatty acids per kg tissue (Vernon 1975, Smith & Walsh 1984, McNamara & Hillers 1986b&c):

C41 = 3*16*63.2/1000 = 3.04 mol C.

It has been questioned if insulin is an important regulator of fatty acid esterification in ruminant adipose tissue (Vernon 1980, Prior & Smith 1982). However, insulin seems to decrease the release of fatty acids from the tissue (Yang & Baldwin 1973a, Bassett 1978), and it is assumed here that insulin stimulates the **maximal rate of fatty acid esterification.** This parameter (R195M) is estimated from the highest reported rate of esterification, 29 nmol fatty acids per min per g tissue (Baldwin et al. 1973):

R195M = 29*16*60*63.2/10^6 = 1.759 mol C/h.

The independent part of the maximal rate is assumed to be zero (L195 = 0.0 mol C/h), and the dependent part (M195) is calculated as:

M195 = R195M/INSUL = 1.759/0.520 = 3.383 mol C*l/(h*µg).

From the parameters obtained above the **affinity constant for fatty acid esterification** is found:

K195 = 3.6442 mol C.

The rate of **glycerol synthesis** from glucose (R192) is equal to the rate of glycerol used for fatty acid esterification (R196):

R192 = R196 = 0.050 mol C/h.

The amount of **glucose** not used for glycerol synthesis is assumed to be **oxidized to CO_2** via the pentose-P pathway thus supplying NADPH for fatty acid synthesis (Baldwin et al. 1973, Yang & Baldwin 1973b, Baldwin et al. 1976):

R193 = R162-R192 = 0.191-0.050 = 0.141 mol C/h.

This rate is within a range of in vitro values of glucose conversion into CO_2 in bovine adipose tissue (Baldwin et al. 1973, Pothoven & Beitz 1973, Smith & Prior 1986): 5.8-6.6 nmol per min per g equivalent to 0.13-0.15 mol C/h.

The fraction of available glucose utilized in glycerol synthesis is: R192/R162 = 0.050/0.191 = 0.26 as found by Yang and Baldwin (1973b) c.f. Vernon (1981).

The intracellular concentration of glucose in adipose tissue is assumed to be 0.06 mol C/l (Eichner & Arnold 1979), which is 5 times higher than in tissues with a high moisture content, i.e. mammary gland and muscles (C30/V5 = C36/V6 = 0.012 mol C/l). Hence, the **glucose pool size in adipose tissue** is:

$$C40 = 0.06*V7 = 0.06*4.42 = 0.265 \text{ mol C.}$$

The **maximal rate of glucose oxidation** is estimated from the highest values of CO_2 production from glucose in subcutaneous adipose tissue (62 nmol per min per g) found by Pothoven & Beitz (1973):

$$R193M = 62*60*63.2/10^6 = 0.235 \text{ mol C/h.}$$

The **affinity constant** is then obtained:

$$K193 = 0.1775 \text{ mol C.}$$

The **release of fatty acids from the adipose tissue** is estimated in the previous subsection 3.3.3:

$$R194 = 1.610 \text{ mol C/h.}$$

This value is in agrement with results from in vitro studies of Metz & van den Bergh (1977) and McNamara & Hillers (1986a).

The **rate constant for fatty acid release** is:

$$K194 = R194/C41 = 1.610/3.04 = 0.5296 \text{ h}^{-1}.$$

The **rate of lipolysis** (R197) is calculated by balancing the intracellular pool of free fatty acids (C41):

R197 = R194+R195-(R173A+R190)
= 1.610+0.800-(0.290+0.667) = 1.453 mol C/h,

which is of the same order as lipolytic rates found in vitro by Metz & van den Bergh (1977): 12-28 nmol fatty acids per min per g tissue corresponding to 0.7-1.7 mol C/h.

The adipose tissue compartment contains 48 kg fat. Assuming that it is all tripalmitin the **pool size of body fat** is obtained as:

C43 = 48*51/0.807 = 3030 mol C.

The **maximal rate of lipolysis** is estimated from a norepinephrine stimulated fatty acid release of 3.5 mmol per h per kg tissue (McNamara & Hillers 1986a):

R197M = 3.5*16*63.2/1000 = 3.539 mol C/h.

As discussed by Danfær (1983b) the "antimobilizing" effect of insulin could be due to a stimulated esterification, an inhibited lipolysis, or both. It is assumed here that insulin to some extent decreases the maximal rate of lipolysis (R197M). It is further assumed that in late lactation when the insulin concentration is increased (INSUL = 0.80 ng/ml), the maximal rate of lipolysis is only 10% of its value in early lactation (INSUL = 0.52 ng/ml):

L197-M197*0.52 = 3.539 mol C/h
L197-M197*0.80 = 0.354 mol C/h
L197 = (3.539*0.80-0.354*0.52)/(0.80-0.52) = 9.454 mol C/h
M197 = (9.454-3.539)/0.52 = 11.375 mol C*l/(h*µg).

The **affinity constant for lipolysis** is now derived:

K197 = 4349.6 mol C.

Glycerol from degraded body fat is not reutilized in the adipose tissue because of a very low activity of glycerol kinase (Khachadurian et al. 1967, Hood et al. 1972, Martin & Wilson 1974). The rate of **glycerol release from degraded body fat** (R198) is obtained from the rate of lipolysis (R197):

$$R198 = 0.0625*1.453 = 0.091 \text{ mol C/h.}$$

The rate of **total outflow of glycerol** from the adipose tissue (R199) is then calculated by balancing the glycerol pool (C44):

$$R199 = R173B+R198 = 0.018+0.091 = 0.109 \text{ mol C/h.}$$

The concentration of glycerol in adipose tissue is probably higher than in the extracellular fluid: $C44/V7>0.105$ mmol C/l (see subsection 3.3.3). The ratio between the concentration of free fatty acids in adipose tissue and in the extracellular fluid is: $(C41/V7)/(C26/V4) = 83$, and the corresponding ratio for glycerol is assumed to be 100: $(C44/V7)/(1.05*10^{-4}) = 100$. Hence, the **mass of free glycerol** in adipose tissue is calculated as:

$$C44 = 100*4.42*1.05/10^{4} = 0.046 \text{ mol C,}$$

and the **rate constant for glycerol outflow** from the adipose tissue is finally obtained as:

$$K199 = R199/C44 = 0.109/0.046 = 2.370 \text{ h}^{-1}.$$

Other tissues

This compartment comprises tissues which are not dealt with in the foregoing subsections, i.e. bones, connective tissue, nerve and brain tissues, blood cells, lungs, hair, hoofs etc. Nutrients

taken up from the extracellular fluid compartment are acetate and ketone bodies (R159), glucose (R163), free fatty acids (R167), and amino acids (R53).

Carbon transactions

The following equations describe the nutrient oxidations:

```
R200 = R200M*C45/(K200+C45)      (oxidation of acetate and
                                  ketone bodies, mol C/h)
R201 = R201M*C46/(K201+C46)      (oxidation of glucose, mol C/h)
R202 = R202M*C47/(K202+C47)      (oxidation of fatty acids,
                                  mol C/h)
```

The rate of **acetate and ketone body oxidation** is equal to the rate of tissue uptake (R159):

R200 = R159 = 1.019 mol C/h,

and this is assumed to occur at 60% of the **maximal rate:**

R200M = 1.019/0.60 = 1.699 mol C/h.

The intracellular concentration of acetate and ketone bodies is assumed to be the same as in mammary and muscle tissues:

C45/V8 = C29/V5 = C35/V6 = 0.01 mol C/l.

The **volume of "metabolic" water** in the other tissue compartment is estimated as:

V8 = 20.0 l,

and the mass of the **acetate and ketone body pool** is consequently:

C45 = 0.01*20.0 = 0.200 mol C.

The **affinity constant for acetate and ketone body oxidation** is calculated as:

K200 = 0.1332 mol C.

The rate of **glucose oxidation** (R201) is equal to the rate of glucose uptake (R163):

R201 = R163 = 0.086 mol C/h.

The intracellular concentration of glucose is assumed to be the same as in the mammary gland and muscle tissue:

C46/V8 = C30/V5 = C36/V6 = 0.012 mol C/l,

and the **glucose pool size** in other tissues is accordingly:

C46 = 0.012*V8 = 0.012*20.0 = 0.240 mol C.

It is assumed that glucose is oxidized at a rate near the **maximal capacity:**

R201M = R201/0.85 = 0.086/0.85 = 0.101 mol C/h,

and the **affinity constant for glucose oxidation** can then be obtained as:

K201 = 0.0449 mol C.

Fatty acids are oxidized (R202) at the same rate as they are taken up (R167):

R202 = R167 = 0.167 mol C/h.

The intracellular concentration of free fatty acids is taken to be equal to that in muscle tissue:

C47/V8 = C37/V6 = 0.00225 mol C/l,

and the **free fatty acid pool size** is therefore:

C47 = 0.00225*V8 = 0.00225*20.0 = 0.045 mol C.

As in muscle tissue, the **affinity constant for fatty acid oxidation** is supposed to be high compared to the substrate pool size:

K202/C47 = K188/C37 = 14.259/0.349,
K202 = 0.045*14.259/0.349 = 1.839 mol C.

Hence, the **maximal rate** is derived as:

R202M = 6.978 mol C/h.

Nitrogen transactions

The last two equations define the amino acid and protein metabolism:

R65 = R65M*A22/(K65+A22) (protein synthesis, mol N/h)
R66 = K66*A23 (protein breakdown, mol N/h)

The **protein synthesis** rate is equal to the rate of amino acid uptake (R53):

R65 = R53 = 0.192 mol N/h.

The intracellular **pool of free amino acids** is estimated in subsection 3.3.3:

A22 = 2.817 mol N.

As in muscle tissue, protein synthesis is taken to be occurring at a rate near the **maximal capacity:**

R65M = R65/0.90 = 0.192/0.90 = 0.214 mol N/h.

From these parameter values the **affinity constant for protein synthesis** is obtained:

K65 = 0.313 mol N.

The rate of **protein breakdown** (R66) can be found by balancing the free amino acid pool (A22):

R66 = R64+R65-R53 = R64 = 0.203 mol N/h,

or from the protein balance (= -0.7 mol N/d) in body tissues estimated in the previous subsection 3.3.3:

(R63-R62)+(R66-R65) = 0.7 mol N/d,
R66 = 0.7/24+R62+R65-R63 = 0.203 mol N/h.

The mass of the **protein pool** (A23) is estimated in the foregoing subsection 3.3.3:

A23 = 330 mol N,

and the **rate constant for protein breakdown** is finally derived:

$K66 = R66/A23 = 0.203/330 = 6.2*10^{-4}\ h^{-1}$.

3.3.5 Whole animal performance

In this subsection equations which relate the appropriate metabolic rates to whole animal performance are presented and commented on.

This part of the computer program is formulated in the SAS programming language (SAS User's Guide 1982a&b) and is shown in Appendix 4. The calculated parameters are feed intake, milk yield and milk composition, live weight gain, and aspects of energy metabolism.

Daily feed intake and the production of milk and milk constituents are derived by the following equations:

```
DMI  = INTGRL(0.0,FT)                    (dry matter intake, kg/d)
LACT = F182*28.525                       (milk lactose production, g/d)
MILK = LACT/48.0                         (milk production, kg/d)
FAT  = F183*(16.174+L179*12.682)/(1+L179)
                                         (milk fat production, g/d)
CFAT = FAT/MILK                          (milk fat content, g/kg)
PRO  = F60*89.384                        (milk protein production, g/d)
CPRO = PRO/MILK                          (milk protein content, g/kg)
```

Intake of feed dry matter is calculated by integration of the rate variable, FT, over 24 h. FT is the rate of dry matter intake and has the numerical value 0.0 or 3.3 kg dry matter per h depending on whether the cow is eating or not (see subsection 3.2.1 and subroutine REGUL1, Appendix 2).

The **production of lactose** is obtained from the rate of lactose secretion (R182):

F182 = INTGRL(0.0,R182).

At this stage the nutrient fluxes (mol/d) are calculated by multiplying the rates (mol/h) estimated previously by 24:

F182 = R182*24 = 2.105*24 = 50.520 mol C/d.

The conversion factor is calculated from the molecular weight (342.3) and the number of carbon atoms per mole (12):

LACT = F182*342.3/12 = 50.520*28.525 = 1441 g/d.

The **milk yield** is calculated on the assumption that the milk lactose concentration is constant (Davies et al. 1983). The content of lactose in milk is taken to be 48 g/kg as in the static model (Danfær 1983b):

MILK = LACT/48.0 = 1441/48.0 = 30.0 kg/d.

The rate of milk fat secretion is derived from the production rates of fatty acids (R179) and glycerol in milk fat (R181). The mass of milk fatty acids produced is given in subsection 3.3.4 as 1138.7 g/d, and the flux of milk fatty acids is: F179 = R179*24 =

70.405 mol C/d. The mass of fatty acids per mol C is then:

1138.7/70.405 = 16.174 g/mol C.

The molecular weights of glycerol and water are 92.094 and 18.016, respectively. Hence, the mass of glycerol per mol C corrected for loss of H_2O during esterification is:

92.094/3-18.016 = 12.682 g/mol C.

The rate of **production of milk fat** can now be obtained:

FAT = F179*16.174+F181*12.682
FAT = F179*(16.174+L179*12.682)
F183 = F179+F181 = F179*(1+L179)
F179 = F183/(1+L179)
F183 = R183*24 = 3.135*24 = 75.240 mol C/d
FAT = F183*(16.174+L179*12.682)/(1+L179)
= 75.240*(16.174+0.06863*12.682)/1.06863 = 1200 g/d
CFAT = FAT/MILK = 1200/30.0 = 40 g/kg.

The rate of **milk protein production** is calculated from the rate of protein secretion (R60). The mass of milk protein per g milk N is 6.38 g (Jenness 1974) and the atomic weight of N is 14.01:

F60 = R60*24 = 0.458*24 = 10.992 mol N/d
PRO = F60*14.01*6.38 = F60*89.384
= 10.992*89.384 = 983 g/d
CPRO = PRO/MILK = 983/30.0 = 33 g/kg.

The tissue energy balance and the live weight gain of the cow are calculated as follows:

```
EBAL = (F147-F152+F195-F197)*10.027/16+
       (F145-F151+F196-F198)*1.66/3+
       (F43-F46+F62-F63+F65-F66)*2.065  (energy balance, MJ/d)
GAIN = EBAL/25.0                        (live weight gain, kg/d)
```

The calculation of **tissue energy balance** is based on the retention of fat (fatty acids and glycerol) and protein in the liver and body tissues. The values for heat of combustion are: 10.027 MJ/mol fatty acid ($C_{16:0}$), 1.66 MJ/mol glycerol, and 2.065 MJ/mol N (Livesey 1984). The total energy balance is composed of energy balances in the pools of liver fat (C20), adipose tissue fat (C43), liver protein (A15), muscle protein (A21), and protein in other tissues (A23). The relevant nutrient fluxes are:

```
F147 = R147*24 = 0.0289*24 =  0.694 mol C/d
F152 = R152*24 = 0.116*24  =  2.784     -
F145 = R145*24 = 0.0018*24 =  0.043     -
F151 = R151*24 = 0.0072*24 =  0.173     -

F195 = R195*24 = 0.800*24  = 19.200     -
F197 = R197*24 = 1.453*24  = 34.872     -
F196 = R196*24 = 0.050*24  =  1.200     -
F198 = R198*24 = 0.091*24  =  2.184     -

F43 = R43*24 = 0.164*24 =     3.936 mol N/d
F46 = R46*24 = 0.164*24 =     3.936    -

F62 = R62*24 = 0.187*24 =     4.488    -
F63 = R63*24 = 0.205*24 =     4.920    -

F65 = R65*24 = 0.192*24 =     4.608    -
F66 = R66*24 = 0.203*24 =     4.872    -

EBAL = (-17.762)*10.027/16+(-1.114)*1.66/3+(-0.696)*2.065
                                        = -13.18 MJ/d.
```

The heat of combustion of **live weight gain** is assigned a value of 25.0 MJ/kg (Vermorel 1978):

GAIN = EBAL/25.0 = -13.18/25.0 = -0.527 kg/d.

Energy metabolism on a whole animal basis is expressed in terms comparable to results from traditional respiration experiments:

```
MAIN = 0.53*(0.90*(BW+GAIN/2))**0.67
                                (net energy requirement for
                                 maintenance, MJ/d)
MILKE = (LACT*16.527+FAT*38.116+PRO*24.518)/1000
                                (energy in milk, MJ/d)
GE = FGE                        (gross energy intake, MJ/d)
FE = FFE                        (faecal energy, MJ/d)
DE = GE-FE                      (digestible energy, MJ/d)
ME = DE*0.84                    (metabolizable energy, MJ/d)
MEE = (FCH111+FCH124)*0.89      (methane energy, MJ/d)
UE = DE-ME-MEE                  (urinary energy, MJ/d)
PRODE = MILKE+EBAL              (net energy for production, MJ/d)
HE = ME-PRODE                   (total heat production, MJ/d)
NE= MAIN+PRODE                  (net energy intake, MJ/d)
SFU = NE/7.89                   (net energy intake, SFU/d)
```

The **net energy requirement for maintenance** is calculated as the fasting metabolism related to empty body weight (ARC 1980): F = 0.53*W**0.67. Empty body weight (W) is estimated as 90% of the live weight, which in turn is calculated as the average of the initial weight (BW = 600 kg) and the final weight of the cow (BW+GAIN):

MAIN = 0.53*(0.90*599.74)**0.67 = 0.53*67.70 = 35.88 MJ/d.

The values for heat of combustion of milk lactose, milk fat, and milk protein are taken as 16.527, 38.116, and 24.518 kJ/g, respectively (Frederiksen 1931). Hence, **milk energy** is obtained as:

MILKE = (1441*16.527+1200*38.116+983*24.518)/1000 = 93.66 MJ/d.

The daily **intake of gross energy** is calculated by integration of the rate of gross energy intake (RGE = 13.596 MJ/h) estimated in subsection 3.3.1:

GE = FGE = INTGRL(0.0,RGE) = 13.596*24 = 326.30 MJ/d.

Faecal energy output is calculated in the same way from the rate of faecal energy loss (RFE = 4.114 MJ/h) estimated in subsection 3.3.2:

FE = FFE = INTGRL(0.0,RFE) = 4.114*24 = 98.74 MJ/d.

Digestible energy is:

DE = GE-FE = 326.30-98.74 = 227.56 MJ/d,

and **metabolizable energy** is assumed to be 84% of the digestible energy (Flatt 1966, Van Es 1978):

ME = DE*0.84 = 227.56*0.84 = 191.15 MJ/d.

The loss of **energy in methane** is derived from the methane production rates in ruminal (RCH111 = 0.917 mol C/h) and in hind gut (RCH124 = 0.092 mol C/h) fermentations. The heat of combustion of methane is 0.89 MJ/mol C according to a standard table (Handbook

of Chemistry and Physics, 54th ed. 1973-74):

MEE = (FCH111+FCH124)*0.89
= (0.917+0.092)*24*0.89 = 21.55 MJ/d.

Urinary energy output is obtained by difference:

UE = DE-ME-MEE = 227.56-191.15-21.55 = 14.86 MJ/d.

Net energy for production is the sum of energy in milk and the tissue energy balance:

PRODE = MILKE+EBAL = 93.66+(-13.18) = 80.48 MJ/d,

and the **total heat loss** from the animal is the difference between metabolizable energy and net energy for production:

HE = ME-PRODE = 191.15-80.48 = 110.67 MJ/d.

Net energy intake is the sum of the net energy used for maintenance and for production:

NE = MAIN+PRODE = 35.88+80.48 = 116.36 MJ/d.

Expressed in **Scandinavian Feed Units** (SFU) this is:

SFU = NE/7.89 = 116.36/7.89 = 14.75 SFU,

as 1 SFU is equivalent to the heat of combustion of 2.5 kg 4% fat corrected milk (Frederiksen 1931): 2.5 kg FCM = 1 SFU = 2.5*3.155 = 7.89 MJ.

It should be noted that the true net energy calculated here (SFU = 14.75) is less than the feed units (SFU = 16.0) estimated from the chemical compostition of the feed (see section 3.1). This discrepancy is related to the level of feed intake (Tyrrell & Moe 1975, Danfær 1983a).

In the last equations the energy terms estimated above are expressed as **percentages of the gross energy:**

FEPCT = 100*FE/GE =	30.3	(faecal energy, %)
DEPCT = 100*DE/GE =	69.7	(digestible energy, %)
MEEPCT = 100*MEE/GE =	6.6	(methane energy, %)
UEPCT = 100*UE/GE =	4.5	(urinary energy, %)
MEPCT = 100*ME/GE =	58.6	(metabolizable energy, %)
HEPCT = 100*HE/GE =	33.9	(heat energy, %)
PRODEP = 100*PRODE/GE =	24.7	(net energy for procudtion, %)
NEPCT = 100*NE/GE =	35.7	(net energy intake, %)

This percentage distribution of the gross energy intake is well within a range of experimental results from respiration trials on cows having milk yields from 11 to 40 kg 4% fat corrected milk (Coppock et al. 1964, Flatt 1966, Moe et al. 1966, Tyrrell et al. 1982a, Coppock 1985).

4 RESULTS OF MODEL SIMULATIONS

In this chapter the behaviour of the model, i.e. the simulation results will be presented. In section 4.1 the solutions of the dynamic model are compared to results from the static model (Hvelplund 1983, Danfær 1983b), which was the basis for the construction of the dynamic model (see section 3.1). Some comparisons with literature data are also made. Examples of simulated daily variations in rates of digestive and metabolic processes, in substrate pool sizes, and in affinity constants are given in section 4.2. The last section of the chapter is concerned with model stability.

4.1 Comparison of results from the dynamic and the static model

In the static model all rates of transaction are regarded to be constant within a day. This means that the outcomes of the static model are daily averages of the individual digestive and metabolic rates. These outcomes are compared to daily fluxes of matter computed by the dynamic model. The daily fluxes are flow rates integrated over 24 h describing the processes in the individual compartments of the model (subsections 4.1.1-4.1.3). Some of the results from the dynamic model are evaluated against literature data. These data are not included in the literature base which was used for development of the model.

The estimations of parameter values in the dynamic model are described in section 3.3. In order to obtain practically the same solutions from the dynamic and the static model many of these parameter values have been adjusted during repeated simulations. The adjustments are commented on in subsection 4.1.4.

In the following presentations the results from the dynamic model are means of 10 runs (run 26-35). The first 25 runs are regarded as a period of model equilibration, and are therefore discarded.

4.1.1 Feed intake, animal performance, and energy balance

The daily feed intake, milk production, and live weight gain of the model cow simulated by the dynamic and by the static model are given in Table 4.1. The stage of lactation of the cow is 44 days post partum as described in subsection 3.3.3.

The simulated results for feed intake and animal performance are almost identical in the two cases. The only difference worth mentioning is that the dynamic model gives a lower milk protein yield (983 g/d) than the static model (1020 g/d). The explanation of this is simply that different values for the molecular weight of protein bound amino acids in milk have been used, i.e. 116 in the dynamic (see subsection 3.3.4) and 120 in the static model.

Table 4.2 shows energy intake, energy losses, and energy balance of the model cow simulated by the dynamic and by the static model. There are hardly any differences between results from the 2 models.

Table 4.1. Daily feed intake, milk production, and live weight gain in a model cow simulated by the dynamic and by the static model.

Variable	Dynamic model	Static model
Feed intake, kg DM	18.0	17.9
Milk yield, kg	30.0	30.0
Milk lactose yield, g	1442	1440
Lactose in milk, g/kg	48.0	48.0
Milk fat yield, g	1204	1200
Fat in milk, g/kg	40.1	40.0
Milk protein yield, g	983	1020
Protein in milk, g/kg	32.7	34.0
Live weight gain,kg	-0.53	-0.51

Table 4.2. Energy balance in a model cow simulated by the dynamic and by the static model.

Variable	Dynamic model MJ/d	%	Static model MJ/d	%
Gross energy intake	327.9	100.0	327.5	100.0
Faecal energy	99.7	30.4	97.1	29.6
Digestible energy	228.2	69.6	230.4	70.4
Methane energy	21.5	6.5	20.7	6.3
Urinary energy	15.0	4.6	14.6	4.5
Metabolizable energy	191.7	58.5	195.1	59.6
Heat energy	111.0	33.9	113.4	34.6
Net energy for production	80.7	24.6	81.7	24.9
Energy in milk	93.8	28.6	94.5	28.8
Energy in tissue gain	-13.1	-4.0	-12.8	-3.9
Net energy for maintenance	35.8	10.9	35.5	10.8
Net energy intake	116.5	35.5	117.2	35.8

In the following subsections simulation results from the dynamic model will be presented in more detail. Not all nutrient fluxes, but some important ones describing digestion and absorption, liver metabolism, mammary gland metabolism, and body tissue metabolism are compared to the corresponding results from the static model.

A complete list of all fluxes of nutrients and metabolites simulated by the dynamic model is given in Appendix 9 together with results of the static model.

4.1.2 Digestion and absorption of nutrients

Simulated results of metabolism in the rumen compartment and in the intestinal compartment are shown in Tables 4.3 and 4.4, respectively (see figures 2.1-2.3 for identification of fluxes). The results of the dynamic model deviate very little (mostly below 1%) from the results of the static model. The absolute deviations do not exceed 1 mol/d of C or N in any of the cases where the relative deviation is more than 1%.

Table 4.3. Aspects of rumen metabolism simulated by the dynamic and by the static model.

Process	Dynamic model	Static model	Deviation[1] %
Carbon transactions, mol C/d			
Feed intake			
Sugar (FSU100)	141.0	140.3	0.5
Starch (FST100)	20.8	20.7	0.5
Cell wall carbohydrates (FCE100)	284.3	283.0	0.5
Lipids (FGL100+FLI100)	47.6	47.4	0.4
Protein-C degradation (F112-F109)	13.6	13.4	1.5
Passage to the small intestine			
Sugar (FSU107)	2.9	2.9	0.0
Starch (FST107+FST110)	3.7	3.2	15.6
Cell wall carbohydrates (FCE101+FCE107+FCE110)	163.0	161.7	0.8
Lipids (FLI101+FLI110)	57.8	56.9	1.6
Microbial fermentation			
Sugar (FSU106)	136.1	135.3	0.6
Starch (FST106)	19.8	19.5	1.5

1)Deviation of the dynamic model from the static model

(to be continued)

Table 4.3. (continued)

Process	Dynamic model	Static model	Deviation[1] %
Carbon transactions, mol C/d			
Cell wall carbohydrates (FCE106)	80.7	80.0	0.9
Protein-C (F114)	44.0	45.3	-2.9
Microbial fermentation products			
Acetate (FAC111)	101.6	101.5	0.1
Propionate (FPR111)	60.2	60.0	0.3
Butyrate (FBU111)	41.2	41.1	0.2
Methane (FCH111)	21.9	22.0	-0.5
Carbon dioxide (FCO111)	55.6	55.6	0.0
Microbial ATP production, mol/d (F108)	176.3	175.1	0.7
Nitrogen transactions, mol N/d			
Crude protein intake (F0)	36.7	36.6	0.3
Protein degradation (F6-F8)	23.9	23.8	0.4
Urea uptake (F55)	4.4	4.4	0.0
NH_3/NH_4^+ absorption (F16)	5.5	5.5	0.0

1)Deviation of the dynamic model from the static model

(to be continued)

Table 4.3. (continued)

Process	Dynamic model	Static model	Deviation[1] %
Nitrogen transactions, mol N/d			
Microbial N metabolism			
Net protein synthesis (F9-F12)	20.0	19.9	0.5
Peptides and amino acids (F10)	0.3	0.3	0.0
NH_3/NH_4^+ (F18)	0.1	0.1	0.0
Passage to the small intestine			
Undegraded feed protein (F5+F7)	12.8	12.8	0.0
Microbial crude protein (F19)	20.4	20.3	0.5
NH_3/NH_4^+ (F14)	2.4	2.4	0.0

1)Deviation of the dynamic model from the static model

Table 4.4. Aspects of intestinal metabolism simulated by the dynamic and by the static model.

Process	Dynamic model	Static model	Deviation[1] %
Carbon transactions, mol C/d			
Inflow to the small intestine			
Cell wall carbohydrates and indigestible fatty acids (F116)	167.7	165.8	1.1
Sugar and starch (F117)	7.6	7.1	7.0
Digestible fatty acids (F118)	52.1	51.8	0.6
Passage to the hind gut			
Cell wall carbohydrates and fatty acids (F119+F122)	172.9	171.0	1.1
Sugar and starch (F120)	0.7	0.7	0.0
Degraded protein-C (F127)	20.3	20.3	0.0
Microbial fermentation in the hind gut (F124)	39.9	39.5	1.0
Faecal excretion (F126)	154.0	152.5	1.0
Digestion in the small intestine			
Sugar and starch (F121)	6.5	6.4	1.6
Fatty acids (F123)	46.9	46.6	0.6

1)Deviation of the dynamic model from the static model

(to be continued)

Table 4.4. (continued)

Process	Dynamic model	Static model	Deviation[1] %
Carbon transactions, mol C/d			
Glucose metabolism in the intestinal wall (F129+F131)	3.1	3.1	0.0
Absorption from the small intestine			
Glucose (F130)	3.4	3.3	3.0
Triglycerides (F132)	49.8	49.5	0.6
Nitrogen transactions, mol N/d			
Inflow to the small intestine			
Indigestible dietary and microbial protein (F22)	8.7	8.6	1.2
Digestible dietary and microbial protein (F23)	24.4	24.4	0.0
NH_3/NH_4^+ from the rumen (F24)	2.5	2.5	0.0
Indigestible endogenous protein (F30)	0.4	0.4	0.0
Digestible endogenous protein (F31)	8.7	8.7	0.0
Passage to the hind gut			
Dietary and microbial protein, peptides and amino acids (F25+F26)	13.6	13.6	0.0

1)Deviation of the dynamic model from the static model

(to be continued)

Table 4.4. (continued)

Process	Dynamic model	Static model	Deviation[1] %
Nitrogen transactions, mol N/d			
Endogenous protein (F32+F33)	2.1	2.1	0.0
Urea uptake in the hind gut (F56)	4.3	4.1	4.9
Net protein degradation in the hind gut (F28-F36)	5.3	5.3	0.0
Faecal excretion of crude protein (F29)	10.4	10.4	0.0
Absorption from the intestines			
Amino acids (F40)	26.5	26.4	0.4
NH_3/NH_4^+ (F35+F37)	12.1	11.9	1.7

1)Deviation of the dynamic model from the static model

In order to obtain an overall picture of the efficiency of ruminal and intestinal digestions simulated by the dynamic model the following expressions have been calculated:

Intake of organic matter, kg/d

Carbohydrates:	(KSU+KST+KCE)*kg DM intake =	
	0.6816*17.985 =	12.26
Lipids:	(KGL+KLI)*kg DM intake =	
	0.0447*17.985 =	0.80
Protein:	(KC+KR)*kg DM intake =	
	0.1788*17.985 =	3.22
Total:		16.28

Fermentation of organic matter, kg/d

Carbohydrates:	(FSU105+FSU106)/LSU+(FST105+FST106)/LST+	
	(FCE105+FCE106)/LCE =	
	140.93/35.087+20.45/37.037+137.25/37.037 =	
	4.02+0.55+3.71 =	8.28
Lipids:	FLI105/LLI = 4.49/62.402 =	0.07
Protein:	(F6-F8)/LC = 23.88/11.423 =	2.09
Total:		10.44

Microbial organic matter, kg/d

Carbohydrates:	FST110/LST+FCE110/LCE =	
	3.30/37.037+15.97/37.037 =	0.52
Lipids:	FLI110/63.181 = 17.42/63.181 =	0.28
Protein:	(F10+F13)/LC = 20.29/11.423 =	1.78
Total:		2.58

True digestibility of organic matter in the rumen

100*10.44/16.28 = 64%

Apparent digestibility of organic matter in the rumen

100*(10.44-2.58)/16.28 =
100*7.86/16.28 = 48%

Absorption of VFA from the rumen, mol/d

Acetate:	FAC111/2 = 101.60/2 =	50.80
Propionate:	FPR111/3 = 60.18/3 =	20.06
Butyrate:	FBU111/4 = 41.19/4	10.30
Total:		81.16

Efficiency of VFA production in the rumen

Per kg organic matter fermented: 81.16/10.44 = 7.8 mol

Degradability of dietary protein

100*(F6-F8)/F0 =
100*23.88/36.73 = 65%

Efficiency of microbial protein synthesis

Synthesis of microbial crude protein:

F19/LC = 20.39/11.423 =

1.78 kg/d = 286 g N/d

Microbial cell DM:

1.78/0.511 = 3.48 kg/d

Y_{ATP} = microbial cell DM per mol ATP =

3480/F108 = 3480/176 = 19.7 g

Microbial N synthesized per:

kg organic matter apparently fermented: 286/7.86 = 36.4 g

kg organic matter truly fermented: 286/10.44 = 27.4 g

Amino acid-N apparently digested in the small intestine:

F23-(F26+F32+F33) =

24.48-7.09 = 17.39 mol N/d

100*17.39/24.48 = 71%

Amino acid-N truly digested in the small intestine

F27+F34 = 26.50 mol N/d

100*26.50/(F23+F41) =

100*26.50/33.59 = 79%

The model estimates given above for the digestibility of organic matter in the rumen, the efficiency of VFA production, the degradability of dietary protein, the efficiency of microbial protein

synthesis, and the digestibility of amino acids in the small intestine are all in good agreement with corresponding experimental values in the literature (Klooster & Boekholt 1972, Leng & Murray 1972, Nolan 1975, Satter & Roffler 1975, Smith et al. 1975, Mercer & Annison 1976, Armstrong et al. 1977, Roy et al. 1977, Smith 1979, Stern & Hoover 1979, Harrison & McAllan 1980, Sutton 1980, Madsen 1986).

4.1.3 Metabolism of absorbed nutrients

Metabolism in the liver

Aspects of liver metabolism simulated by the 2 models are given in Table 4.5 (see figure 2.5 for identification of fluxes). The rates of the listed liver processes simulated by the dynamic model differ very little from the results of the static model. In the few cases where the relative deviation is more than 1%, the absolute deviations are not higher than 0.4 mol/d of C or N.

The relative contributions to gluconeogenesis from the different substrates as simulated by the dynamic model are:

Propionate:	100*F136/F139 = 100*54.0/82.3 = 65.6%
Amino acids:	100*F142/F139 = 100*16.3/82.3 = 19.8%
Lactate and glycerol:	100*F144/F139 = 100*12.0/82.3 = 14.6%

Quantitatively, propionate is the most important substrate - as generally confirmed in the literature. The simulated contribution of propionate to the total glucose turnover rate is:

100*F136/(F130+F139) =
100*54.0/85.7 = 63.0%,

which is close to an in vivo estimate of 61% (Wiltrout & Satter 1972).

In vivo estimates of the significance of amino acids as substrates for gluconeogenesis differ widely from different authors using different experimental approaches. Boekholt (1976) and Bruckental et al. (1980) concluded that 0-2% of the total glucose turnover could be derived from amino acids. At the other extreme Black et al. (1968) and Lomax & Baird (1983) estimated that amino acids could contribute to at least 35% of the glucose synthesis. The amino acid contribution of 20% simulated by the model falls in the middle of this range and is in line with an estimate by Elliot (1976).

The simulated partitioning of propionate and amino acids (keto acids) between gluconeogenesis and oxidation is as follows:

Propionate to glucose:	100*F136/F133 = 100*54.0/74.1	= 72.9%
Propionate to CO_2:	100*F137/F133 = 100*20.1/74.1	= 27.1%
Amino acids to glucose:	100*F142/(F142+F143) =	
	100*16.3/27.0 =	60.4%
Amino acids to CO_2:	100*F143/(F142+F143) =	
	100*10.7/27.0 =	39.6%

It is difficult to confirm these figures since information in the literature about liver oxidation of propionate and amino acids is scarce (Elliot 1980), but the estimated proportion of propionate used for oxidation is probably not too high (Annison & Armstrong 1970, Young 1977).

Table 4.5. Aspects of liver metabolism simulated by the dynamic and by the static model.

Process	Dynamic model	Static model	Deviation[1] %
Carbon transactions, mol C/d			
Uptake in the liver			
Propionate (F133)	74.1	73.8	0.4
Lactate and glycerol (F164+F168)	13.2	13.2	0.0
Fatty acids (F165+F169)	34.3	34.3	0.0
Gluconeogenesis from			
Propionate (F136)	54.0	54.1	-0.2
Keto acids (F142)	16.3	16.3	0.0
Lactate and glycerol (F144)	12.0	12.0	0.0
Lipid synthesis			
Depot fat (F145+F147)	0.7	0.7	0.0
Lipoproteins (F146+F148)	22.1	22.1	0.0
Lipolysis of depot fat (F151+F152)	2.9	2.9	0.0
Synthesis of ketone bodies and acetate (F149)	13.8	13.8	0.0

1)Deviation of the dynamic model from the static model

(to be continued)

Table 4.5. (continued)

Process	Dynamic model	Static model	Deviation[1] %
Carbon transactions, mol C/d			
Oxidations			
Propionate (F137)	20.1	19.7	2.0
Butyrate (F138)	4.4	4.4	0.0
Keto acids (F143)	10.7	10.3	3.9
Fatty acids (F150)	1.8	1.8	0.0
Outflow from the liver			
Glucose (F139)	82.3	82.4	-0.1
Triglycerides (F153)	22.1	22.1	0.0
Ketone bodies and acetate (F154)	13.8	13.8	0.0
Nitrogen transactions, mol N/d			
Uptake in the liver			
Amino acids from portal blood (F40)	26.5	26.4	0.4
Amino acids from arterial blood (F54)	9.8	9.8	0.0
NH_3/NH_4^+ (F16+F35+F37)	17.7	17.4	1.7

1)Deviation of the dynamic model from the static model

(to be continued)

Table 4.5. (continued)

Process	Dynamic model	Static model	Deviation[1] %
Nitrogen transactions, mol N/d			
Protein turnover			
Synthesis (F43)	4.0	3.9	2.6
Breakdown (F46)	4.0	3.9	2.6
Net amino acid catabolism (F45-F47)	7.1	7.0	1.4
Urea synthesis (F48)	24.7	24.4	1.2
Outflow from the liver			
Amino acids (F44)	29.2	29.2	0.0
Urea (F49)	24.8	24.4	1.6
Urea excretion in the urine (F57)	16.1	15.9	1.2

1)Deviation of the dynamic model from the static model

The rate of urea synthesis simulated by the model (F48) is 24.7 mol N/d equivalent to 12.4 mol urea/d. This value can be compared to results from the study of Bruckental et al. (1980). They estimated the average irreversible loss rate of urea as 8 mol urea/d in 3 cows at 8-9 weeks post partum producing 28 kg milk/d. These cows, however, had a lower protein intake (2364 g crude protein/d) than the model cow (3216 g crude protein/d). The urea-N is derived partly from absorbed NH_3/NH_4^+ (F16+F35+F37) and partly from catabolized amino acids (F45-F47). The proportion contributed by amino acid catabolism in the liver is: (F45-F47)/F48 = 7.09/24.75 = 0.29, exactly as estimated by Nolan (1975).

Metabolism in the mammary gland

The simulations of mammary gland metabolism are listed in Table 4.6 (see figure 2.6 for identification of fluxes). As in the previous subsections there are practically no differences between results from the dynamic and the static model.

Glucose taken up by the mammary gland is used for synthesis of lactose and glycerol-P as well as for oxidation - mainly in the pentose phosphate cycle (Smith 1971, Chaiyabutr et al. 1980). The simulated partitioning of glucose between these pathways is as follows:

Lactose synthesis:	100*F177/F160 = 100*50.5/68.6 =	73.6%
Glycerol synthesis:	100*F176/F160 = 100*1.8/68.6 =	2.6%
Oxidation:	100*F178/F160 = 100*16.3/68.6 =	23.8%

This distribution of the glucose consumption in the mammary gland is very similar to that found by Annison & Linzell (1964) and by Smith (1971). In other studies with lactating cows it was found that 72-83% of glucose taken up by the udder was secreted as lac-

tose (Annison et al. 1974, Bickerstaffe et al. 1974, Peeters et al. 1979, Williams & Elliot 1980).

Some aspects of energy metabolism in the mammary gland can be calculated from the model simulations for comparison with literature data:

Nutrient uptake in the udder

Acetate and ketone bodies (F156):	38.3	MJ/d
Glucose (F160):	32.1	-
Fatty acids (F172A):	30.7	-
Glycerol (F172B):	1.7	-
Amino acids (F51):	24.1	-
Total energy uptake:	126.9	MJ/d
Energy secreted in milk:	93.8	-
Heat production:	33.1	-

The proportion of total energy uptake secreted in the milk is: 100*93.8/126.9 = 74% as estimated by Linzell (1974).

The individual substrates are oxidized at different proportions of their uptakes:

	Mol CO_2/d	% of total CO_2	% of uptake	MJ/d
Acetate and ketone bodies (F175):	55.9	72.6	67.9	26.0
Glucose (F178):	16.3	21.2	23.8	7.6
Fatty acids (F180):	4.8	6.2	6.4	3.0
Total:	77.0	100.0		36.6

Table 4.6. Aspects of mammary gland metabolism simulated by the dynamic and by the static model.

Process	Dynamic model	Static model	Deviation[1] %
Carbon transactions, mol C/d			
Uptake in the mammary gland			
Acetate and ketone bodies (F156)	82.3	82.1	0.2
Glucose (F160)	68.6	68.6	0.0
Fatty acids (F172A)	49.0	48.8	0.4
Glycerol (F172B)	3.1	3.0	3.3
Syntheses			
Fatty acids (F174)	26.4	26.4	0.0
Glycerol (F176)	1.8	1.8	0.0
Milk fat (F179+F181)	75.5	75.2	0.4
Lactose (F177)	50.5	50.5	0.0
Oxidations			
Acetate and ketone bodies (F175)	55.9	55.7	0.4
Glucose (F178)	16.3	16.3	0.0
Fatty acids (F180)	4.8	4.8	0.0

1)Deviation of the dynamic model from the static model

(to be continued)

Table 4.6. (continued)

Process	Dynamic model	Static model	Deviation[1] %
Carbon transactions, mol C/d			
Secretion of milk components			
Lactose (F182)	50.5	50.5	0.0
Fat (F183)	75.5	75.2	0.4
Nitrogen transactions, mol N/d			
Amino acid uptake (F51)	11.0	11.0	0.0
Milk protein synthesis (F59)	11.0	11.0	0.0
Protein secretion (F60)	11.0	11.0	0.0

1)Deviation of the dynamic model from the static model

The difference between the calculated heat energy output (33.1 MJ/d) and energy in the oxidized nutrients (36.6 MJ/d) is due to a conservation of energy in NADPH produced by oxidation of glucose and acetate and used in fatty acid synthesis (Bauman & Davis 1975).

The estimated proportion of acetate and ketone bodies which is oxidized (68%) is much higher than that found for acetate alone by Bickerstaffe et al. (1974) in lactating cows (av. 29%, range 11-57%). In the same study the proportion of glucose oxidized in the udder was 11% (range 4-17%), which is considerably lower than estimated by the model (24%).

The oxidation of acetate and glucose has been found to contribute 50-60% of total CO_2 production in the mammary gland of lactating cows (Bickerstaffe et al. 1974) and rather more in lactating goats (Annison & Linzell 1964). The much higher contribution to CO_2 from acetate, ketone bodies and glucose (94%) estimated by the model cannot be accounted for by oxidation of ketone bodies, which seems to be low, at least in fed animals (Smith et al. 1983). Instead, these authors concluded that the deficit from the oxidation of acetate and glucose to total CO_2 production could be covered by amino acid oxidation.

Metabolism in body tissues

The metabolism simulated by the 2 models in muscle tissue, adipose tissue, and other tissues is shown in Tables 4.7, 4.8 and 4.9, respectively (see figure 2.6 for identification of fluxes). All deviations of the dynamic model from the static model are well below 1%.

Table 4.7. Aspects of muscle tissue metabolism simulated by the dynamic and by the static model.

Process	Dynamic model	Static model	Deviation %
Nitrogen transactions, mol N/d			
Carbon transactions, mol C/d			
Uptake in muscle tissue			
Acetate and ketone bodies (F157)	13.90	13.86	0.3
Glucose (F161)	10.45	10.43	0.2
Fatty acids (F166)	12.03	12.00	0.3
Amino acid-C degradation (F184)	3.40	3.41	-0.3
Oxidations			
Acetate and ketone bodies (F185)	17.30	17.27	0.2
Glucose to lactate (F186)	9.85	9.83	0.2
Glucose to CO_2 (F187)	0.60	0.60	0.0
Fatty acids (F188)	12.03	12.00	0.3
Outflow of lactate (F189)	9.85	9.83	0.2
Nitrogen transactions, mol N/d			
Amino acid uptake (F52)	4.48	4.48	0.0

1)Deviation of the dynamic model from the static model

(to be continued)

Table 4.7. (continued)

Process	Dynamic model	Static model	Deviation[1] %
Nitrogen transactions, mol N/d			
Protein turnover			
Synthesis (F62)	4.49	4.48	0.2
Breakdown (F63)	4.90	4.90	0.0
Amino acid outflow (F61)	4.89	4.90	-0.2

1)Deviation of the dynamic model from the static model

Table 4.8. Aspects of adipose tissue metabolism simulated by the dynamic and by the static model.

Process	Dynamic model	Static model	Deviation[1] %
Carbon transactions, mol C/d			
Uptake in adipose tissue			
Acetate and ketone bodies (F158)	33.13	33.05	0.2
Glucose (F162)	4.59	4.58	0.2
Fatty acids (F173A)	6.96	6.97	-0.1
Glycerol (F173B)	0.44	0.44	0.0
Syntheses			
Fatty acids (F190)	16.03	16.00	0.2
Glycerol (F192)	1.20	1.20	0.0
Oxidations			
Acetate and ketone bodies (F191)	17.11	17.05	0.4
Glucose (F193)	3.39	3.38	0.3
Lipid turnover			
Synthesis (F195+F196)	20.41	20.40	0.0
Breakdown (F197+F198)	37.06	37.05	0.0

1)Deviation of the dynamic model from the static model

(to be continued)

Table 4.8. (continued)

Process	Dynamic model	Static model	Deviation[1] %
Carbon transactions, mol C/d			
Outflow from adipose tissue			
Fatty acids (F194)	38.65	38.64	0.0
Glycerol (F199)	2.62	2.62	0.0

1)Deviation of the dynamic model from the static model

Table 4.9. Aspects of other tissue metabolism simulated by the dynamic and by the static model.

Process	Dynamic model	Static model	Deviation[1] %
Carbon transactions, mol C/d			
Uptake in other tissues			
Acetate and ketone bodies (F159)	24.54	24.47	0.3
Glucose (F163)	2.04	2.04	0.0
Fatty acids (F167)	4.01	4.00	0.3
Oxidations			
Acetate and ketone bodies (F200)	24.54	24.47	0.3
Glucose (F201)	2.04	2.04	0.0
Fatty acids (F202)	4.01	4.00	0.3
Nitrogen transactions, mol N/d			
Amino acid uptake (F53)	4.62	4.62	0.0
Protein turnover			
Synthesis (F65)	4.63	4.62	0.2
Breakdown (F66)	4.91	4.90	0.2
Amino acid outflow (F64)	4.90	4.90	0.0

1)Deviation of the dynamic model from the static model

The partitioning of available nutrients between the mammary gland and the body tissues is a major factor in determining animal performance, in terms of level of milk yield and rate of live weight change. The simulated uptakes of nutrients (acetate and ketone bodies, glucose, fatty acids, and amino acids) in the different compartments of the model cow (digestive tract, liver, body tissues, and mammary gland) are shown in Table 4.10. The total amounts of available nutrients are those delivered to the peripheral circulation, except for amino acids which are calculated as the sum of absorbed (F40) and mobilized amino acids (F61+F64). This implies that the amino acid uptake in the liver from the peripheral blood is calculated as the net uptake (F40+F54-F44) and not the actual uptake (F54) (see figure 2.5).

The model estimates of mammary uptake of the different nutrients in relation to their total availability are:

Acetate and ketone bodies:	49%
Glucose:	80%
Fatty acids:	46%
Amino acids:	30%

These figures illustrate clearly the dominant impact of the mammary gland on nutrient utilization in the high-yielding cow.

Experimental data also show a high mammary uptake of glucose, but not of acetate. In cows with low to moderate milk yields (12-25 kg/d) Bickerstaffe et al. (1974) found that the udder uptake of acetate and of glucose varied from 5 to 23% and from 37 to 87%, respectively, of the total entry rates of these nutrients. In cows fed low or high roughage diets and yielding 17-29 kg milk/d the mammary gland extracted 6-16% of total acetate, and 41-92% of total available glucose (Annison et al. 1974). Thilsted (1980) has

Table 4.10. Nutrient partitioning between compartments of the model cow.

Compartment	Acetate and ketone bodies Mol C/d	%	Glucose Mol C/d	%	Fatty acids Mol C/d	%	Amino acids Mol N/d	%
Dig. tract	15.43	9.1	-	-	-	-	-	25.1
Liver	-	-	-	-	34.32	32.3	7.09	19.5
Muscle, adipose and other tissues	71.56	42.3	17.08	19.9	22.99	21.6	9.09	25.1
Mammary gland	82.34	48.6	68.59	80.1	49.00	46.1	11.00	30.3
Total available	169.33	100.0	85.67	100.0	106.31	100.0	36.30	100.0

estimated that the mammary gland utilized 70-100% of the glucose flux rate in early lactating cows having milk yields from 21 to 34 kg/d.

Of the listed nutrients amino acids are taken up by the mammary gland in the smallest amount (30%) relative to their total availability. The 70% taken up by extra-mammary tissues is distributed almost evenly among the digestive tract, the liver, and the body tissues. It is difficult to find literature data for a direct evaluation of these figures. However, a term called EPU introduced by Oldham (1978) to express the efficiency of protein utilization can be calculated from the model simulations. EPU is defined as the ratio: protein products/protein supply. When the body protein balance is zero or negative, the only protein product is milk protein. The protein supply is then calculated as milk protein + catabolized protein converted to urea (Oldham 1978):

EPU = milk protein-N/(milk protein-N + catabolized protein-N in urea).

This is easily derived from the model (see figures 2.5 and 2.6, and Table 4.5):

EPU = F60/(F60+F45-F47) = 11.00/(11.00+7.09) = 0.61.

This simulated value of EPU is exactly as estimated by Bruckental et al. (1980) in their cows yielding 28 kg milk/d 8-9 weeks post partum.

4.1.4 Adjustment of parameters

The assignment of numerical values to the equation parameters, i.e. pool sizes, rate constants, affinity constants, maximal rates etc., is described in subsections 3.3.1-3.3.4. Most of these parameter values have been changed to some extent during repeated simulations in order to achieve close agreement between solutions of the dynamic model and those of the static model. The outcome of this endeavour has been presented in the foregoing subsections.

The original parameter values derived from the literature or otherwise estimated are listed together with the finally adjusted values in Appendices 5-8. From these Tables it can be seen which parameter values have been critically altered (more than 100%) by the adjustments. Those parameters are given in Table 4.11.

It should be noticed that the numerical value of the parameters which are labelled with *) in Table 4.11 (i.e. nutrient pools and regulated affinity constants) can vary during each run of the model. This means that the initial value of these parameters can be very different from the "average" value during a run, depending on how the particular parameter is fluctuating in the course of the run (see next section 4.2). The original numerical values are estimated as if the model was a static one and are therefore to be regarded as "average" values.

For this reason the adjustments of the parameters K106, A3, N1B, K128 and C12 are not real changes from their first estimation. The values of some other constants (G, K9, KATP, K15 and K45) have been adjusted because other parameters in their respective equa-

Table 4.11. Critical adjustments of parameter values in the dynamic model.

Parameter or state variable	Symbol	Numerical value Original[1)]	Final[2)]
Rumen compartment			
Affinity constant for carbohydrate fermentation	K106	9.270	2.50*)
Cell wall fermentation rate factor	G	0.04	0.0006
Microbial amino acids and peptides	A3	0.140	0.001*)
Affinity constant for microbial protein synthesis	K9	0.0068	0.001
Affinity constant	KATP	0.1483	0.07
Microbial NH_3/NH_4^+	N1B	0.026	0.11652*)
Affinity constanty for microbial uptake of NH_3/NH_4^+	K15	0.002	0.189
Intestinal compartment			
Affinity constant for acetate and ketone body oxidation	K128	0.00156	$1*10^{-6}$*)
Glucose in intestinal wall	C12	0.086	0.02556*)
Liver compartment			
Propionate in liver tissue	C14	0.021	0.1846*)
Affinity constant for glucose synthesis from propionate	K136	0.032	0.1610*)

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Table 4.11. (continued)

Parameter or state variable	Symbol	Numerical value Original[1]	Final[2]
Liver compartment			
Affinity constant for propionate oxidation	K137	0.008	0.0463*)
Keto acids in liver tissue	C17	0.02	0.1168*)
Affinity constant for glucose synthesis from keto acids	K142	0.0467	0.2315*)
Affinity constant for keto acid oxidation	K143	0.02	0.1155*)
Free fatty acids in liver tissue	C19	0.030	0.1684*)
Affinity constant for liver fat synthesis	K147	0.270	1.391
Affinity constant for lipoprotein synthesis	K148	0.0075	0.0386
Affinity constant for acetate and ketone body synthesis	K149	0.10	0.513
Affinity constant for fatty acid oxidation	K150	0.02	0.1430
Affinity constant for amino acid deamination	K45	0.0202	0.0655
NH_3/NH_4^+ in liver tissue	N3	0.0006	0.04838*)
Affinity constant for amino acid synthesis	K47	0.00032	0.05755
Affinity constant for urea synthesis	K48	0.00027	0.024*)

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Table 4.11. (continued)

Parameter or state variable	Symbol	Numerical value Original[1]	Final[2]
Extracellular fluid compartment			
Independent part of rate constant for acetate and ketone body uptake in the mammary gland	L156	0.0	-441.730
Dependent part of rate constant for acetate and ketone body uptake in the mammary gland	M156	47.538	83.128
Independent part of max. rate of glucose uptake in the mammary gland	L160	0.0	-6.4605
Dependent part of max. rate of glucose uptake in the mammary gland	M160	0.3288	0.8491
Dependent part of max. rate of fatty acid and glycerol uptake in adipose tissue from lipoproteins	M171B	0.903	0.2028
Independent part of max. rate of amino acid uptake in the mammary gland	L51	0.0	-1.4889
Dependent part of max. rate of amino acid uptake in the mammary gland	M51	0.059	0.1790

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

tions are fluctuating. An example of this is the rate of microbial protein synthesis:

```
R9 = R9M*A3/(K9+A3)
R9M = YATP*M9*(R108+R115)
YATP = YATPM*A2*N1A/(KATP+A2*N1A).
```

The values of A3, R108, A2 and N1A fluctuate strongly, and therefore it was not possible to calculate in advance the constant values of K9 and KATP with which a given microbial synthesis rate (R9) will be obtained.

The original pool sizes of C14, C17, C19 and N3 in the liver compartment were so small in relation to their turnover rates, that they became unstable and had to be increased. Consequently, the affinity constants for the processes which use these pools as substrates (K136, K137, K142, K143, K147, K148, K149, K150, K47 and K48) have also been adjusted to higher values.

The last group of parameters in Table 4.11 (L156, M156, L160, M160, M171B, L51 and M51) are all related to nutrient uptake in the mammary gland and in adipose tissue, i.e. to nutrient partitioning. The change in these parameters was a nescessity for the ability of the model to simulate animal performances at different lactational stages in a realistic way. Unfortunately, the adjustments have resulted in some negative parameter values which have no biological meaning, e.g. the maximal rate of glucose uptake in the mammary gland:

```
R160M = L160+M160*GH = -6.46+0.85*GH.
```

If GH (plasma growth hormone concentration) is lower than 6.46/0.85 = 7.6 ng/ml, then the maximal rate (R160M) will be nega-

tive and therefore meaningless.

Some of the parameters in Table 4.11 (K15, K128, C14, K136, K137, C17, C19, K148, K150, K45, N3 and K47) have been altered in such a way by the adjustments that they can no longer be regarded as derived from the literature. But apart from these parameters and those with negative values the vast majority of the adjusted parameter values are in no conflict with the scientific data and the assumptions used for their original estimation.

4.2 Diurnal variations of substrate pool sizes, affinity factors, and rates of transaction

In the previous section (4.1) the simulated transactions of matter are presented only as daily fluxes which show nothing of the dynamic behaviour of the model. One advantage of a dynamic model is that it presents the possibility of simulating, for instance, metabolic responses to short term variations in nutrient supply or other regulatory factors. This is illustrated in the following subsections by examples of within run variations of pool sizes, rates, and regulated affinity factors in the different compartments of the model. A run means a 24 h period to the model cow.

The examples chosen for presentation are from the rumen compartment (figures 4.1-4.19), the intestinal compartments (figures 4.20-4.25), the liver compartment (figures 4.26-4.30), the peripheral blood compartment (figures 4.31-4.41), and the mammary gland and body tissue compartments (figures 4.42-4.47).

4.2.1 The rumen compartment

Figure 4.1 shows the rate of feed intake during the day simulated by the dynamic model. The feed intake is represented by the rate variable R100 which is the rate of carbohydrate and lipid intake (mol C/h). The day starts at midnight.

The model cow eats her daily ration in 8 meals. The time for, and the length of, each meal is determined by the amount of unfermented organic matter in the rumen, except for the time interval between 1 and 5 h in which the cow does not eat (see subsection 3.2.1). The total eating time is 5.45 h and the interval between meals is about 2 h, apart from the night pause. This simulated eating behaviour resembles experimental findings of Tibor (1980), Blum et al. (1985) and Krohn & Konggaard (1987).

The processes in the rumen are clearly affected by the pattern of feed intake. Pool sizes of fermentable carbohydrates change almost in parallel to variations in feed intake with peaks occurring at the end of each meal (figures 4.2-4.4). The easily fermentable carbohydrates, sugar and starch, almost disappear from the rumen fluid between meals (figure 4.2), while the pool of cell wall carbohydrates does not fluctuate to the same extent and only becomes really low just before the first morning meal at 5 h (figure 4.3).

The alterations in the amount of fermentable carbohydrates (C2) will in turn affect the affinity factor (K106) for carbohydrate fermentation (see subsection 3.2.1). When C2 increases to or beyond a certain value (C2MX = 42) then K106 is decreased, and when C2 decreases to or below a certain value (C2MN = 30.25), K106 is increased. A decrease in the value of K106 will increase, and an

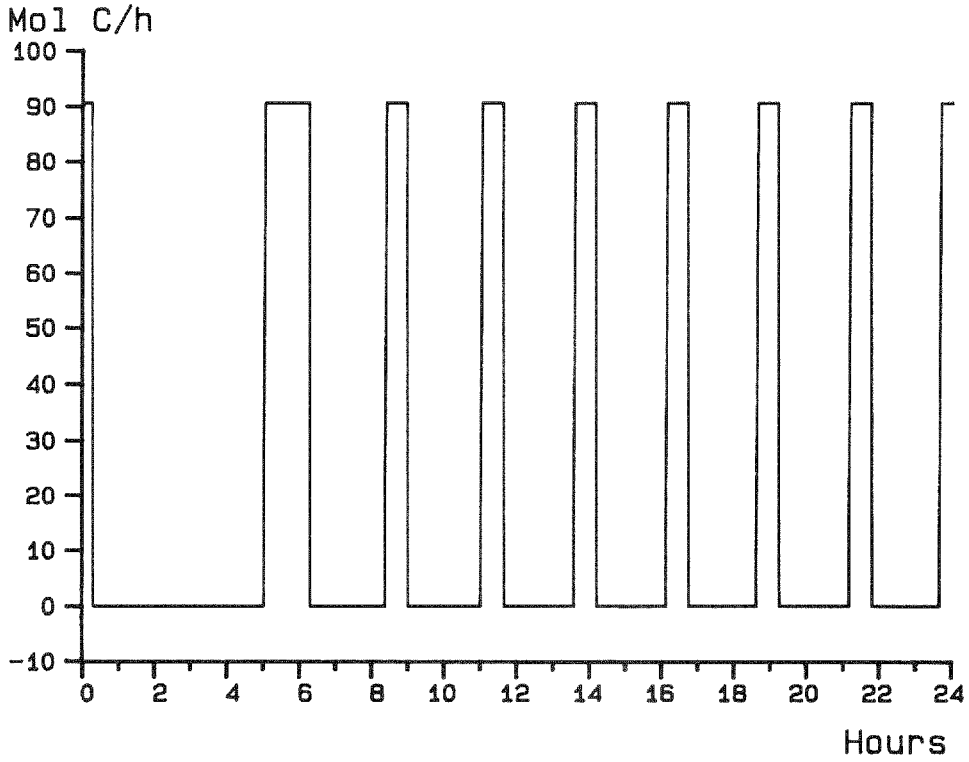


Figure 4.1. Simulated rate of feed intake of carbohydrates and lipids during the day (R100).

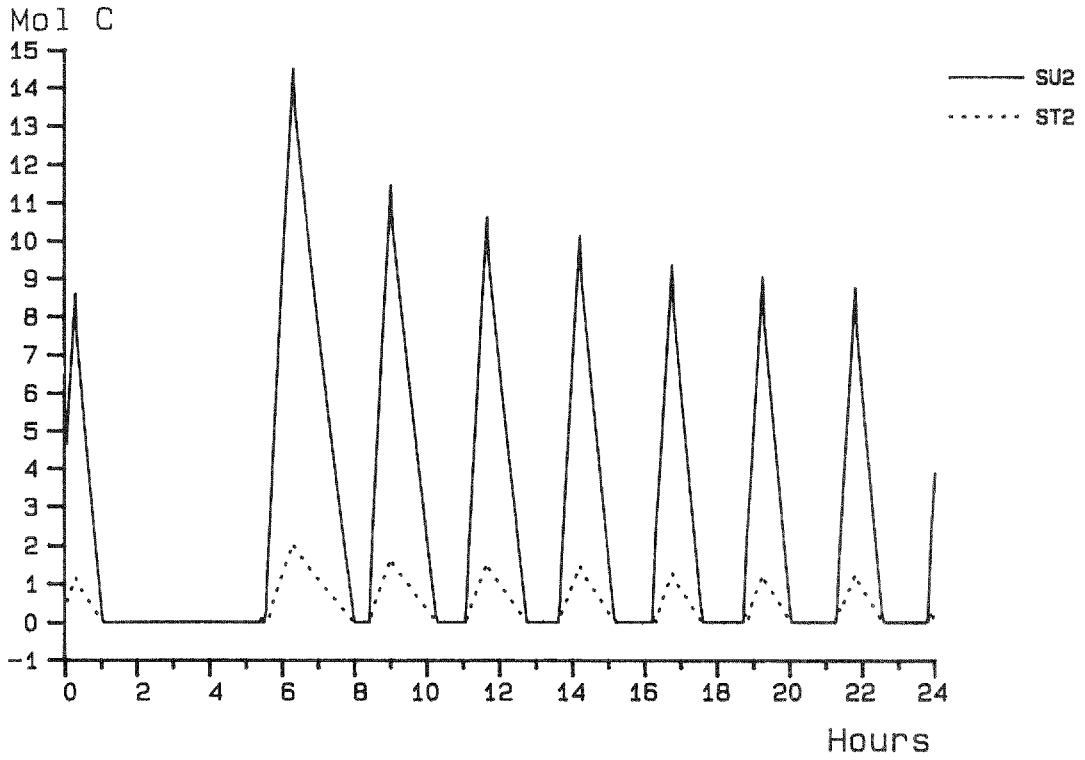


Figure 4.2. Simulated diurnal variations of rumen pool sizes of fermentable sugar (SU2) and starch (ST2).

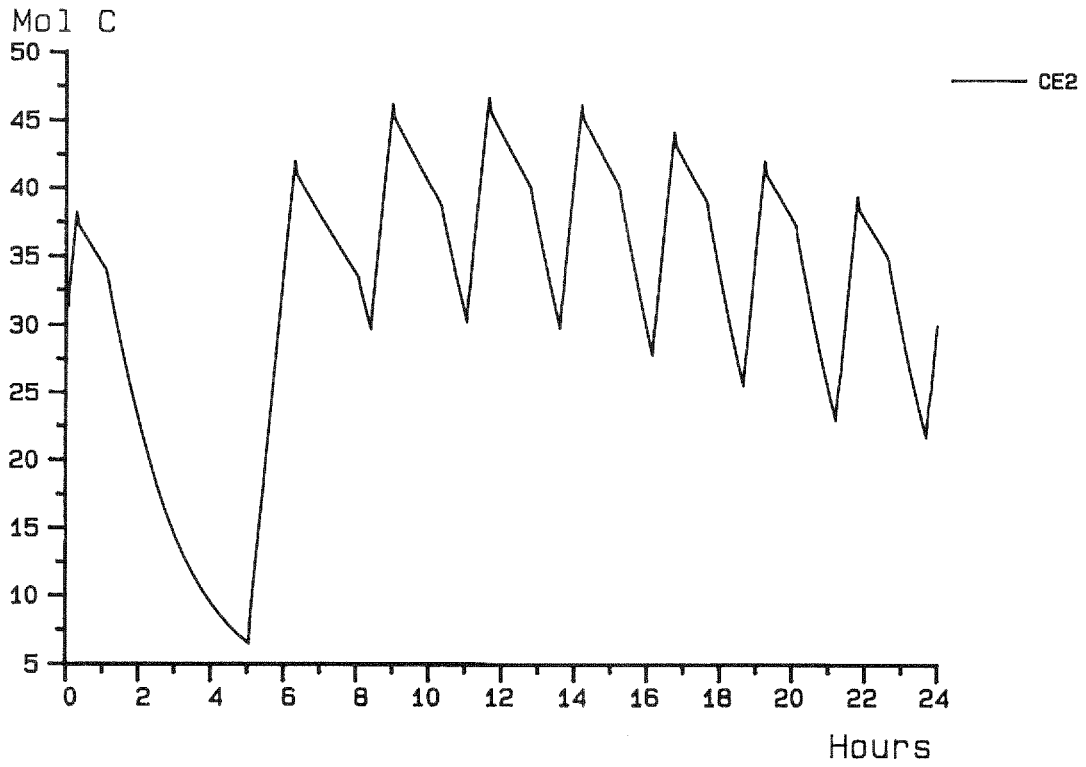


Figure 4.3. Simulated diurnal variation of the rumen pool size of fermentable cell wall carbohydrates.

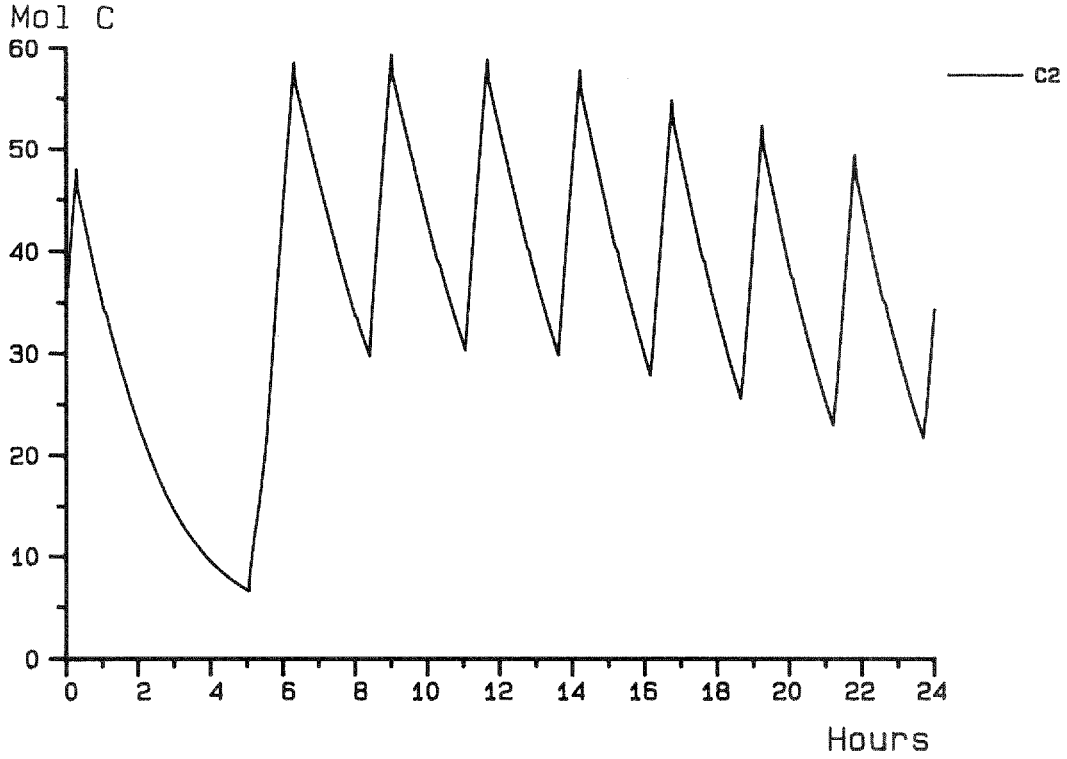


Figure 4.4. Simulated diurnal variation of the rumen pool size of fermentable carbohydrates.

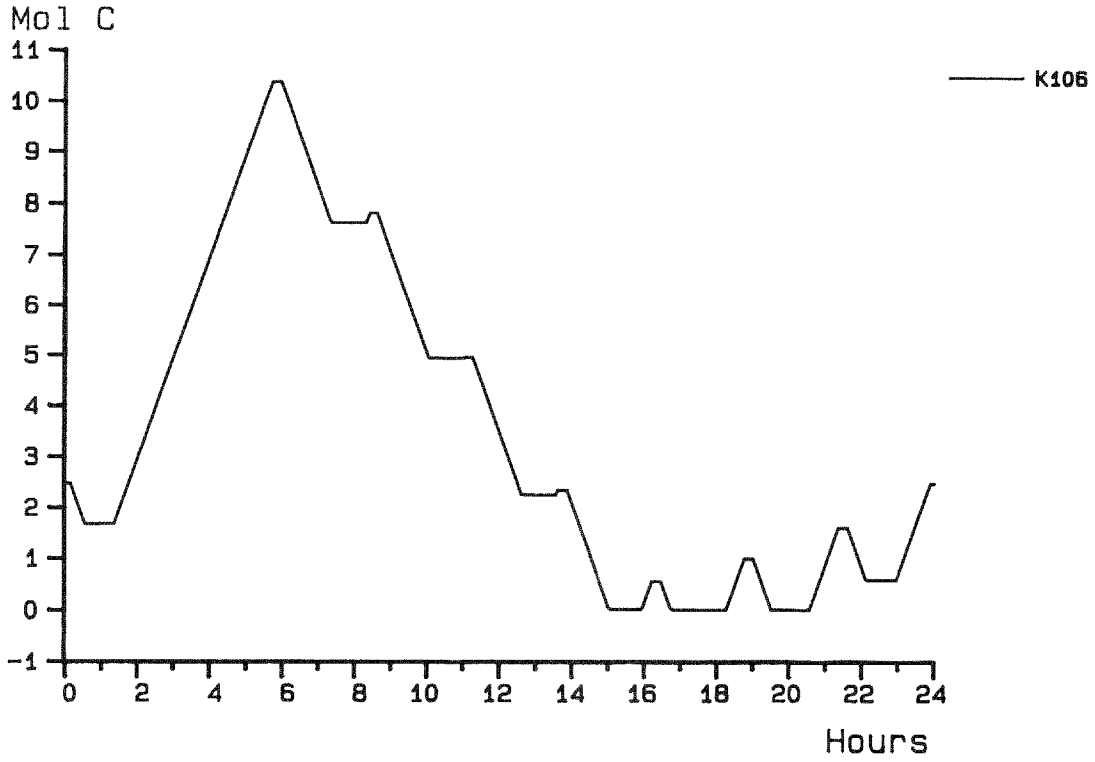


Figure 4.5. Simulated diurnal variation of the affinity factor for carbohydrate fermentation in the rumen.

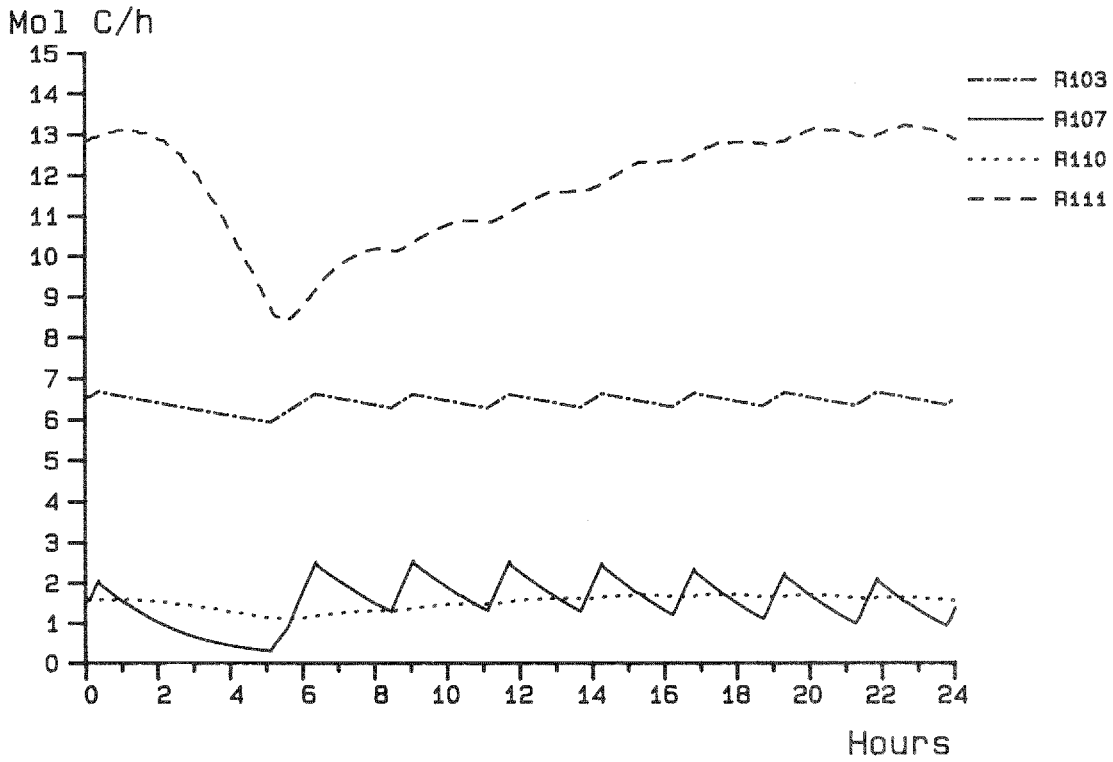


Figure 4.6. Simulated diurnal variations of rumen outflow rates of unfermentable carbohydrates and lipids (R103), fermentable carbohydrates (R107), microbial carbohydrates and lipids (R110) and fermentation products (R111).

increase in K106 will decrease the fermentation rate (R106). Figure 4.5 shows that the variations in the value of K106 follow this principle, a consequence of which is that the decrease in C2 between 0.5 and 5 h becomes curvilinear (figure 4.4).

Outflow rates of carbohydrates, lipids and fermentation end-products are depicted in figures 4.6-4.7. The rate of ATP formation is shown in figure 4.8. All rates seem to be affected by the variations in feed intake during the day, but the rate of microbial matter outflow (R110) varies only little. The production of acetate (RAC111) occurs without distinct peaks at the times of feed intake, which is not the case with the other fermentation products (figure 4.7). It can further be observed that when the rate of propionate production (RPR111) has peaks, production rates of butyrate (RBU111), methane (RCH111) and carbon dioxide (RCO111) have valleys - and vice versa.

A typical pattern of simulated daily variations of rumen pools is also seen in A2, fermentable protein, peptides and amino acids in rumen liquor, while A4, the pool of microbial protein, is relatively constant (figure 4.9).

Figure 4.10 shows how the affinity factor for microbial uptake of amino acids and peptides (K6) is regulated by the size of the substrate pool A2, which in turn is regulated by variations in the rate R6. These variations (figure 4.11) are therefore both a mean and a result in the regulation of the substrate pool size.

Variations in outflow rates of unfermentable protein (R5) and fermentable protein (R7) are shown in figure 4.11. Both R5 and R7 are calculated as fixed proportions of their respective substrate pool

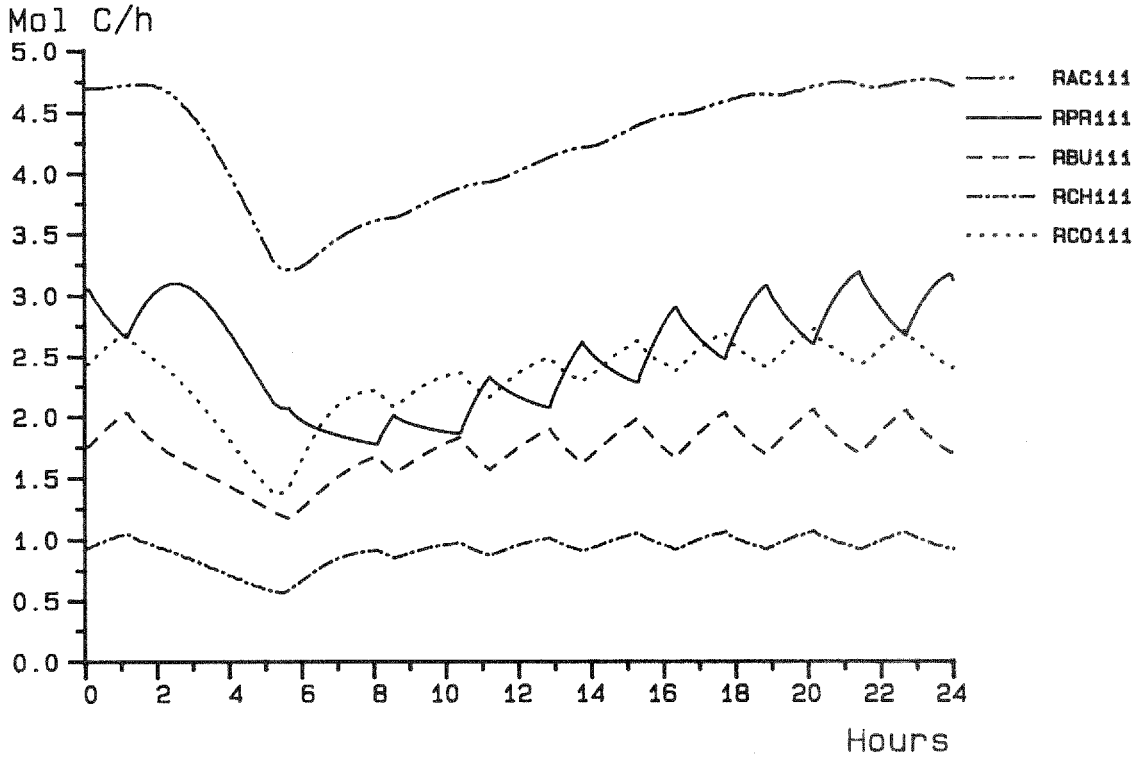


Figure 4.7. Simulated diurnal variations of absorption rates of acetate (RAC111), propionate (RPR111) and butyrate (RBU111), and outflow rates of methane (RCH111) and carbon dioxide (RCO111) from the rumen.

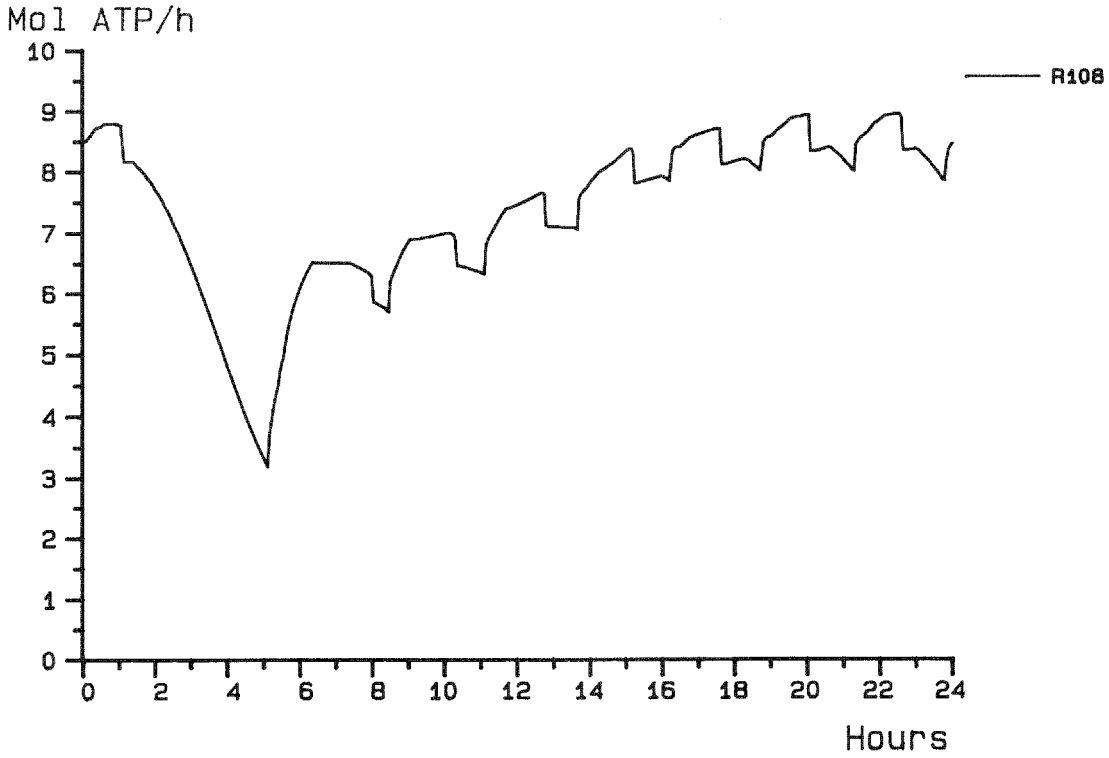


Figure 4.8. Simulated diurnal variation of the rate of ATP formation in the rumen.

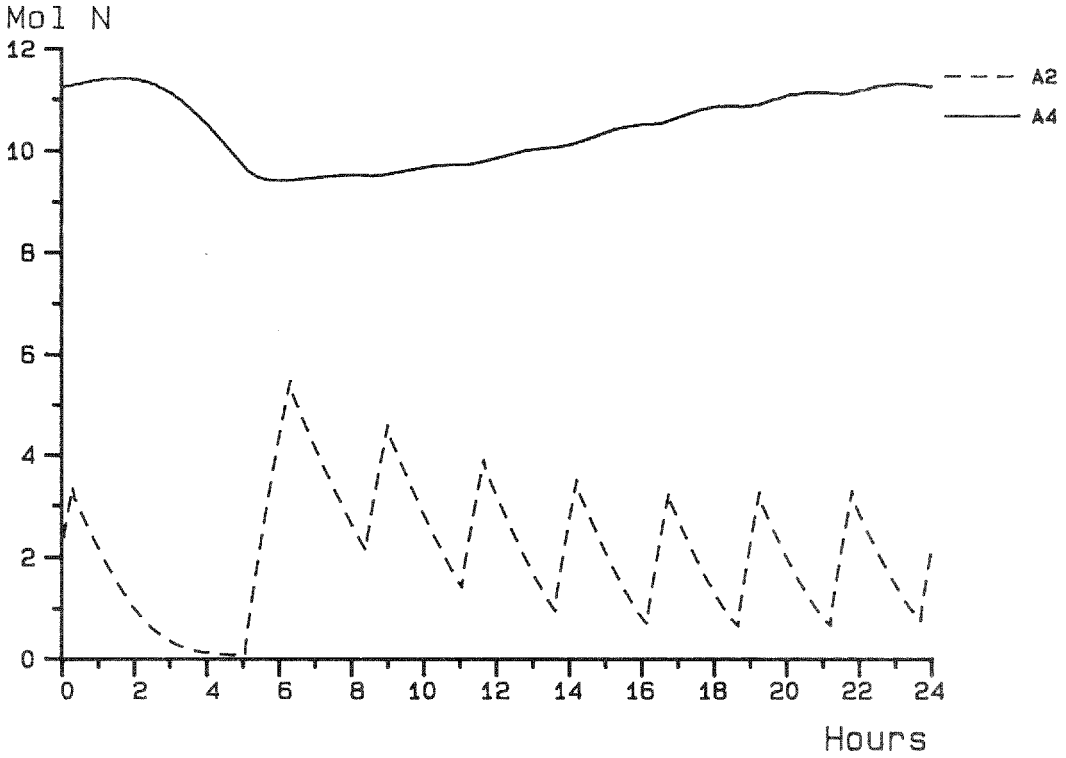


Figure 4.9. Simulated diurnal variations of rumen pool sizes of fermentable protein, peptides and amino acids (A2), and microbial protein and nucleic acids (A4).

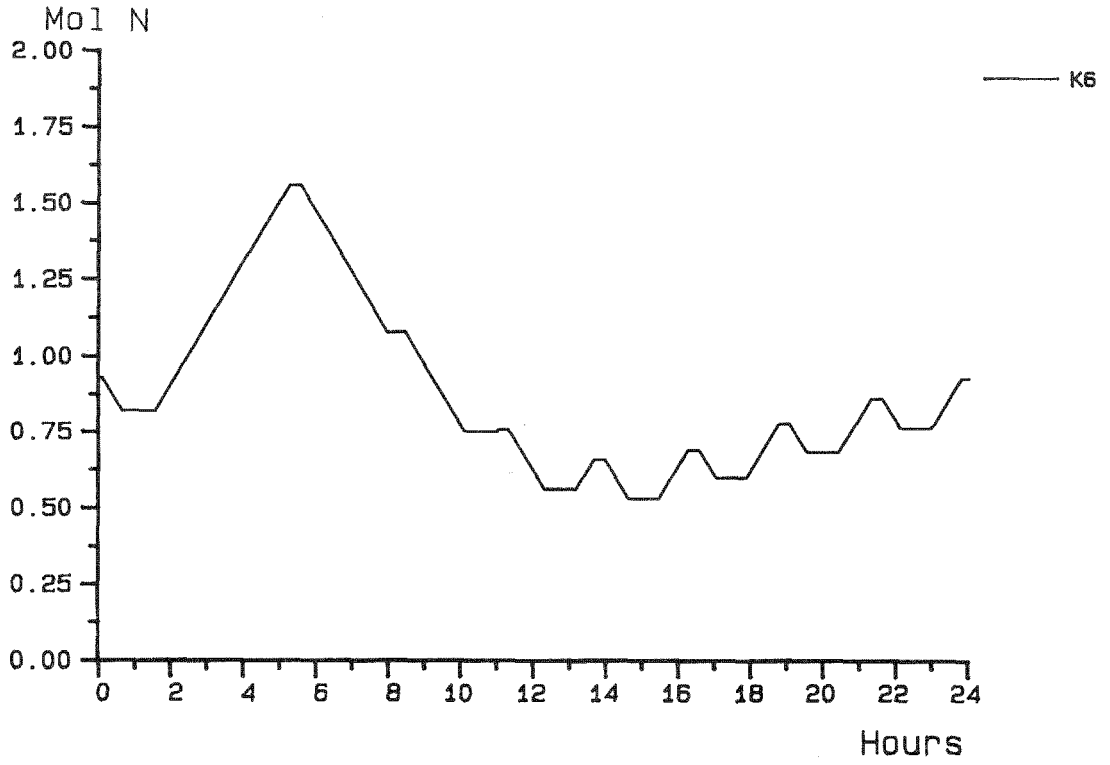


Figure 4.10. Simulated diurnal variation of the affinity factor for amino acid and peptide uptake in rumen microbes.

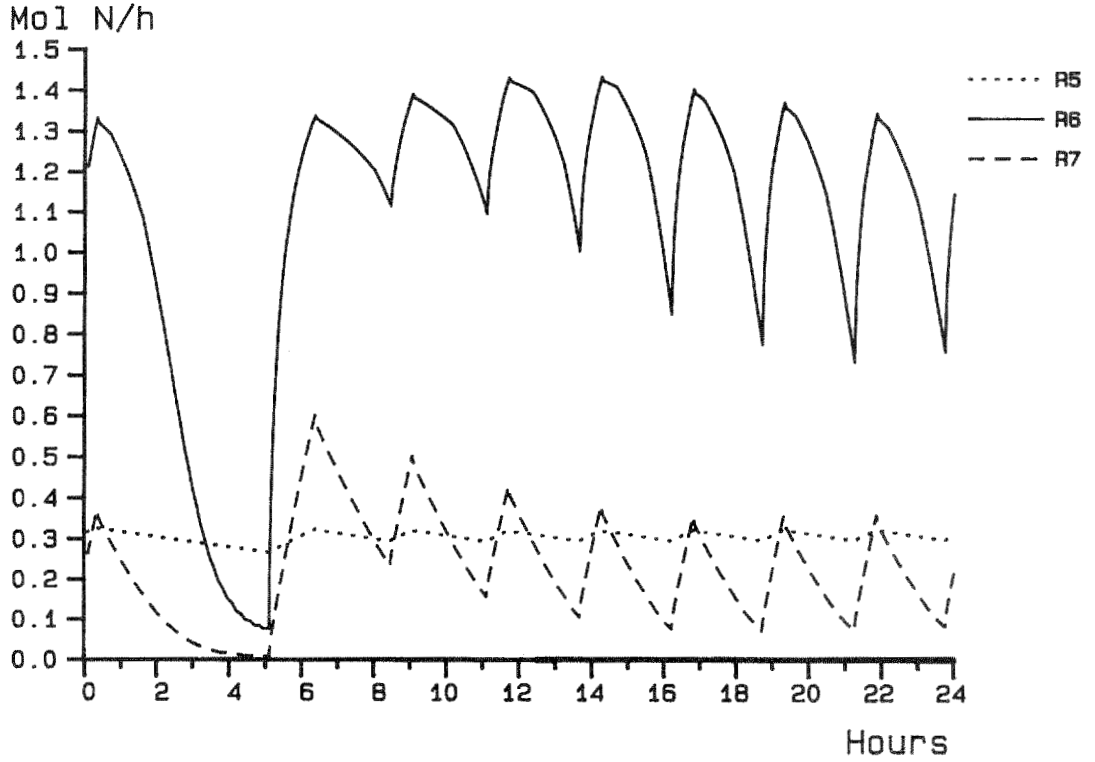


Figure 4.11. Simulated diurnal variations of rumen outflow rates of unfermentable protein (R5), fermentable protein (R7), and rate of amino acid and peptide uptake in rumen microbes (R6).

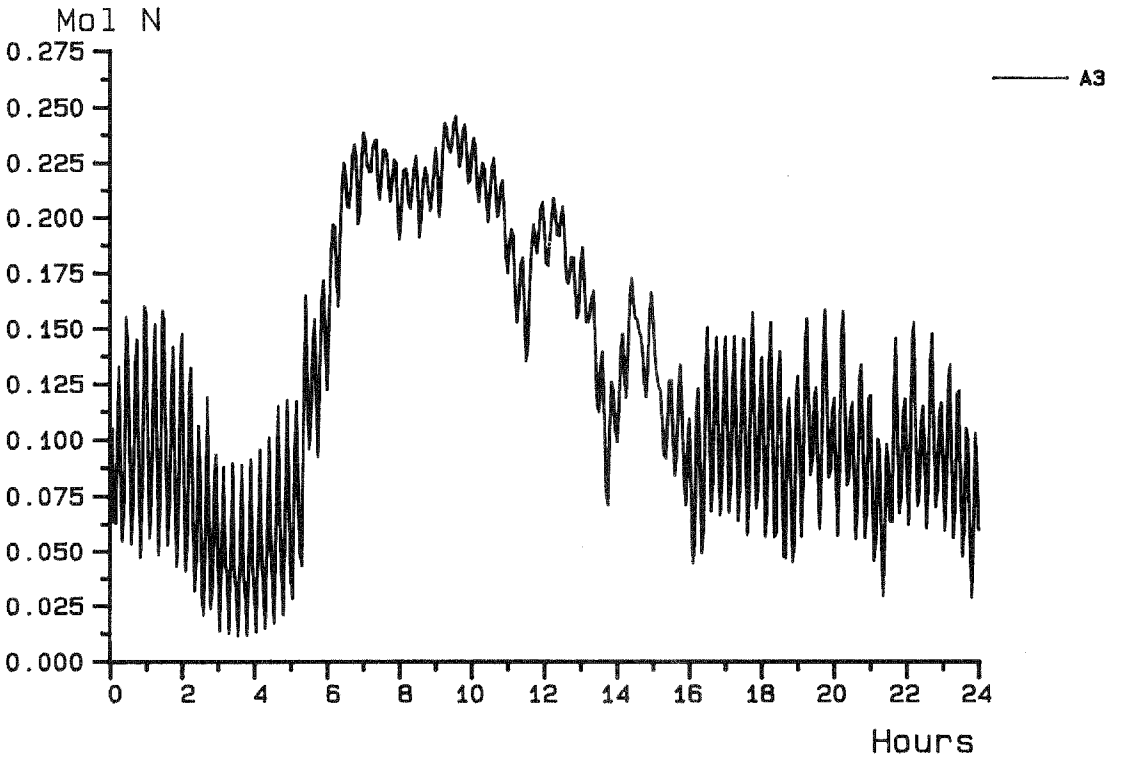


Figure 4.12. Simulated diurnal variation of the rumen pool size of amino acids and peptides in rumen microbes.

sizes (R5 = K5*A1, R7 = K7*A2), and their daily variations therefore show the same patterns as the daily variations of the substrate pools. Hence, it can be inferred that the daily fluctuations are much less in pool A1 (unfermentable protein) than in pool A2 (fermentable protein). This is explained as follows:

The only outflow rate from A1 is R5, which is proportional to A1 and decreases immediately when A1 decreases during periods with no feed intake. The outflow from A2 is dominated by R6, which is described as an enzymatic reaction operating near its maximal rate. This means that A2 can decrease substantially before R6 decreases enough to prevent a further decline in the size of A2; but it also means that A2 will increase faster during periods of feed intake. Therefore A2 fluctuates more than A1, although the difference is damped by changes in the value of K6.

The time course of N-metabolism within the rumen microbes is illustrated in figures 4.12-4.19. The central pool is that for the microbial amino acids and peptides (A3). It takes part in many reactions and varies greatly. The general trend is that the pool size is low during the night, it increases after the start of feed intake in the morning and remains high for about 6 h. That trend is superimposed by frequent and large oscillations (figure 4.12). This picture is reflected in the rates of amino acid excretion (R8), protein synthesis (R9) and amino acid degradation (R11). The affinity factor for amino acid degradation (K11) is regulated by the pool size of A3 as shown in figure 4.14. The variations of the rate of protein synthesis (R9, figure 4.13) illustrate the interaction with the rate of carbohydrate fermentation as the pattern of ATP formation (R108, figure 4.8) is clearly reflected in R9, especially during the period when A3 is relatively stable. The microbial pool of NH_3/NH_4^+ (N1B) and the rates of amino acid synthesis (R17) and NH_3/NH_4^+ excretion to rumen liquor (R20) are in

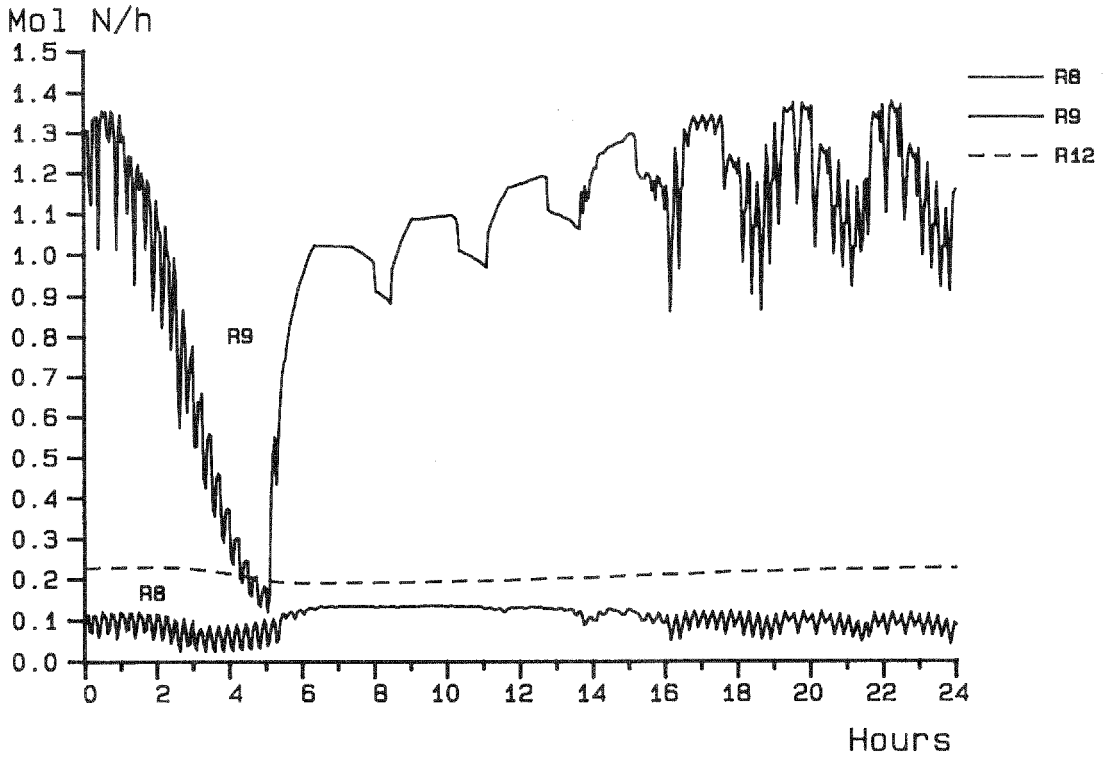


Figure 4.13. Simulated diurnal variations of rates of amino acid excretion (R8), protein synthesis (R9) and protein degradation (R12) in rumen microbes.

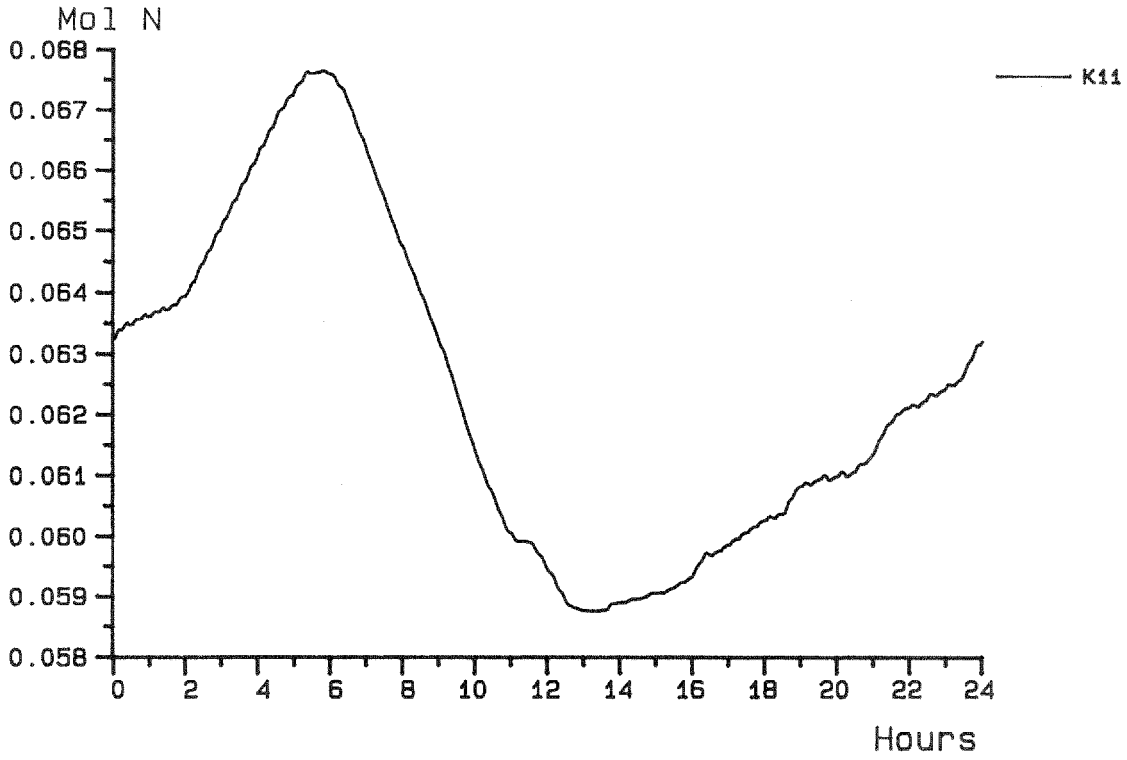


Figure 4.14. Simulated diurnal variation of the affinity factor for amino acid degradation in rumen microbes.

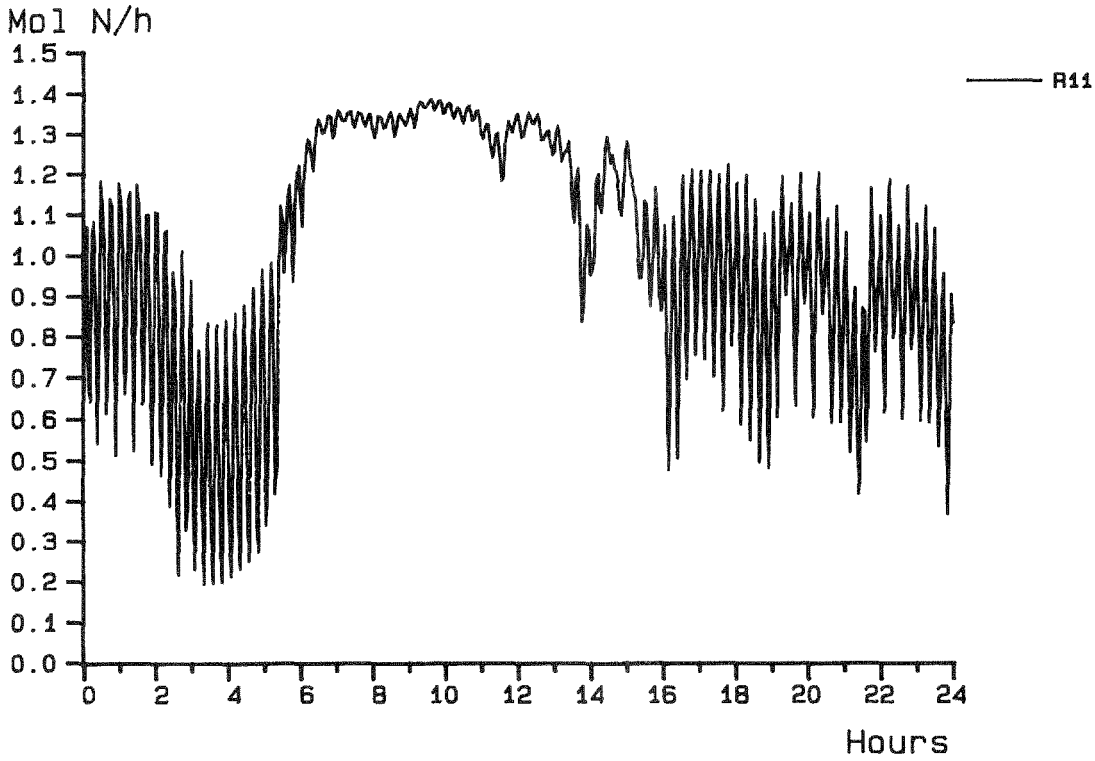


Figure 4.15. Simulated diurnal variation of the rate of amino acid degradation in rumen microbes.

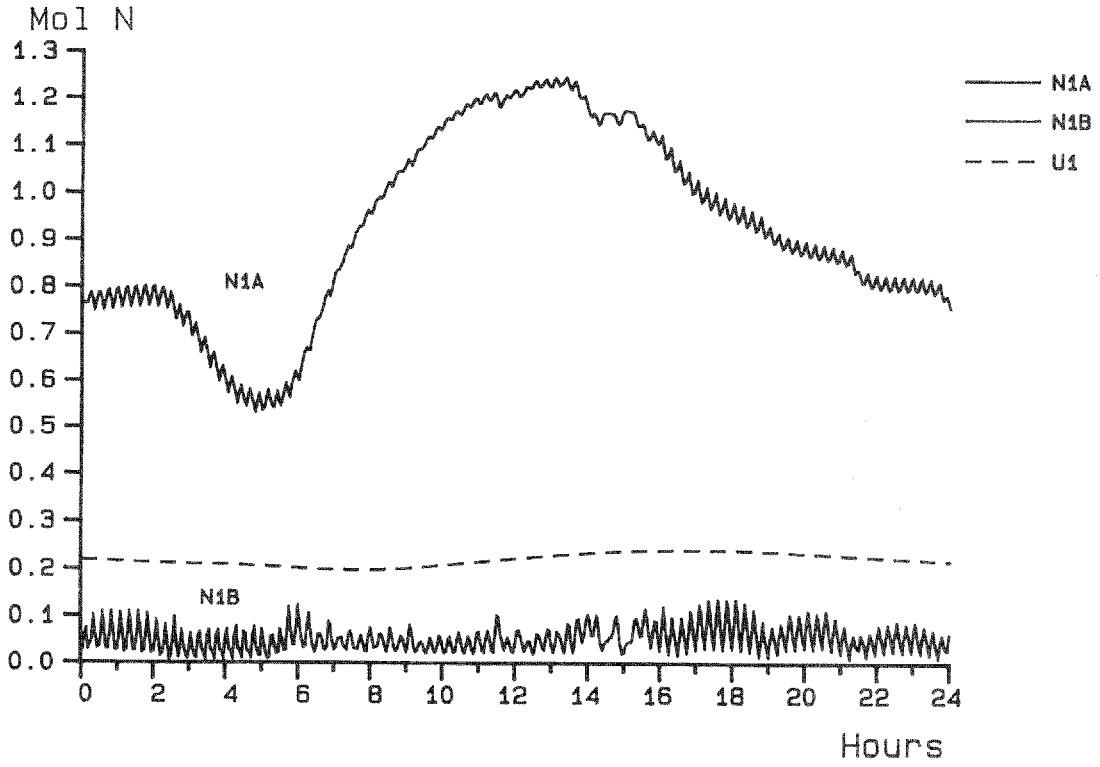


Figure 4.16. Simulated diurnal variations of pool sizes of ruminal NH_3/NH_4^+(N1A), microbial NH_3/NH_4^+ (N1B) and ruminal urea (U1).

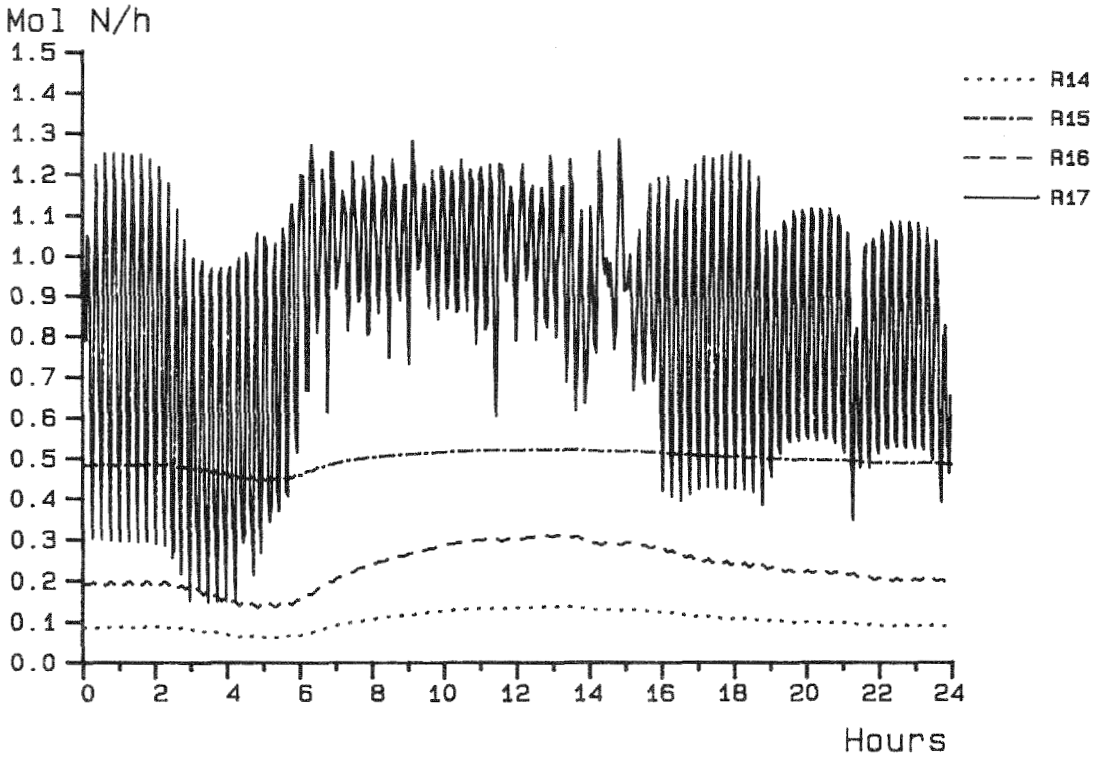


Figure 4.17. Simulated diurnal variations of rates of NH_3/NH_4^+ outflow to the intestines (R14), absorption (R16) and uptake in rumen microbes (R15), and amino acid synthesis in rumen microbes (R17).

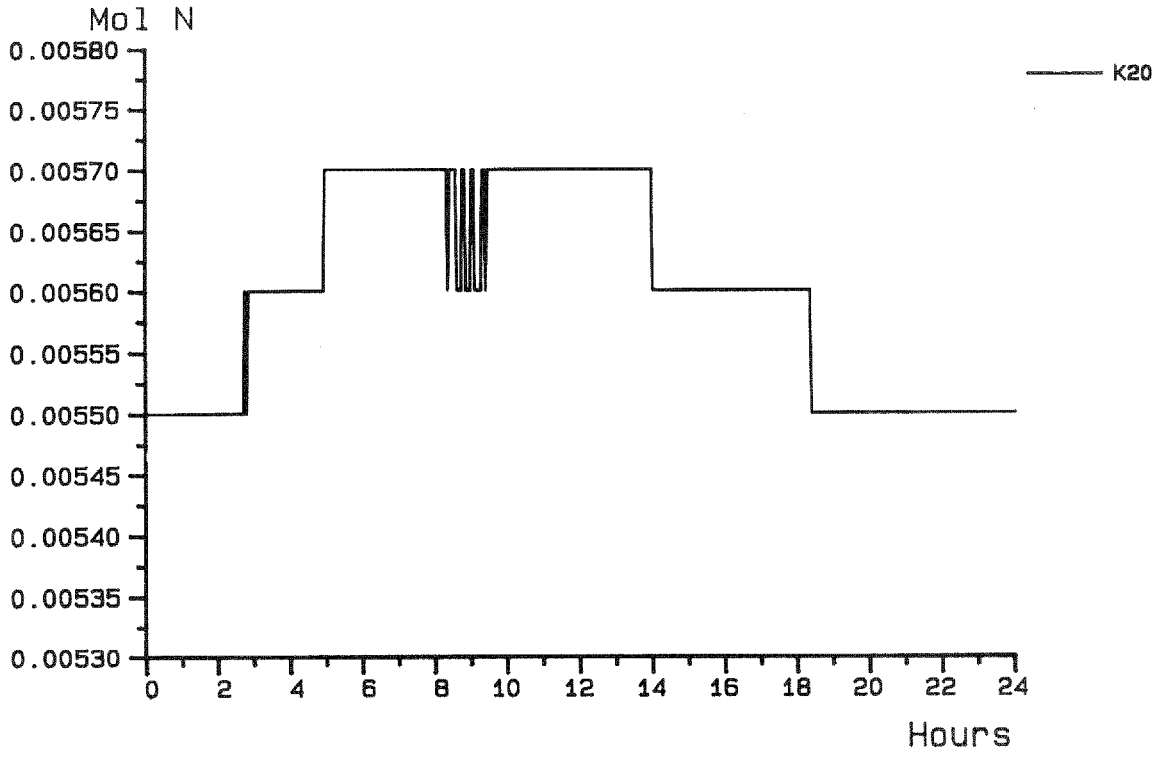


Figure 4.18. Simulated diurnal variation of the affinity factor for NH_3/NH_4^+ excretion from rumen microbes.

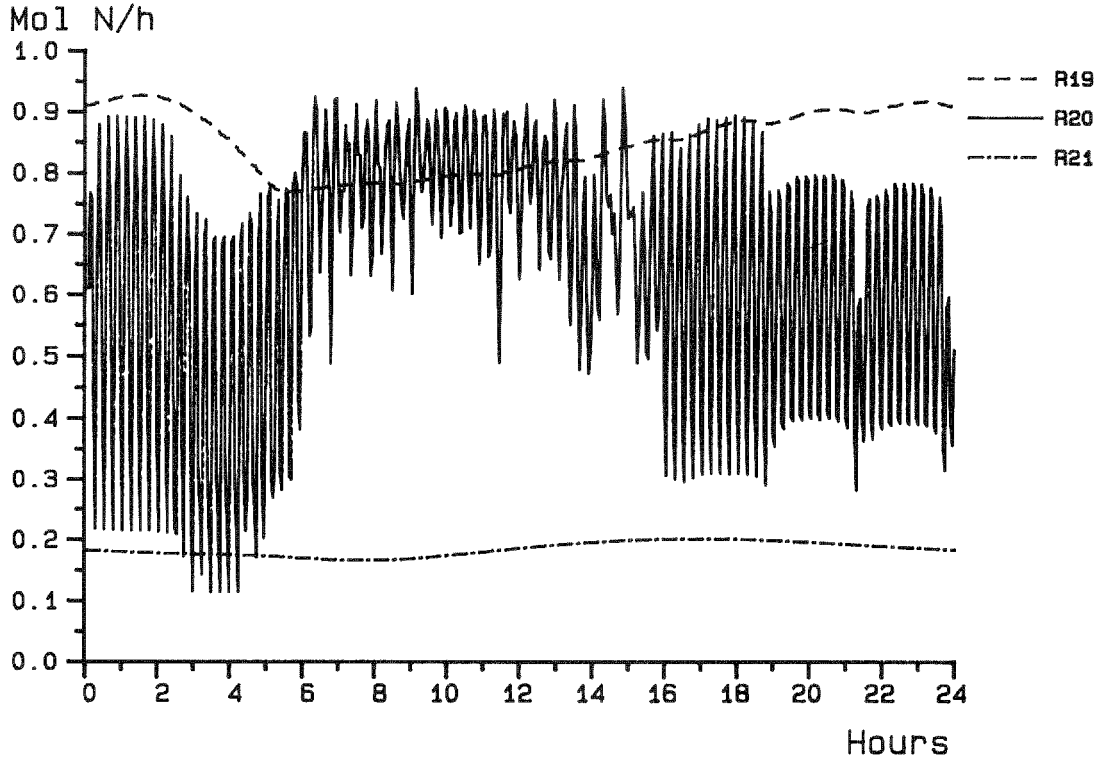


Figure 4.19. Simulated diurnal variations of rates of microbial crude protein outflow (R19), NH_3/NH_4^+ excretion from rumen microbes (R20) and hydrolysis of ruminal urea (R21).

figures 4.16-4.19. The value of N1B which regulates the affinity factor for NH_3/NH_4^+ excretion (K20, figure 4.18), fluctuates throughout the day without any clear trends either of increases or decreases.

Variations in pool sizes of NH_3/NH_4^+ (N1A) and urea (U1) in the rumen liquor are shown in figure 4.16, rates of NH_3/NH_4^+ utilization in figure 4.17, and rate of urea hydrolysis in figure 4.19.

4.2.2 The intestinal compartments

Compared with the rumen the absorption rates of VFA from the hind gut show less variation during the day (figure 4.20), but the influence of the pattern of feed intake is still to be seen.

This is also the case for the pools of digestible carbohydrates in the small intestine (C8) and glucose in the intestinal wall (C12) even though their variations are much greater (figure 4.21). These pools are under self-regulation as a consequence of controlling the values of the affinity factors for the rates of glucose transfer to the intestinal wall (K121) and for glucose absorption to the blood (K130, figure 4.22).

Figures 4.23 and 4.25 show absorption rates from the small intestine of glucose (R130), triglycerides (R132) and amino acids (R40). The rates of amino acid uptake from the intestinal lumen to the intestinal wall (R27 = dietary and microbial amino acids, R34 = endogenous amino acids) are also shown. These rates vary more or less but they all follow the same pattern which is influenced by

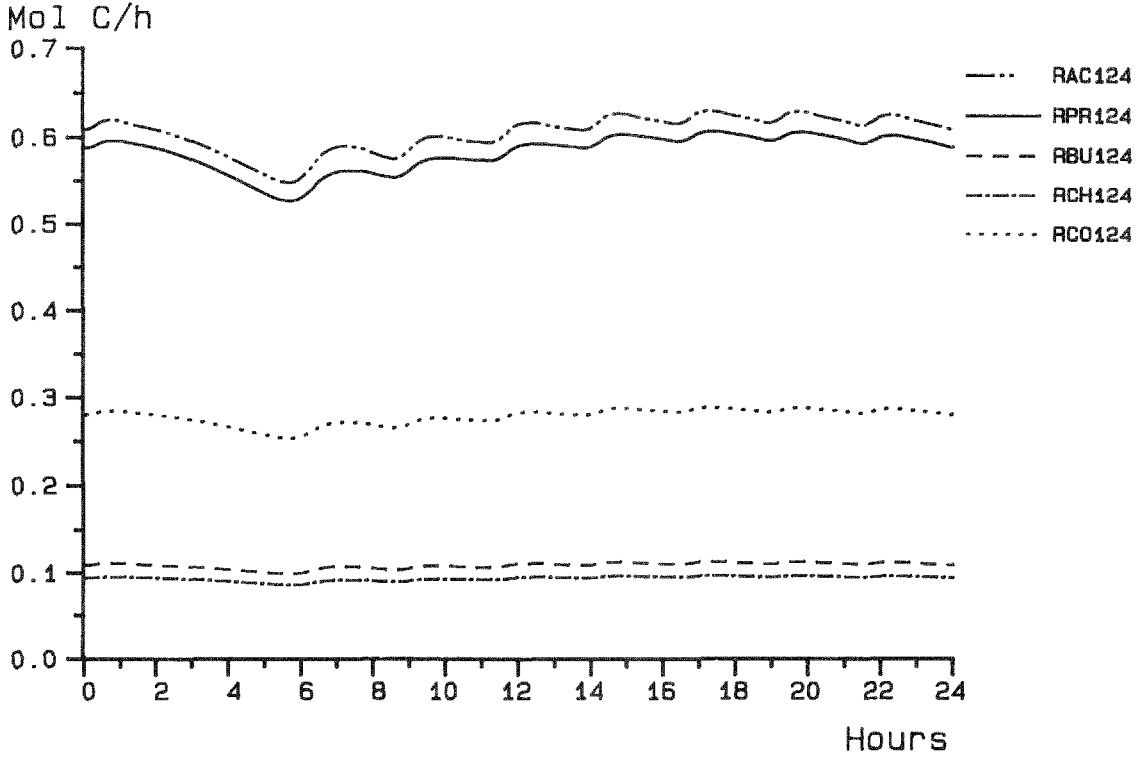


Figure 4.20. Simulated diurnal variations of absorption rates of acetate (RAC124), propionate (RPR124) and butyrate (RBU124), and outflow rates of methane (RCH124) and carbon dioxide (RCO124) from the hind gut.

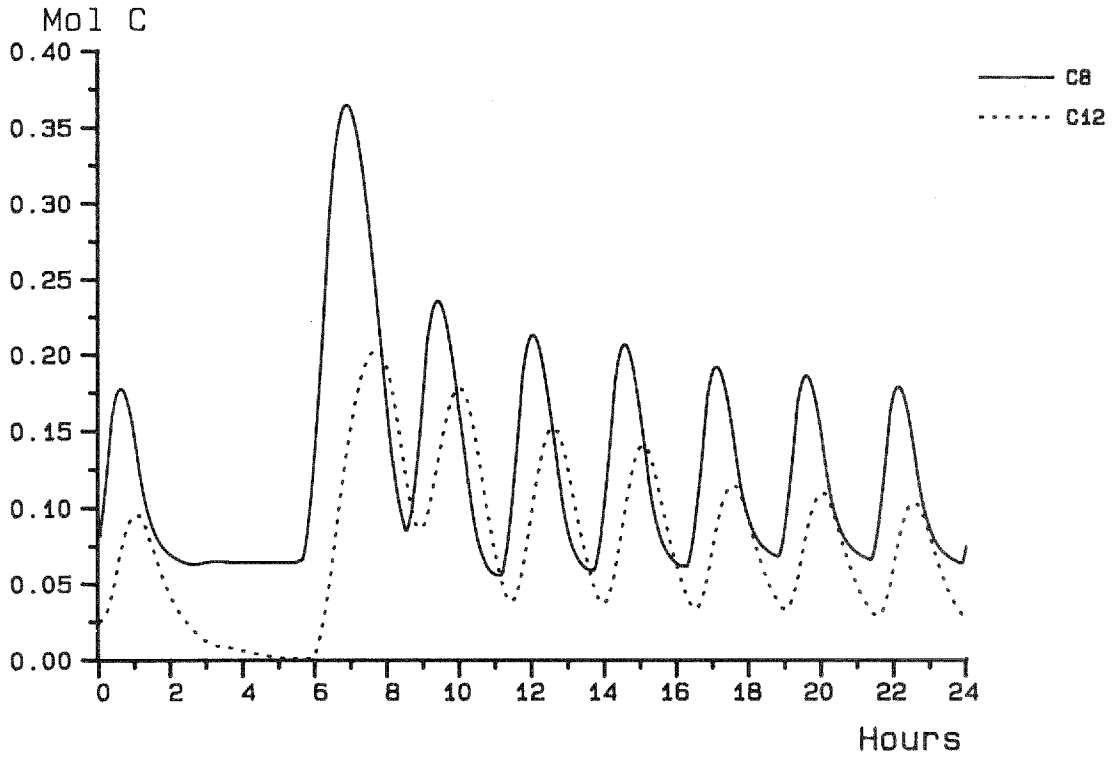


Figure 4.21. Simulated diurnal variations of pool sizes of digestible carbohydrates in the intestinal lumen (C8) and glucose in the intestinal wall (C12).

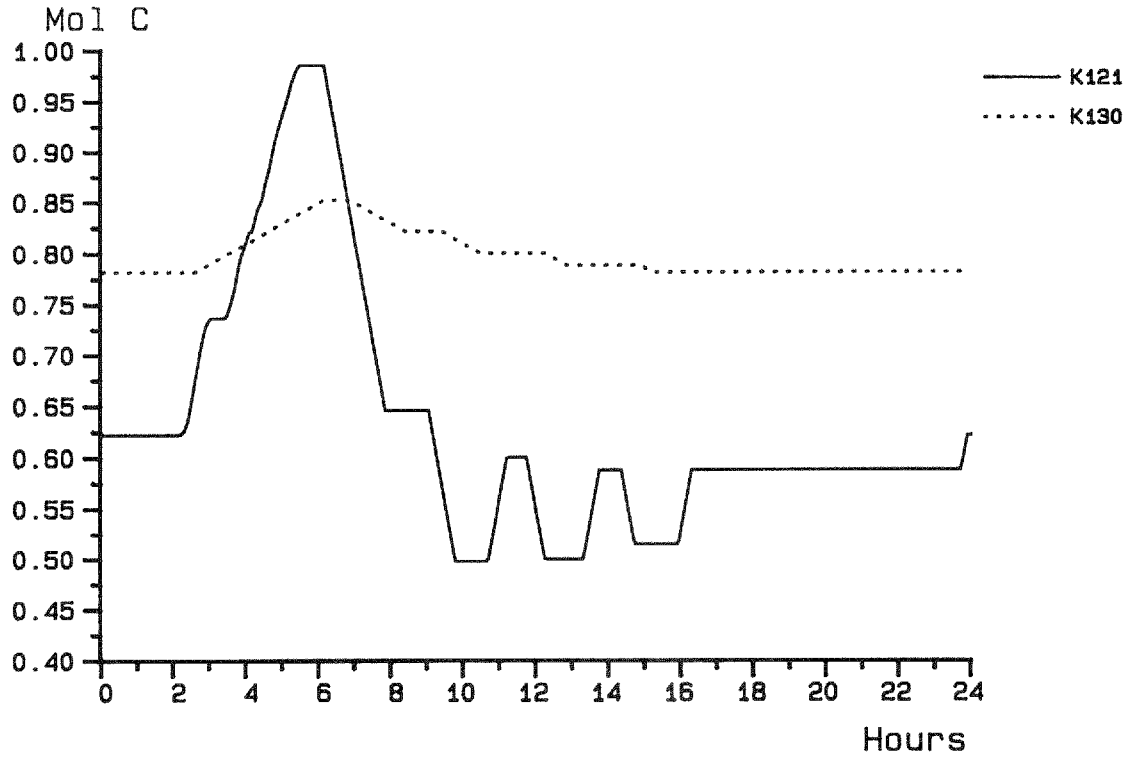


Figure 4.22. Simulated diurnal variations of affinity factors for glucose uptake from the intestinal lumen (K121) and for glucose absorption to the blood (K130).

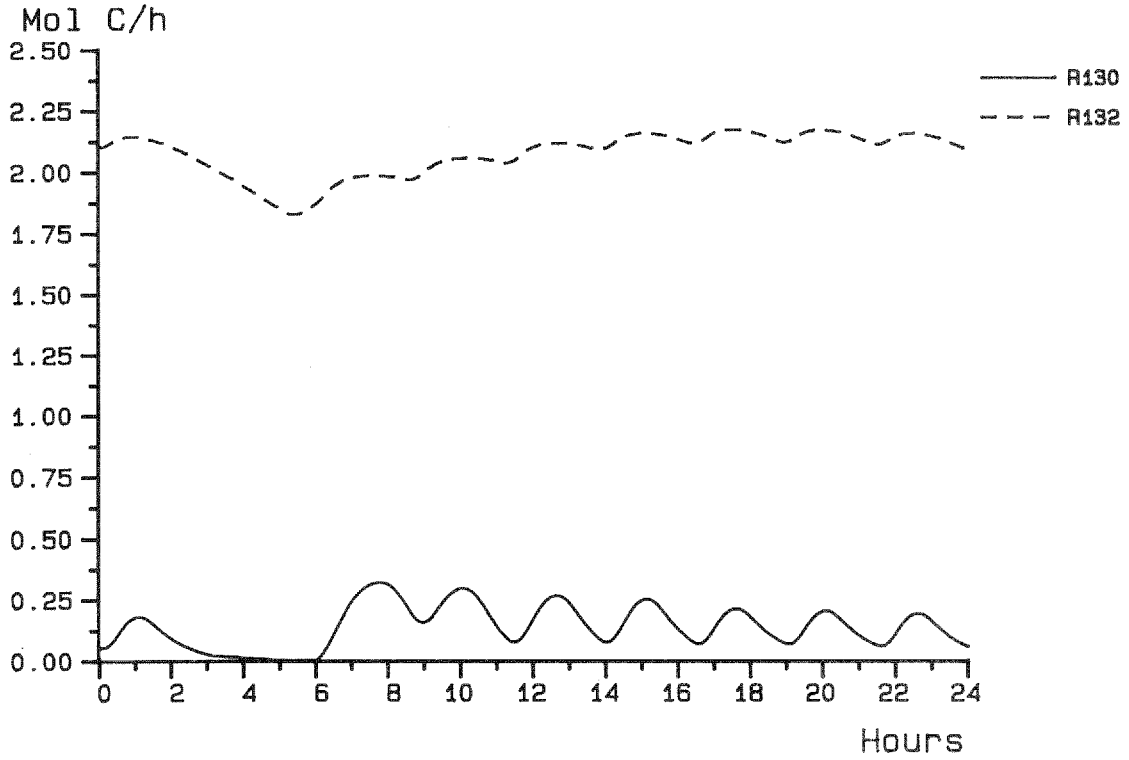


Figure 4.23. Simulated diurnal variations of absorption rates of glucose (R130) and triglycerides (R132) from the small intestine.

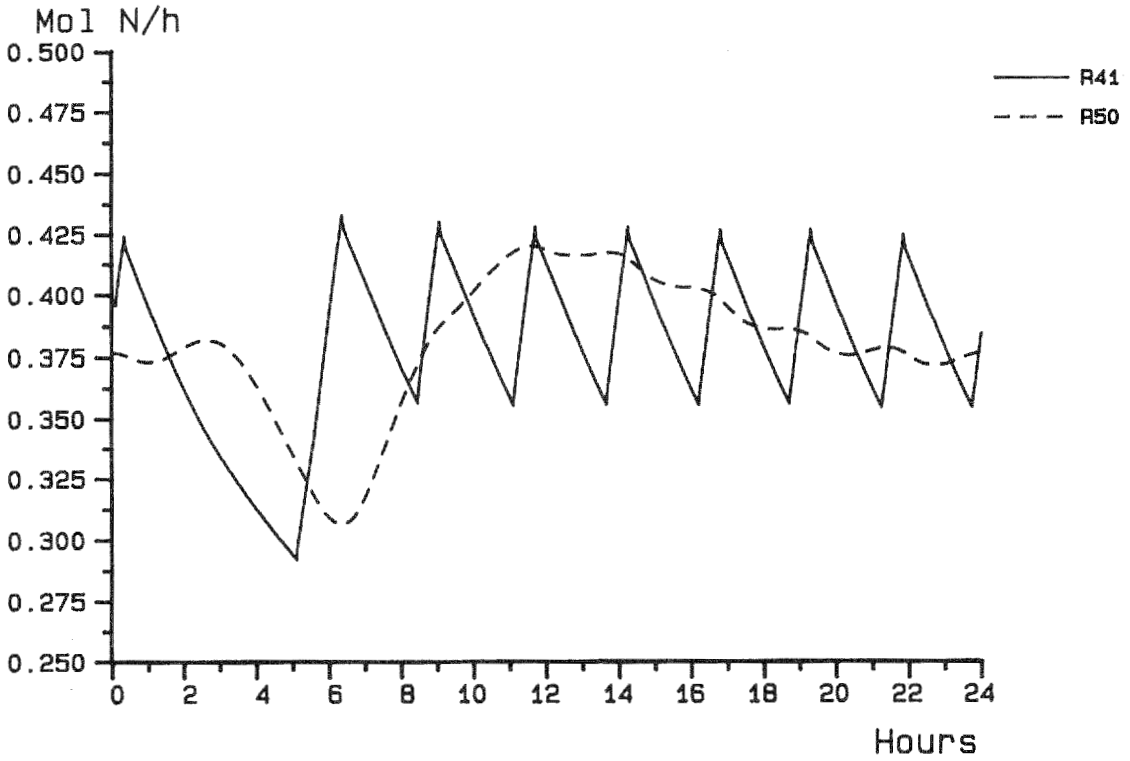


Figure 4.24. Simulated diurnal variations of rates of endogenous protein secretion (R41) and intestinal amino acid uptake from the blood (R50).

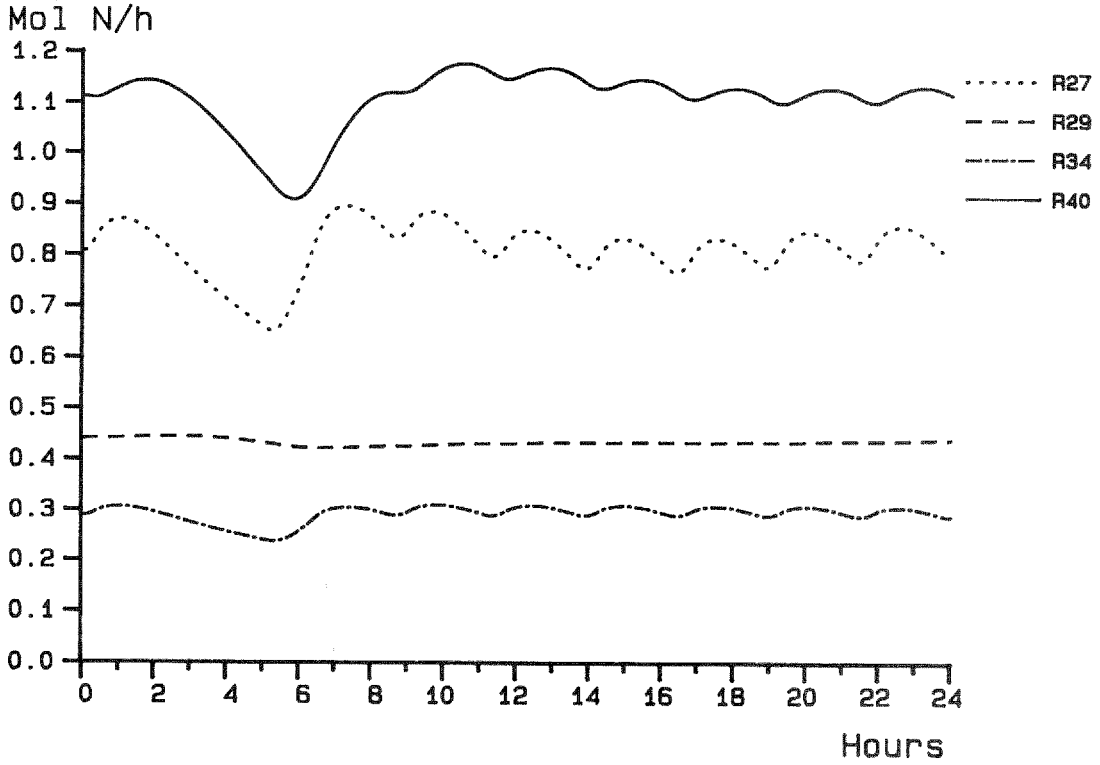


Figure 4.25. Simulated diurnal variations of rates of amino acid uptake from the intestinal lumen (R27, R34), amino acid absorption to the blood (R40) and faecal excretion of crude protein (R29).

the feed intake.

This pattern is much more distinct in the variation of endogenous protein secretion to the intestinal lumen (R41, figure 4.24) because the maximal rate of this process (R41M) is proportional to the rate of organic matter inflow from the stomachs. On the other hand the rate of faecal N excretion is almost constant throughout the day (R29, figure 4.25).

4.2.3 The liver compartment

The daily variations in rates of propionate (R133) and butyrate (R134) uptake, and of acetate and ketone body passage through the liver are shown in figure 4.26.

Figure 4.27 gives the liver pool sizes of propionate (C14), glucose (C16) and free fatty acids (C19) during the day. The variations in the propionate pool are very much like the variations in the rate of propionate production (RPR111, figure 4.7) and uptake in the liver (R133, figure 4.26), but after the first morning feed the pool starts to fluctuate for about 7 h and then returns to the normal rythm. The same picture is seen in the product pool of glucose. The variation of the affinity factor for propionate oxidation (K137), which is controlled by the size of the propionate pool (C14), is shown in figure 4.28. The parameter is constant most of the day except for a period of 3.4 h during which C14 oscillates most intensely.

The rates of gluconeogenesis and glucose output from the liver are

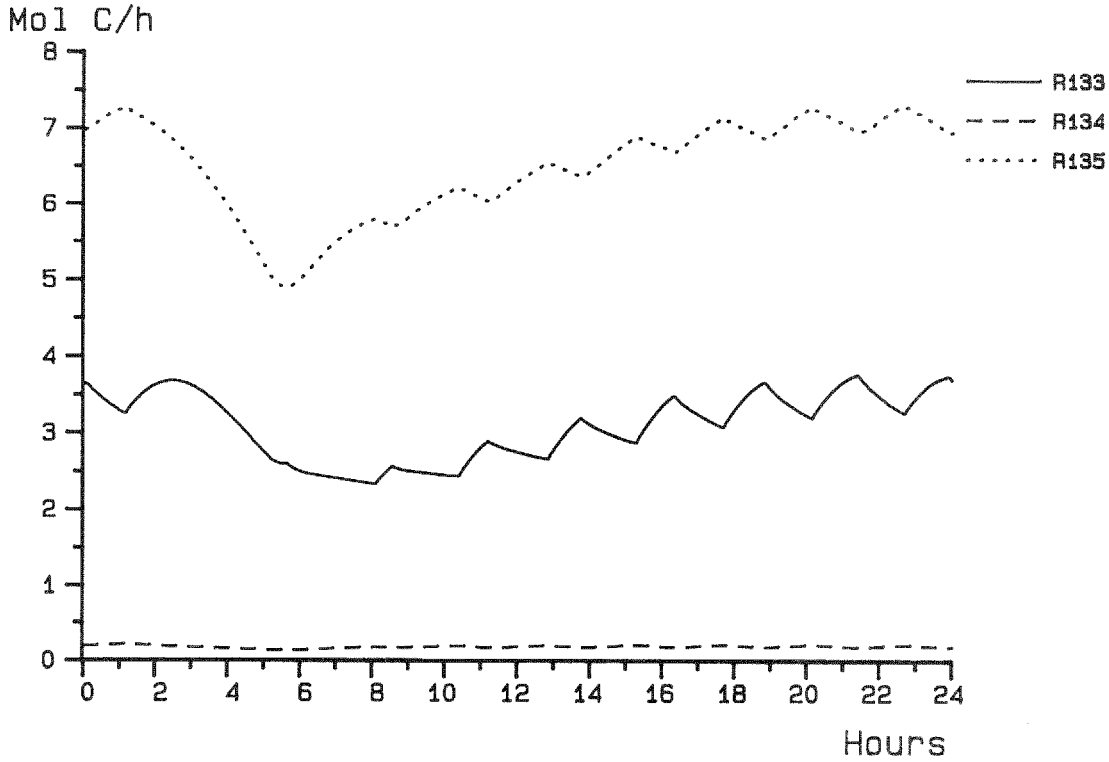


Figure 4.26. Simulated diurnal variations of rates of propionate uptake (R133), butyrate uptake in the liver (R134), and passage of acetate and ketone bodies (R135).

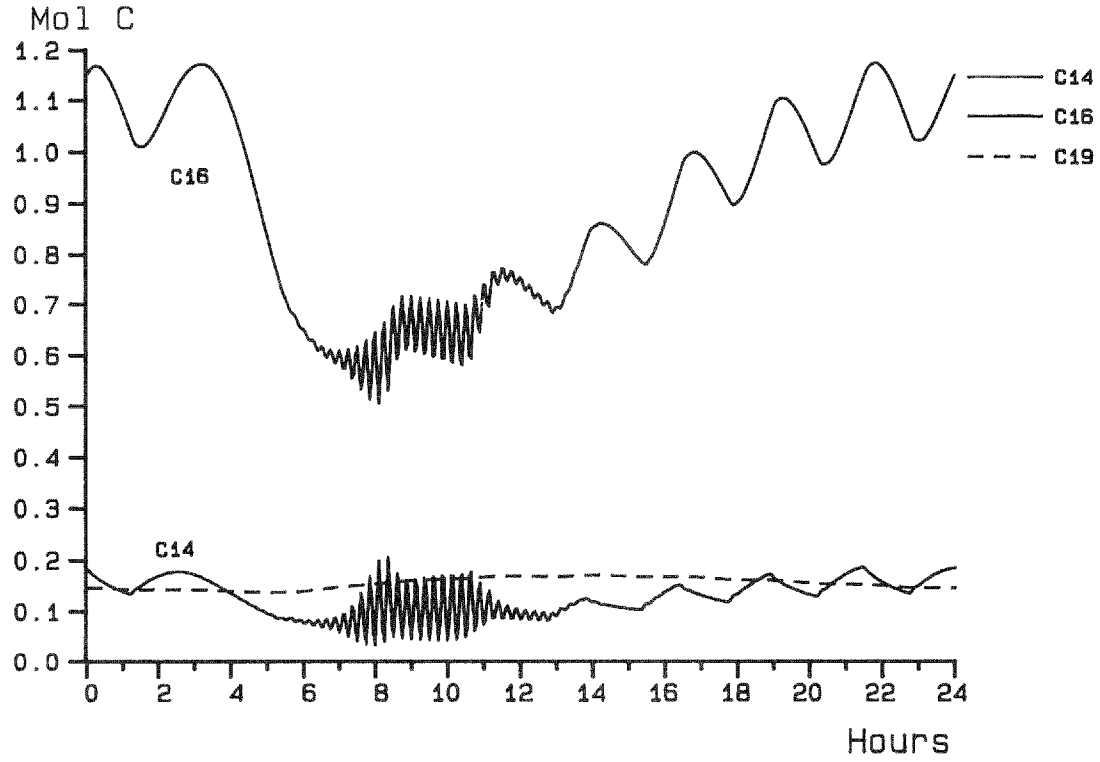


Figure 4.27. Simulated diurnal variations of liver pool sizes of propionate (C14), glucose (C16) and free fatty acids (C19).

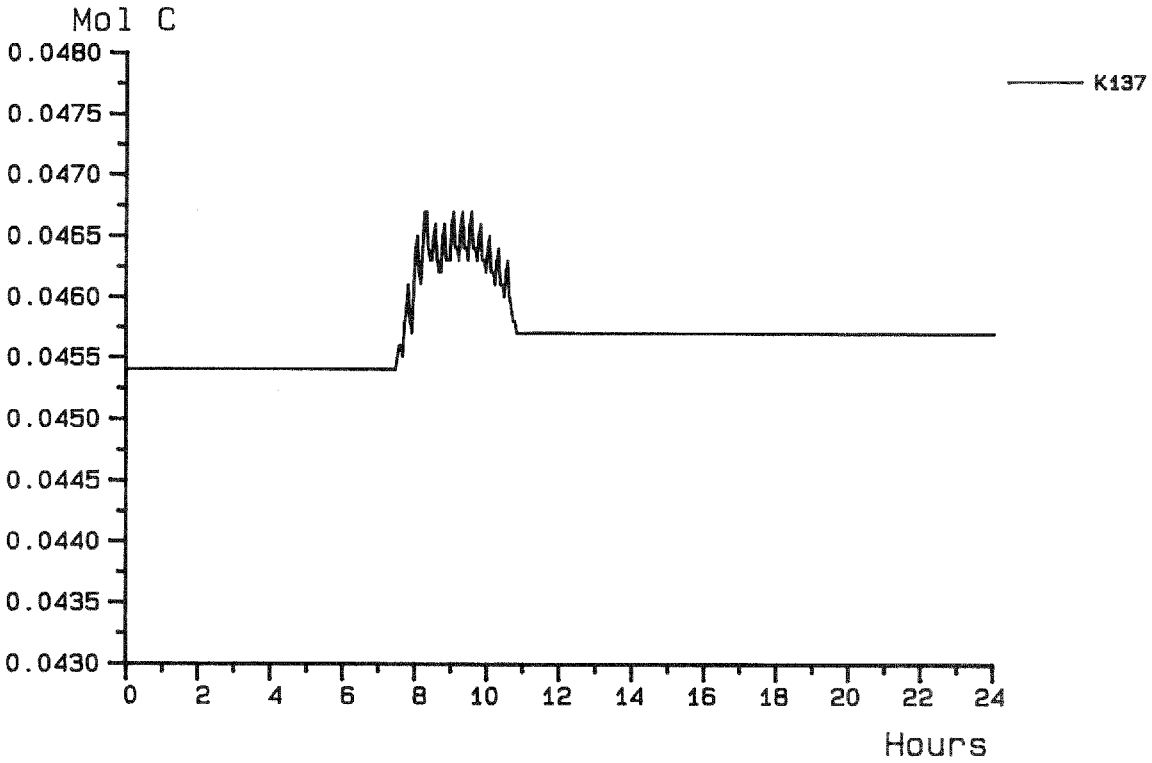


Figure 4.28. Simulated diurnal variation of the affinity factor for propionate oxidation in the liver.

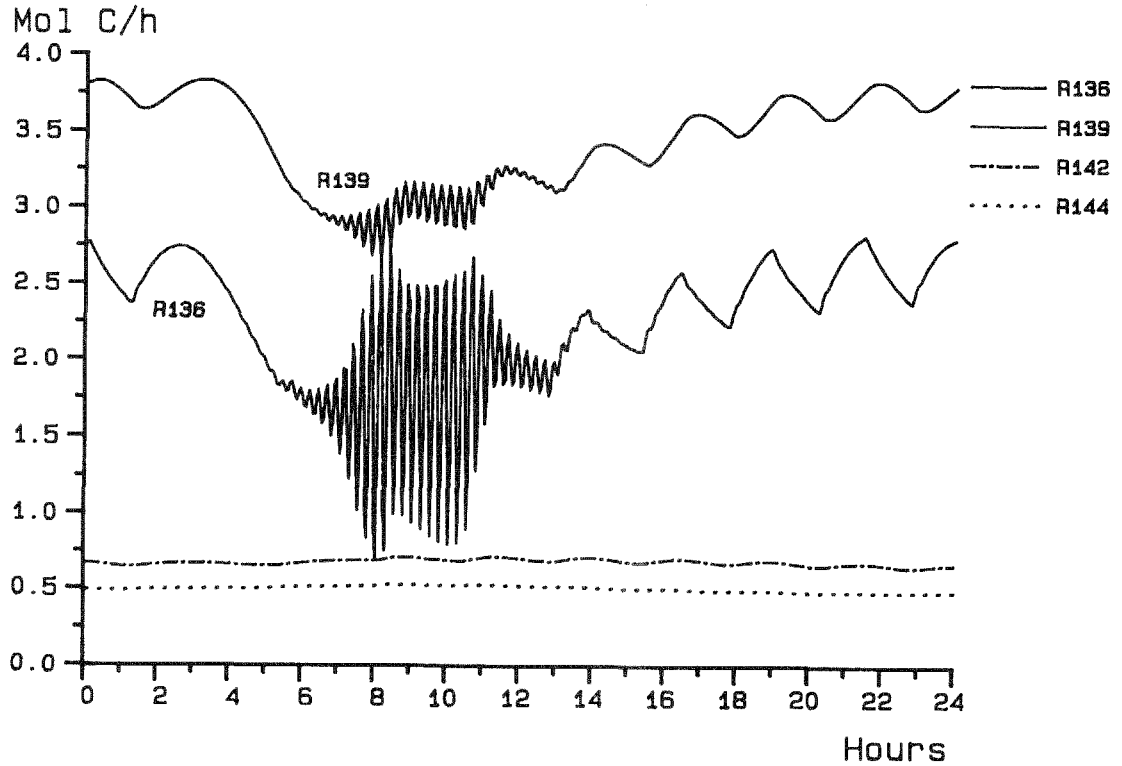


Figure 4.29. Simulated diurnal variations of rates of gluconeogenesis from propionate (R136), amino acids (R142), and glycerol and lactate (R144), and rate of glucose output from the liver (R139).

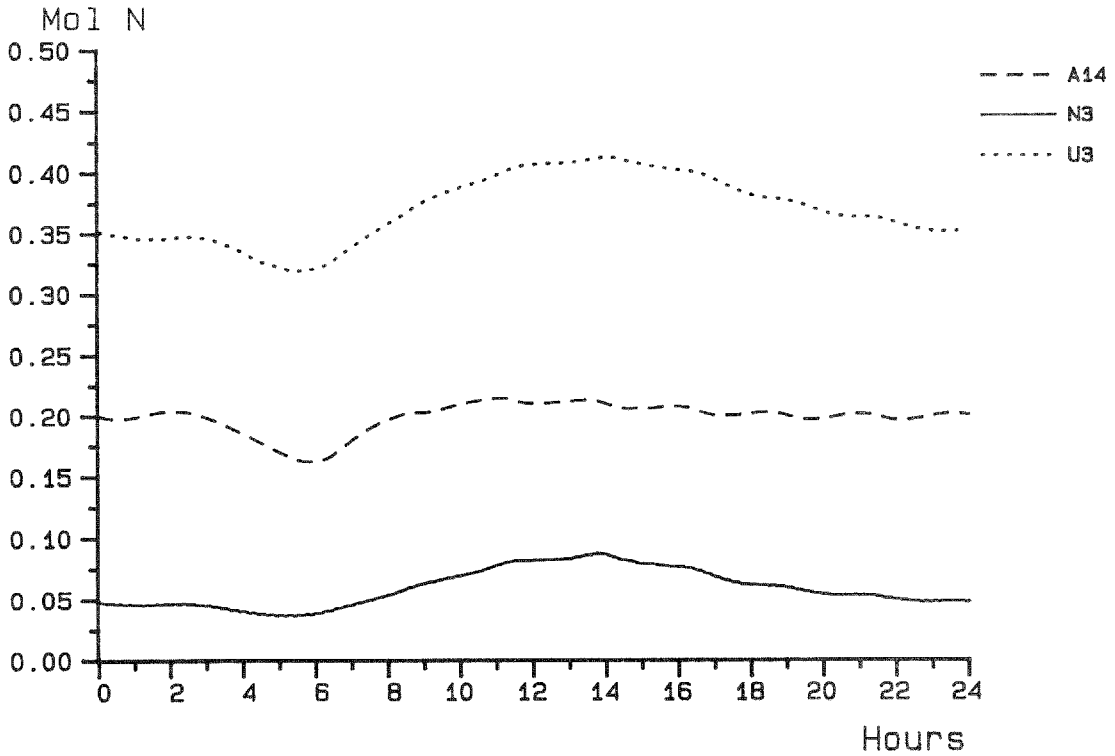


Figure 4.30. Simulated diurnal variations of liver pool sizes of amino acids (A14), NH_3/NH_4^+(N3) and urea (U3).

in figure 4.29. The variation of the propionate pool is clearly reflected in the rate of glucose synthesis from propionate (R136), and to a lesser extent in the rate of glucose output (R139). This confirms the dominant role of propionate in gluconeogenesis. The rates of glucose synthesis from amino acids (R142), and from glycerol and lactate (R144) are almost constant throughout the day.

Variations in the nitrogenous pools, amino acids (A14), NH_3/NH_4^+ (N3) and urea (U3) are illustrated in figure 4.30. The pool size of NH_3/NH_4^+ remains low at all times of the day.

4.2.4 The peripheral blood compartment

The blood plasma concentrations of insulin and glucagon during the day are shown in figure 4.31. The variation in plasma insulin is dependent on the absorption rates of propionate (R133, figure 4.26) and amino acids (R40, figure 4.25), and on the plasma glucose pool size (C24, figure 4.33). The shape of the insulin curve with a minimum at about 6 a.m. is similar to experimental findings of Blum et al. (1985). The variation in plasma glucagon is dependent on the absorption rate of propionate (R133). The ratio of glucagon to insulin concentrations, which among other things regulates the rates of gluconeogenesis and fatty acid metabolism in the liver (see subsection 3.3.3), is given in figure 4.32.

Figure 4.33 shows the variations of acetate and ketone bodies (C23), glucose (C24) and glycerol+lactate (C25) in the blood. The glucose pool varies more than the other nutrients according to the daily variations in the rate of glucose output (figure 4.29). The glycerol and lactate pool originates from endogenous sources and

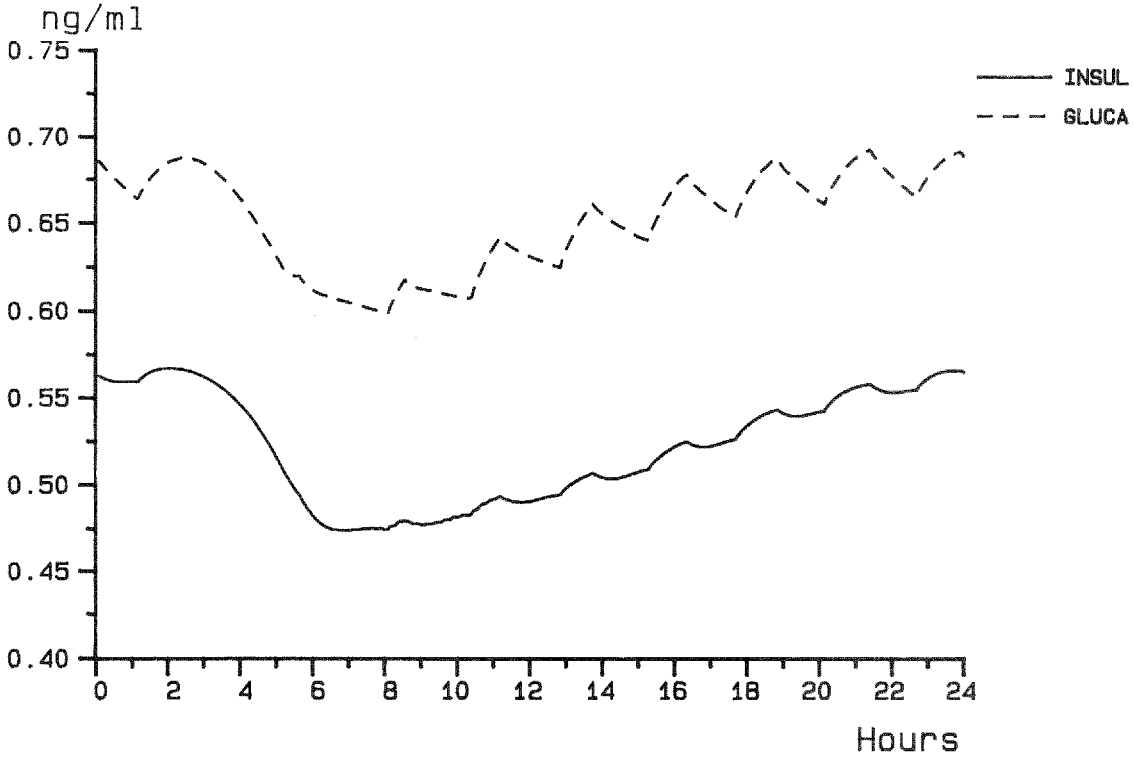


Figure 4.31. Simulated diurnal variations of blood plasma concentrations of insulin (INSUL) and glucagon (GLUCA).

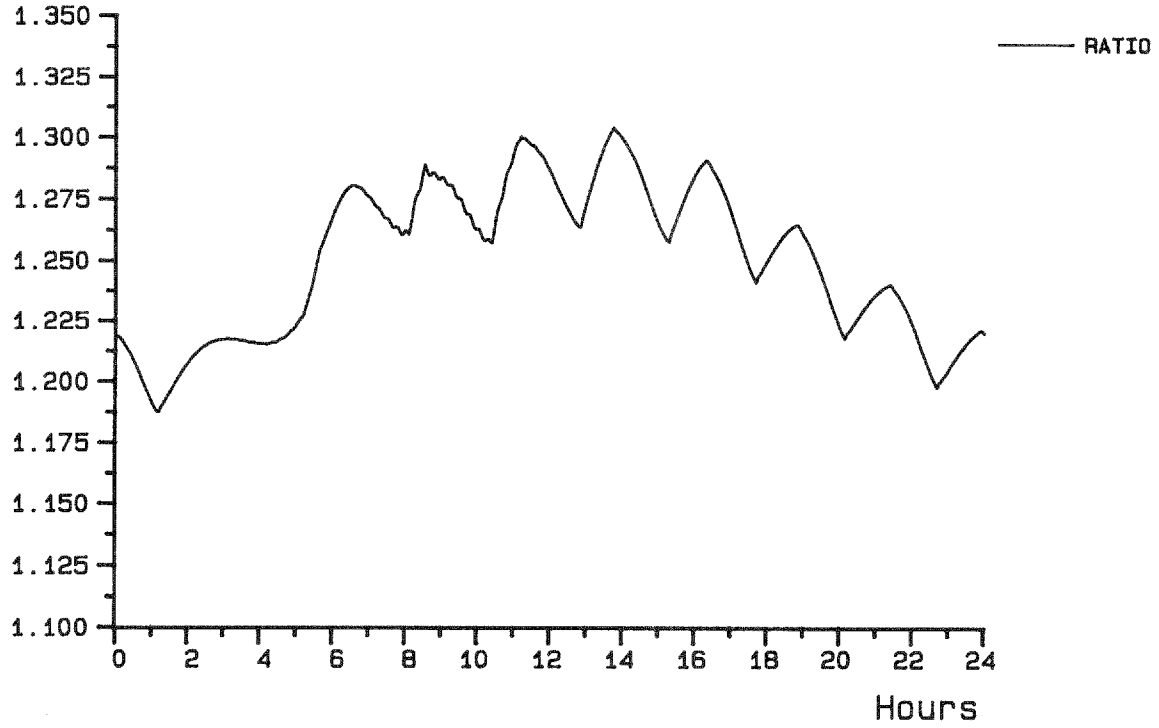


Figure 4.32. Simulated diurnal variation of the ratio of glucagon to insulin concentrations in blood plasma.

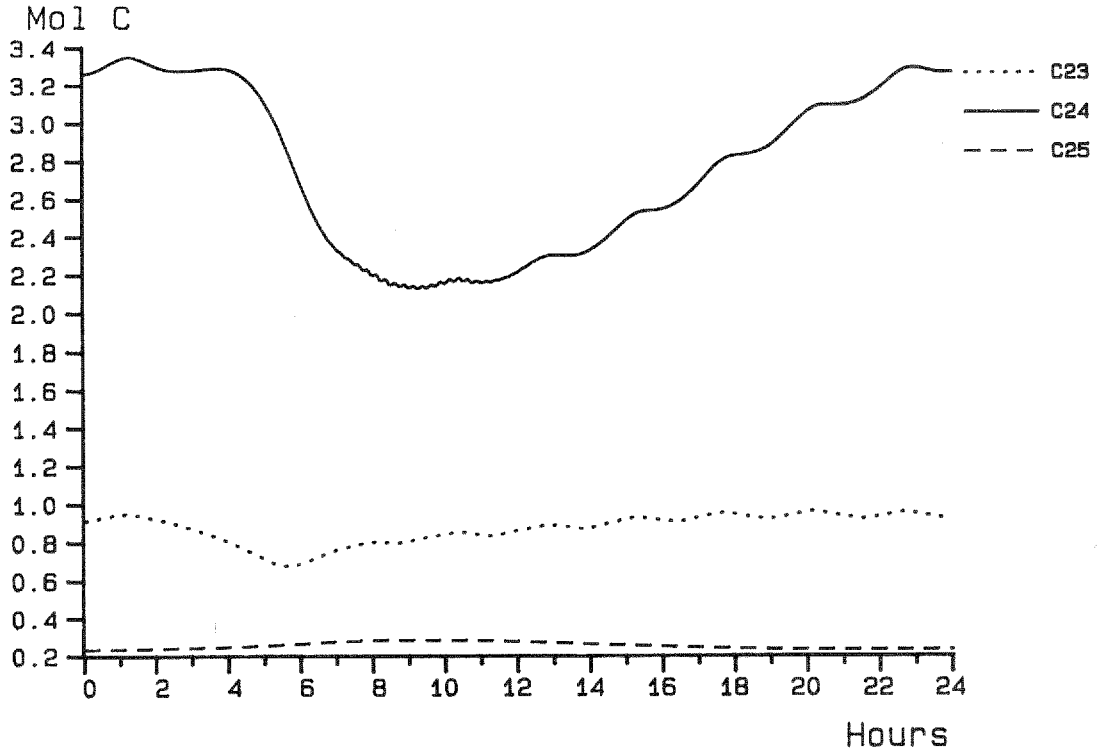


Figure 4.33. Simulated diurnal variations of blood plasma pool sizes of acetate and ketone bodies (C23), glucose (C24), and glycerol and lactate (C25).

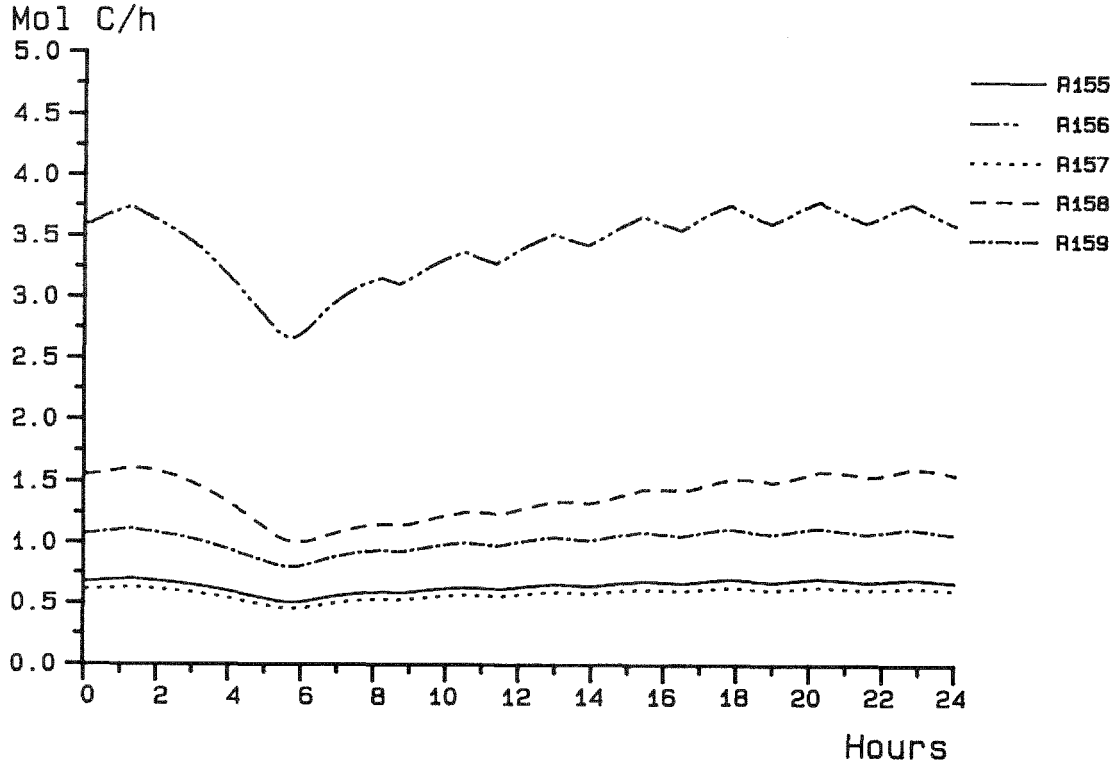


Figure 4.34. Simulated diurnal variations of rates of acetate and ketone body uptake in the intestinal wall (R155), mammary gland (R156), muscle tissue (R157), adipose tissue (R158) and other tissues (R159).

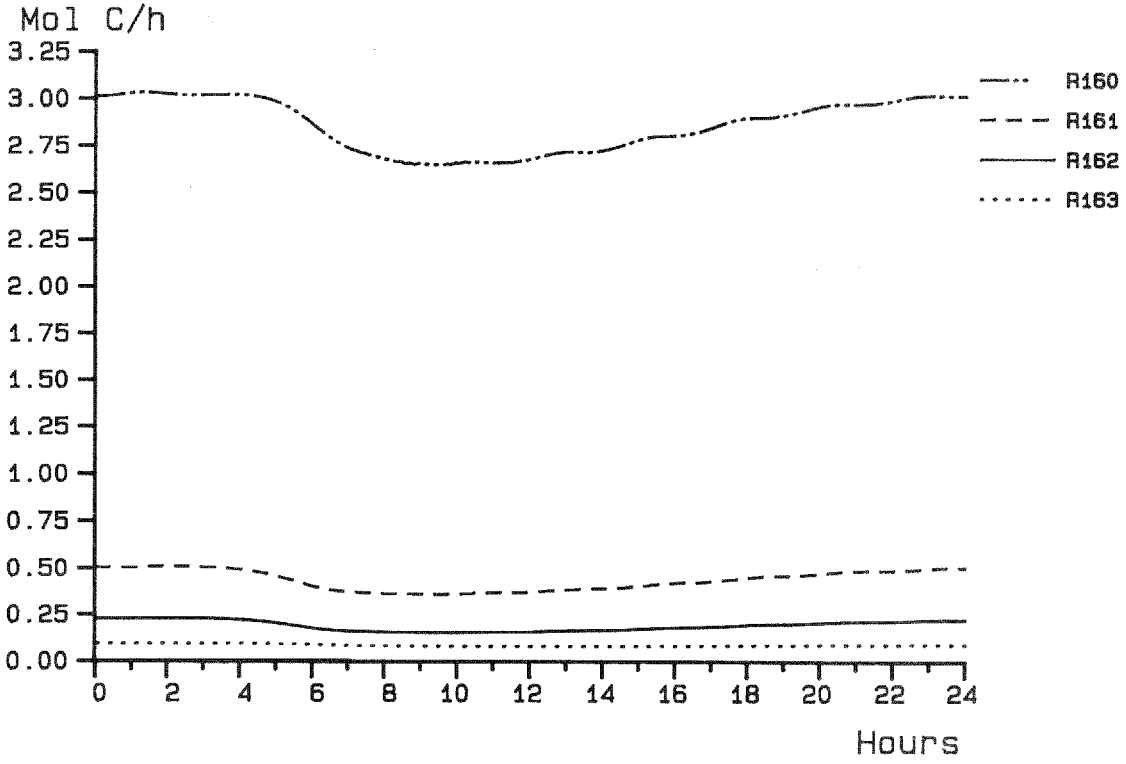


Figure 4.35. Simulated diurnal variations of rates of glucose uptake in the mammary gland (R160), muscle tissue (R161), adipose tissue (R162) and other tissues (R163).

varies only little. There is an amazing similarity between the time course of these three curves on the one hand and curves of in vivo diurnal variations in plasma glucose, 3-OH-butyrate and lactate found by Blum et al. (1985) on the other. The cows in that study were at the same lactational stage and had the same feed intake and milk production as the model cow.

The rates of uptake of acetate and ketone bodies (figure 4.34) and of glucose (figure 4.35) in the different tissues show the dominant role of the mammary gland in the extraction of nutrients from the blood.

The daily variations in plasma pool sizes and rates of tissue uptake of free fatty acids and triglycerides are shown in figures 4.36-4.38. The pool of free fatty acids (C26) do not vary much during the day - much less than found in cows by Bines et al. (1983) and by Blum et al. (1985). However, the pattern of the variations in C26, small as they are, is biologically reasonable because it is opposite to the pattern of the variations in the glucose pool size (figure 4.33) and insulin concentration (figure 4.31) as shown to be the case in many experiments (e.g. Blum et al. 1985, Fröhli & Blum 1988). The simulated variations in the pool of chylomicrons (C27) and in the rates of tissue uptake (R170A and R170B) reflect the pattern of the rate of lipid absorption from the small intestine (figure 4.23).

Figure 4.39 gives the daily profiles of amino acids (A16) and urea (U4) in blood plasma. The concentrations of these metabolites are rather constant during the day as also observed in vivo (Blum et al. 1985). The diurnal variations in rates of amino acid uptake in the mammary gland (R51) and in body tissues (R52, R53) are shown

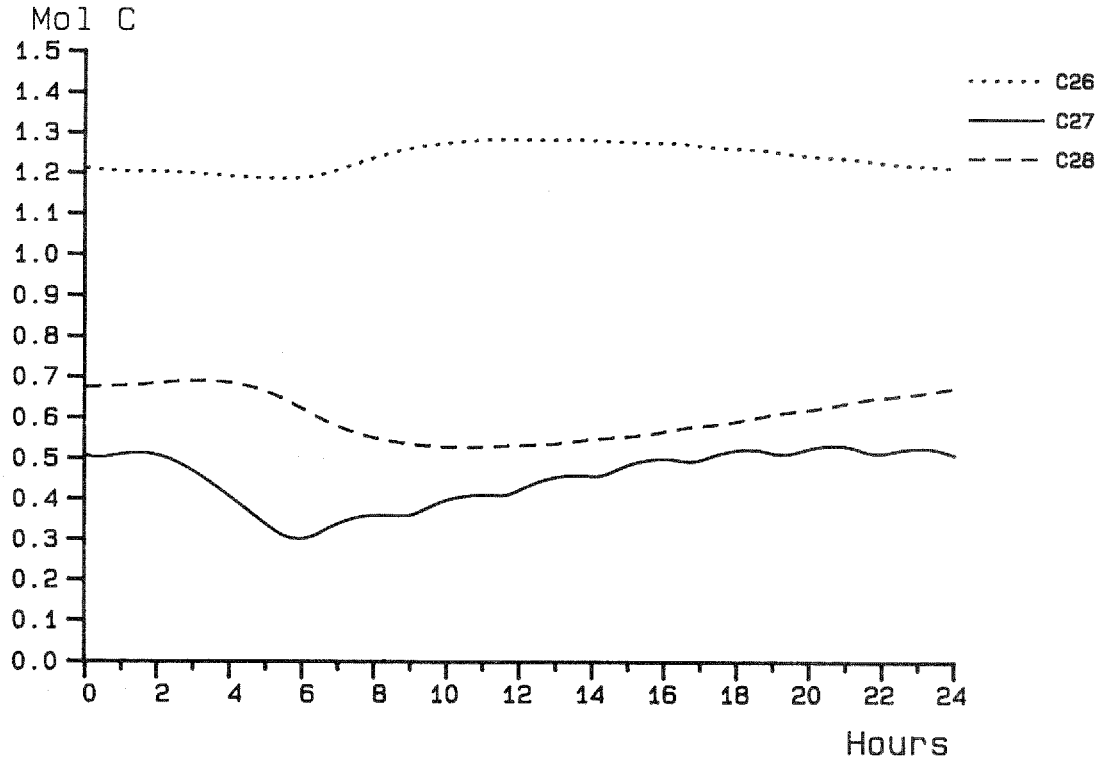


Figure 4.36. Simulated diurnal variations of blood plasma pool sizes of free fatty acids (C26), triglycerides in chylomicrons (C27) and triglycerides in liver lipoproteins (C28).

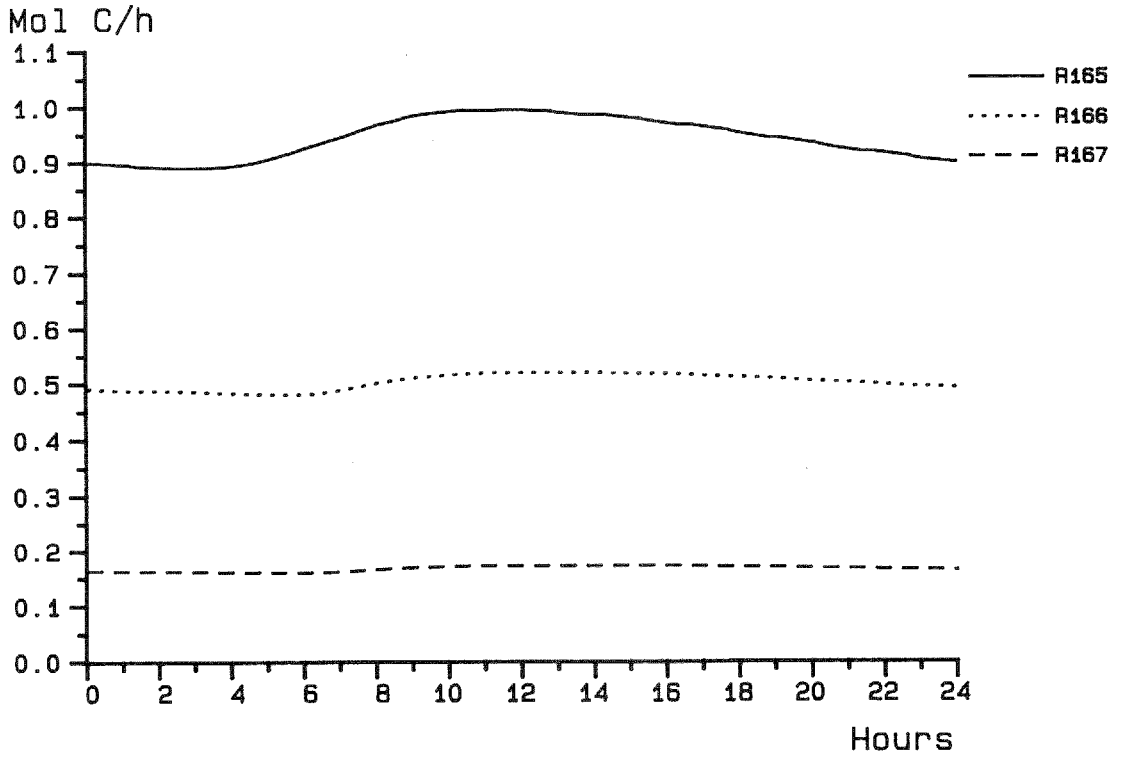


Figure 4.37. Simulated diurnal variations of rates of free fatty acid uptake in the liver (R165), muscle tissue (R166) and other tissues (R167).

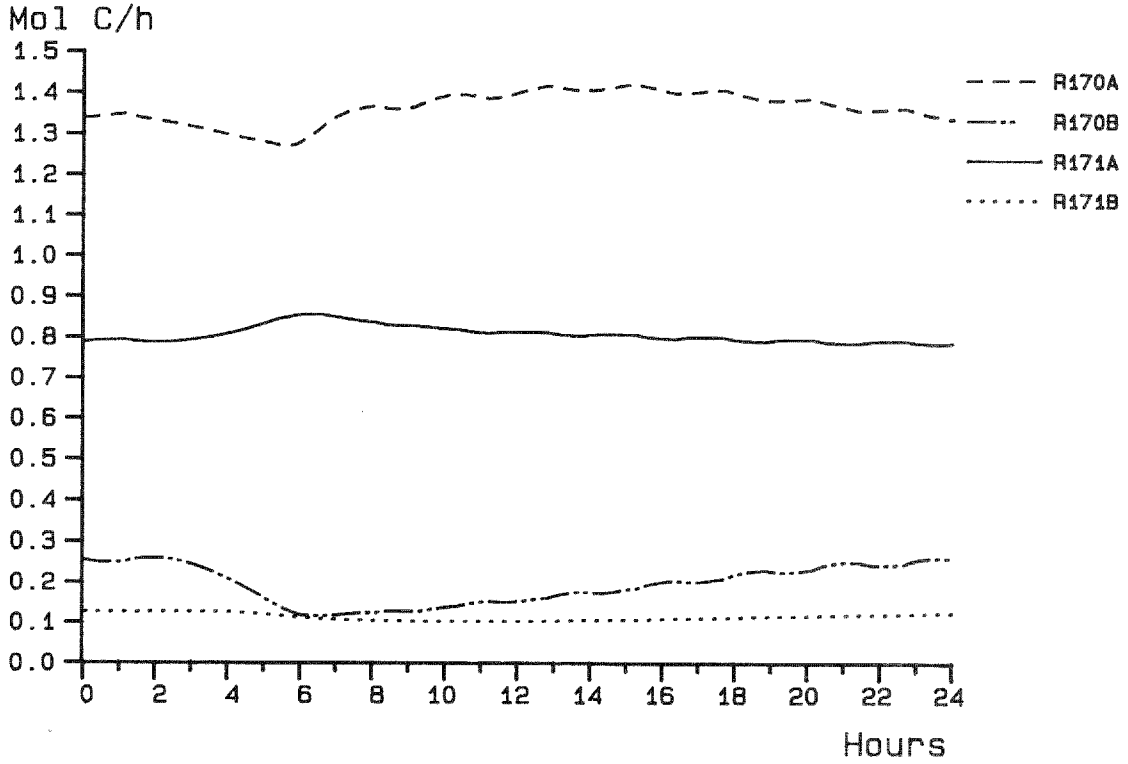


Figure 4.38. Simulated diurnal variations of rates of fatty acid and glycerol uptake in the mammary gland from chylomicrons (R17OA) and from lipoproteins (R171A), and in adipose tissue from chylomicrons (R17OB) and from lipoproteins (R171B).

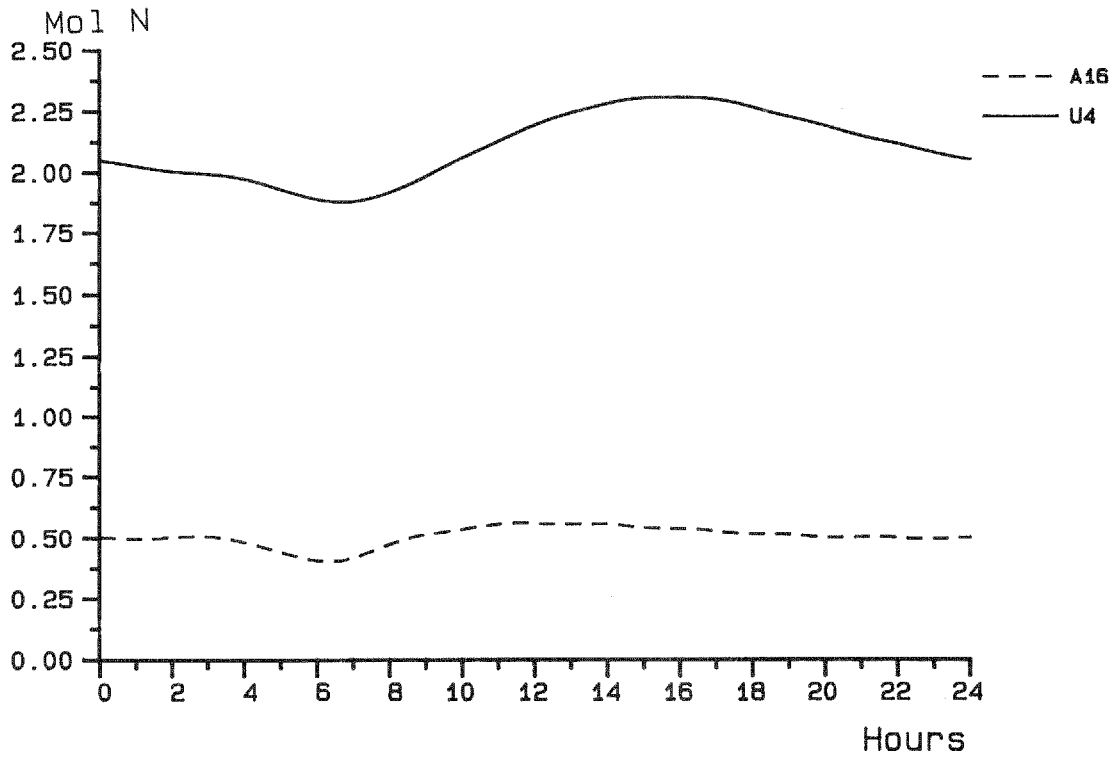


Figure 4.39. Simulated diurnal variations of blood plasma pool sizes of amino acids (A16) and urea (U4).

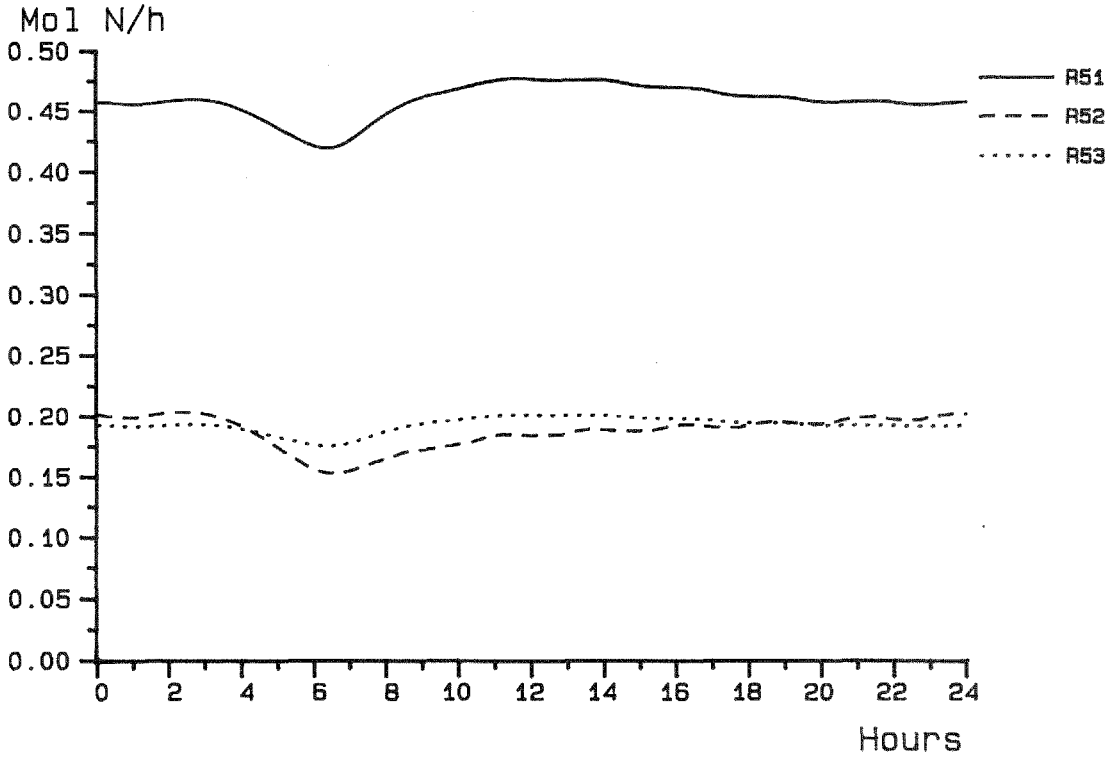


Figure 4.40. Simulated diurnal variations of rates of amino acid uptake in the mammary gland (R51), muscle tissue (R52) and other tissues (R53).

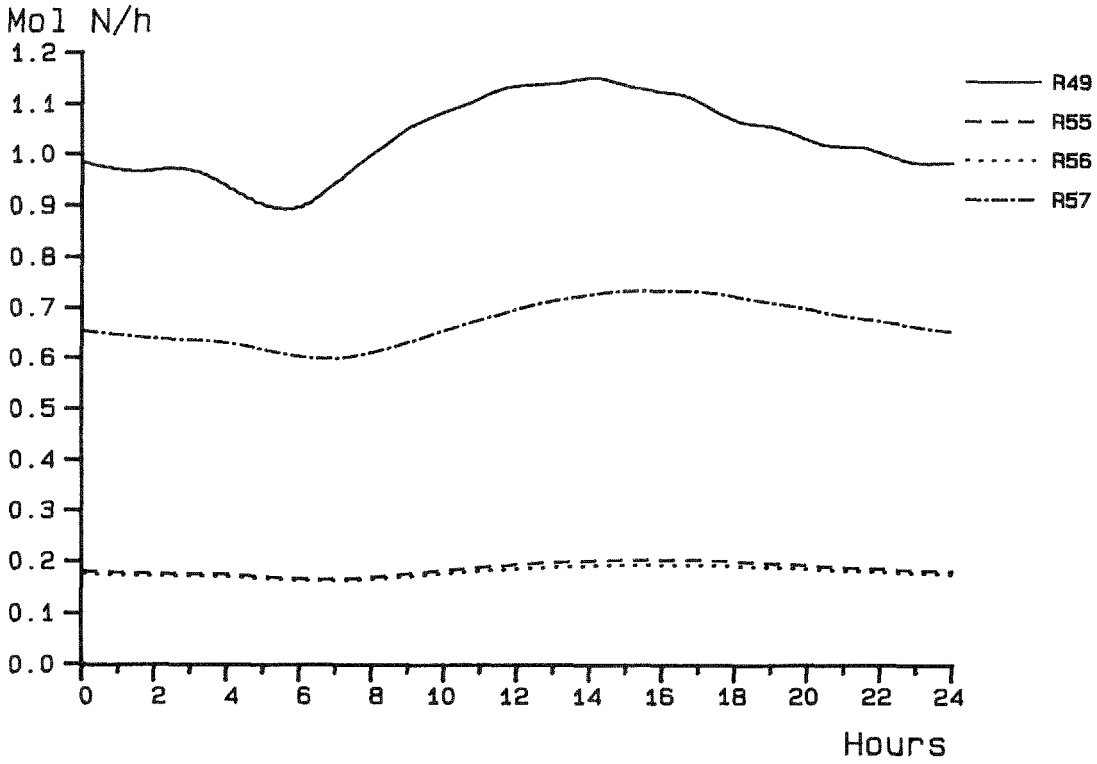


Figure 4.41. Simulated diurnal variations of rates of urea output from the liver (R49), urea uptake in the rumen (R55) and in the hind gut (R56), and urea excretion in the urine (R57).

in figure 4.40, and rates of urea production (R49), recycling (R55, R56) and excretion (R57) are in figure 4.41.

4.2.5 The mammary gland and body tissue compartments

The pool size of free fatty acids (C31) in the mammary tissue is very small in relation to the rate of flow through the pool (R179), and therefore its turnover rate constant is very high: R179/C31 = 2.94/0.12 = 25 h^{-1}. This results in very frequent and large oscillations in the pool during the day (figure 4.42) and consequently also in the rate of milk fat synthesis (R179, figure 4.43). However, the pool of milk fat in the gland (C34) is so large that the fluctuations in the rate of fat synthesis are absorbed in such a way, to make the milk fat secretion rate (R183) become almost constant. The secretion rates of lactose (R182) and milk protein (R60) are shown in figures 4.43 and 4.44.

Rates of muscle protein metabolism are given in figure 4.45. Protein breakdown (R63) and amino acid outflow from the tissue (R61) are almost equal and constant. The rate of protein synthesis (R62) decreases during the night until 06^{00} h from where it increases steadily with small peaks at times of feed intake. The shape of this curve resembles that of the plasma insulin concentration (figure 4.31) which regulates the rate of muscle protein synthesis (see subsection 3.3.4).

Figure 4.46 shows the simulated daily variations in rates of lipid metabolism in adipose tissue. The rate of fatty acid uptake (R173A) and the rates of the anabolic processes, fatty acid synthesis (R190) and fat synthesis (R195) vary in accordance with the

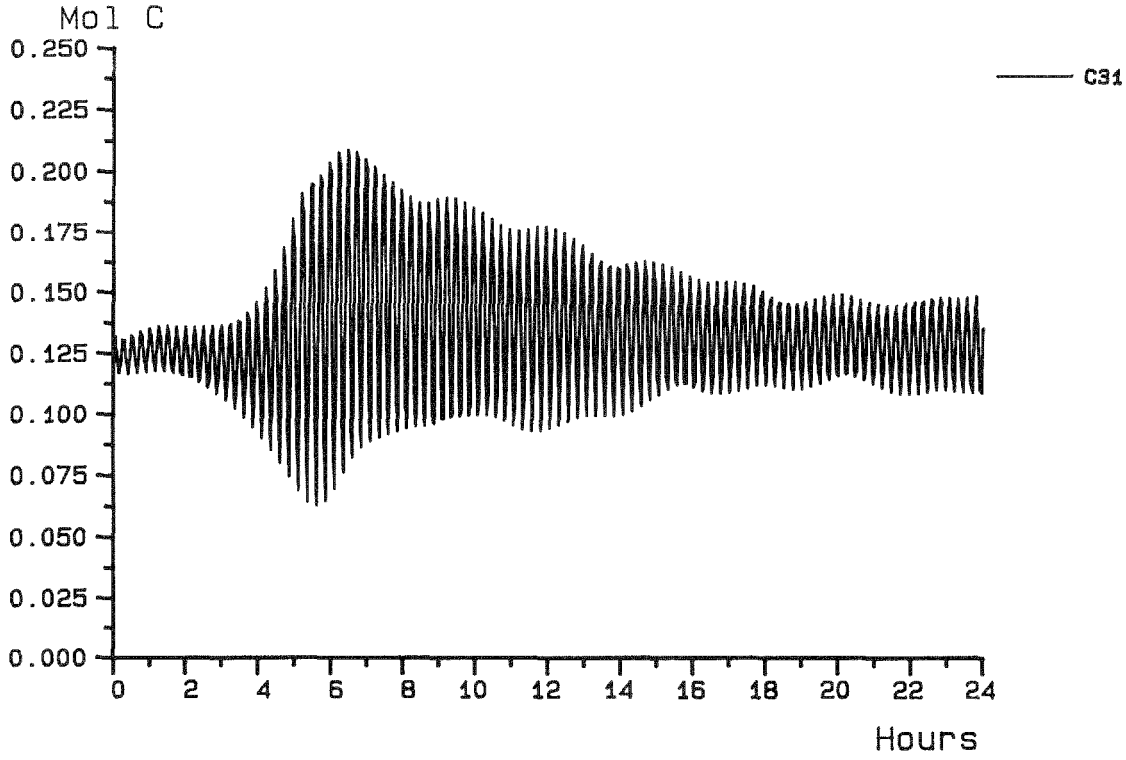


Figure 4.42. Simulated diurnal variation of the fatty acid pool in the mammary gland.

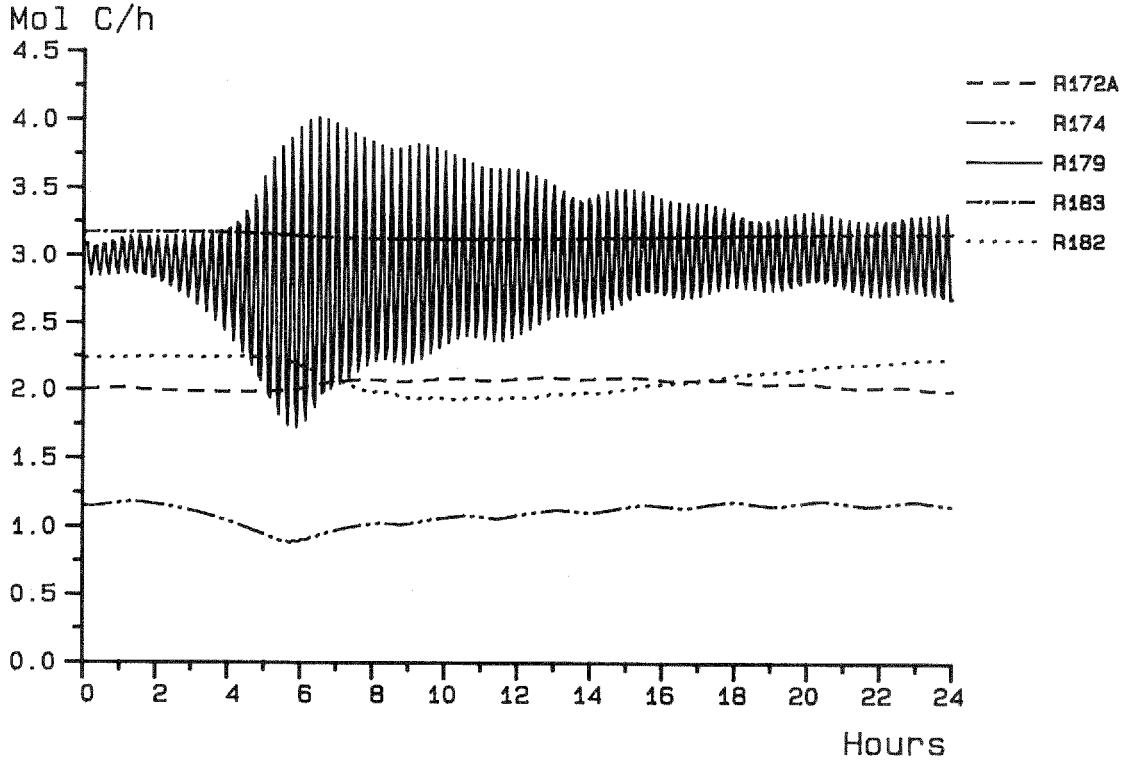


Figure 4.43. Simulated diurnal variations of metabolic rates in the mammary gland: uptake of fatty acids from blood lipids (R172A), fatty acid synthesis (R174), milk fat synthesis (R179), milk fat secretion (R183) and lactose secretion (R182).

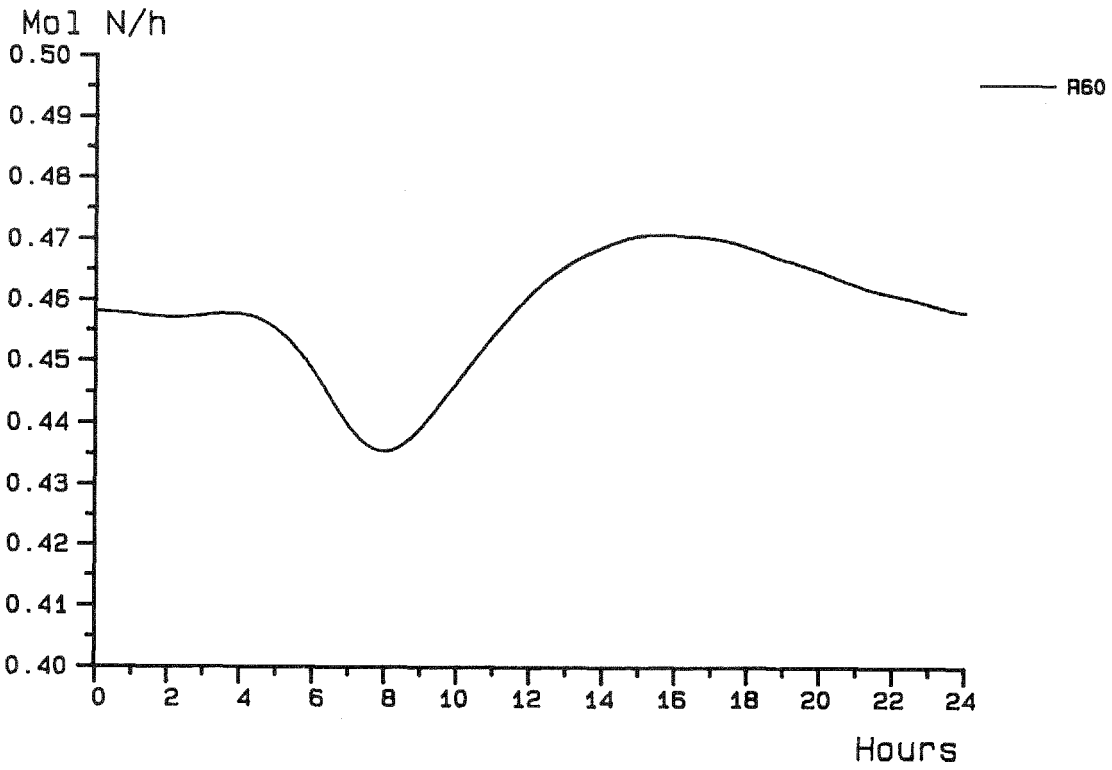


Figure 4.44. Simulated diurnal variation of the rate of milk protein secretion.

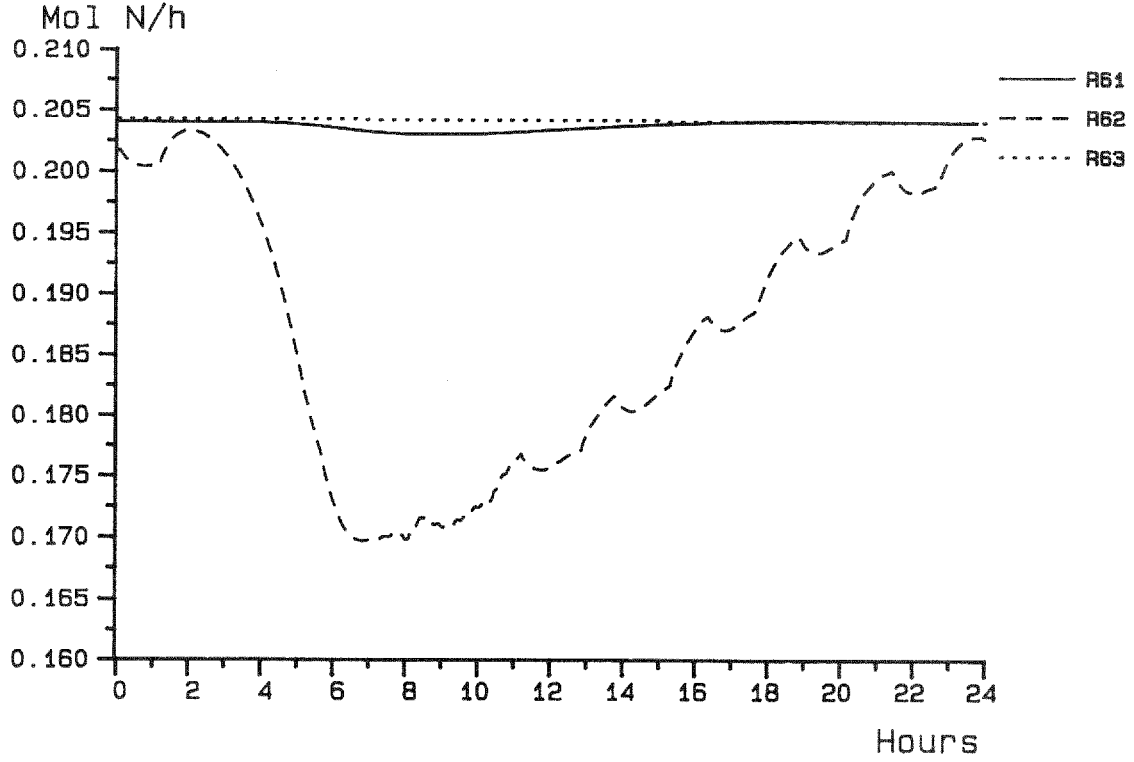


Figure 4.45. Simulated diurnal variations of rates of muscle protein metabolism: amino acid outflow (R61), protein synthesis (R62) and protein breakdown (R63).

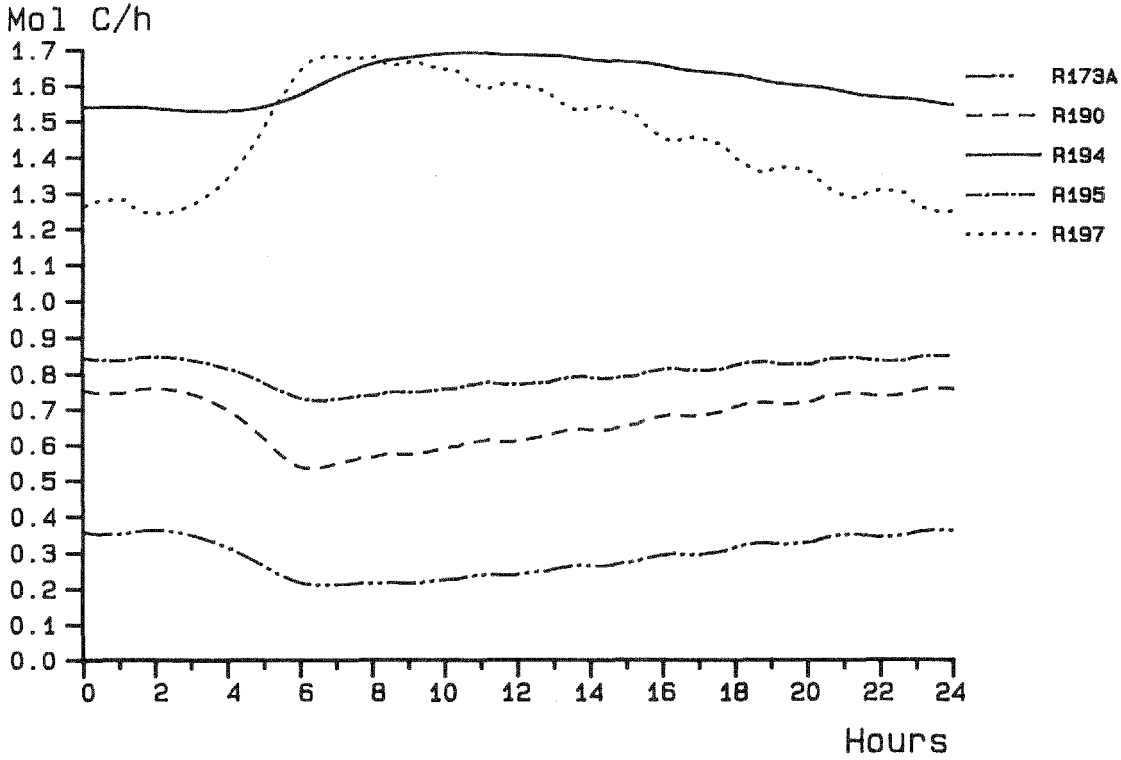


Figure 4.46. Simulated diurnal variations of rates of lipid metabolism in adipose tissue: uptake of fatty acids from blood lipids (R173A), fatty acid synthesis (R190), fatty acid outflow (R194), depot fat synthesis (R195) and depot fat breakdown (R197).

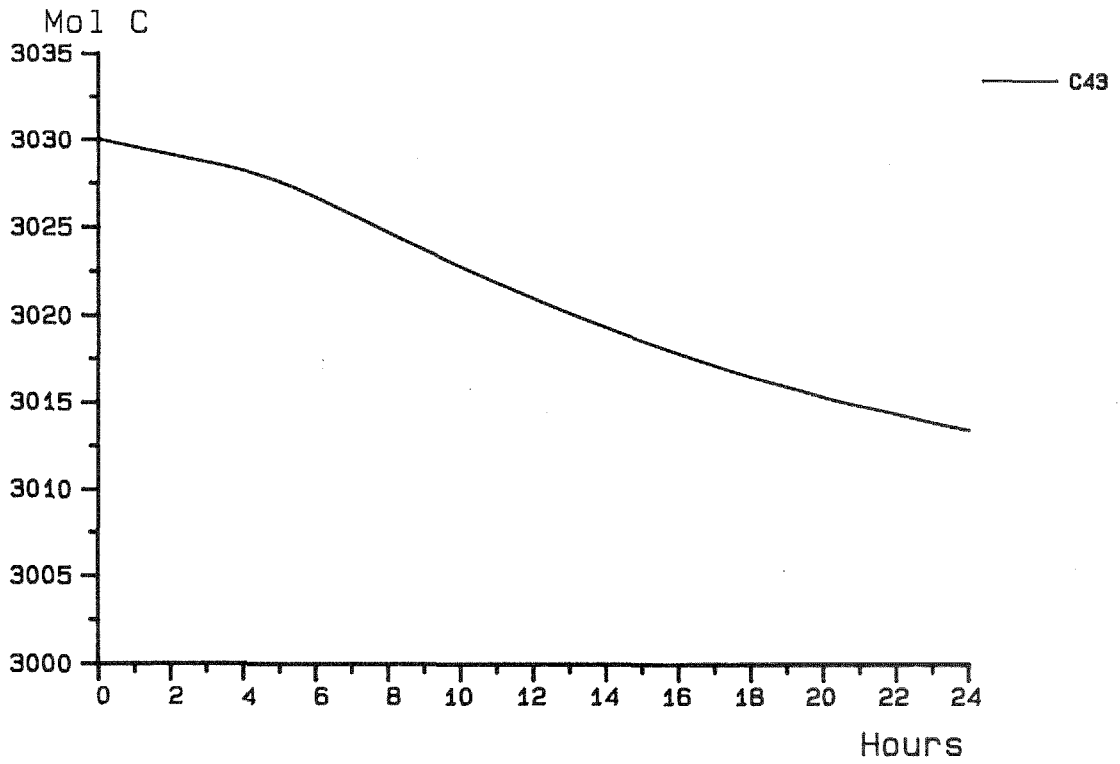


Figure 4.47. Simulated decrease of depot fat in adipose tissue during the day.

simulated blood plasma profiles of acetate and ketone bodies (C23, figure 4.33) and triglycerides (C27 and C28, figure 4.36). As the rate of lipolysis (R197) is inhibited by the plasma insulin concentration (INSUL), its curve has a different time course with a maximum at about 6 h, at which time INSUL is lowest (figure 4.31). The rate of fat mobilization is illustrated by the simulated decrease of depot fat during the day (figure 4.47).

In general, the very distinct diurnal variations in rumen nutrient pool sizes (e.g. figure 4.4) and in absorption rates from the rumen (e.g. figure 4.7) caused by the pattern of feed intake (figure 4.1) are more or less smoothed out in the nutrient pool sizes in the blood (e.g. figures 4.33 and 4.39) and in the rates of nutrient uptake by the tissues (e.g. figures 4.34 and 4.40). Although the fluctuations during the day of the parameter values in some cases are very large and irregular (e.g. figures 4.5, 4.12 and 4.17) all parameters return to or approach their initial values at the end of the day (i.e. the end of the run).

4.3 Stability of the model

The dynamic model has not been tested for stability using strictly mathematical methods. That would be an overwhelming task. Instead, the model is evaluated by examining some of the simulation results for stability through sequential runs.

The mean value, the standard deviation, and the minimum and maximum values of 10 runs (run 26-35) are given in Table 4.12 for some of the output variables. These are selected to represent feed in-

Table 4.12. Stability of output variables from the dynamic model through 10 runs (26-35).

Output variable	Mean value	Standard deviation	Minimum value	Maximum value
Dry matter intake, kg/d	17.98	0.00	17.98	17.98
Fermentation of carbohydrates, mol C/d	236.51	0.274	236.18	237.04
Absorption of acetate and ketone bodies, mol C/d	155.51	0.100	155.37	155.66
Absorption of propionate, mol C/d	74.14	0.061	74.05	74.25
Absorption of triglycerides, mol C/d	49.79	0.049	49.70	49.86
Absorption of amino acids, mol N/d	26.52	0.023	26.48	26.56
Gluconeogenesis, mol C/d	82.31	0.087	82.20	82.43
Lipoprotein synthesis, mol C/d	22.10	0.007	22.09	22.12
Urea excretion, mol N/d	16.06	0.024	16.03	16.12
Faecal energy, MJ/d	99.65	0.021	99.62	99.67
Milk production, kg/d	30.03	0.029	29.99	30.08
Live weight gain, kg/d	-0.526	0.0020	-0.529	-0.523
Net energy intake, MJ/d	116.54	0.065	116.46	116.65

Table 4.13. Stability of feed intake, milk production and live weight gain simulated by the dynamic model through 500 runs.

Output variable	Value	1-50	51-100	101-150	151-200	201-250	251-300	301-350	351-400	401-450	451-500	1-500
Dry matter intake, kg/d	Mean	17.98	17.98	17.98	17.98	17.98	17.98	17.98	17.98	17.98	17.98	17.98
	S.D.	0.085	0.00	0.155	0.00	0.00	0.00	0.132	0.082	0.00	0.00	0.074
	Min.	17.82	17.98	17.57	17.98	17.98	17.98	17.57	17.82	17.98	17.98	17.57
	Max.	18.48	17.98	18.64	17.98	17.98	17.98	18.64	18.48	17.98	17.98	18.64

(to be continued)

Table 4.13. (continued)

Output variable	Value	1-50	51-100	101-150	151-200	201-250	251-300	301-350	351-400	401-450	451-500	1-500
Milk production kg/d	Mean	30.03	30.06	30.02	30.07	30.08	30.02	30.45	30.54	30.56	30.56	30.24
	S.D.	0.050	0.046	0.142	0.029	0.037	0.064	0.202	0.046	0.019	0.032	0.253
	Min.	29.92	29.96	29.71	30.02	29.98	29.91	29.82	30.46	30.51	30.47	29.71
	Max.	30.17	30.13	30.44	30.13	30.14	30.12	30.60	30.62	30.60	30.61	30.62
Live weight gain, kg/d	Mean	-0.526	-0.525	-0.528	-0.524	-0.523	-0.527	-0.502	-0.497	-0.496	-0.496	-0.514
	S.D.	0.0037	0.0029	0.0102	0.0019	0.0025	0.0041	0.0133	0.0037	0.0016	0.0022	0.015
	Min.	-0.535	-0.532	-0.552	-0.528	-0.531	-0.535	-0.551	-0.505	-0.499	-0.502	-0.552
	Max.	-0.516	-0.520	-0.492	-0.521	-0.518	-0.521	-0.491	-0.490	-0.492	-0.492	-0.490

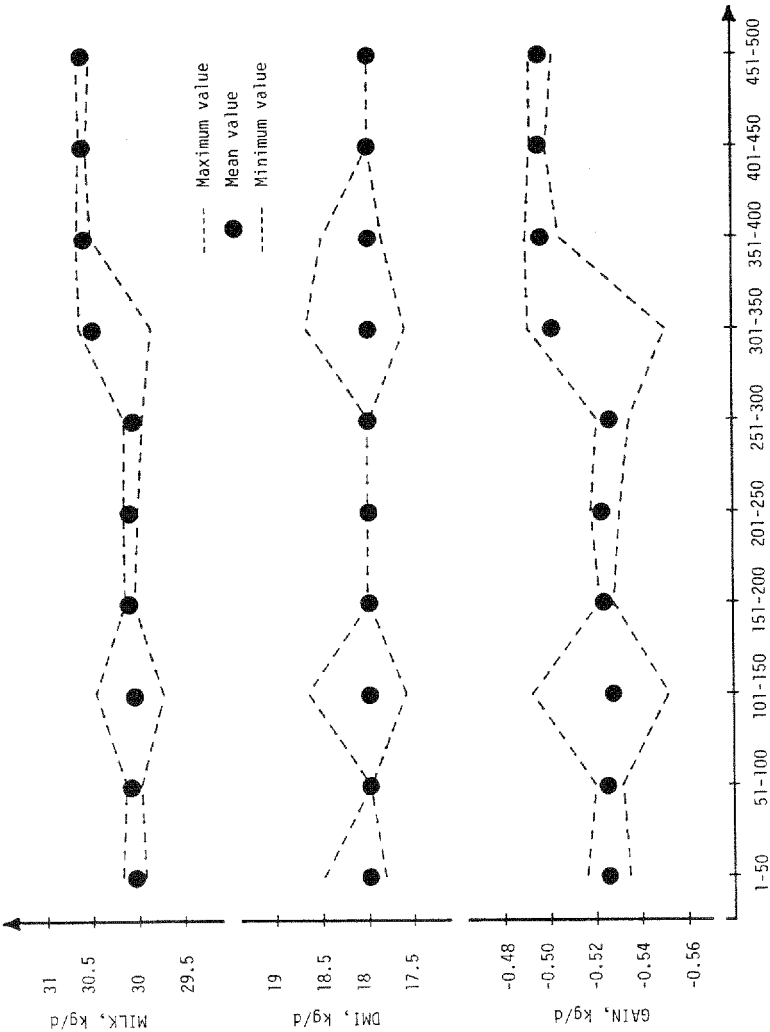


Figure 4.48. Mean, maximum and minimum values of dry matter intake, milk yield and live weight gain of the model cow in every 50 runs of simulation.

take, digestion, nutrient absorption, endogenous nutrient synthesis, urinary and faecal excretions, and production. The variations within 10 runs of the output variables in Table 4.12 are small and representative for practically all other output variables of the model.

Results of a more critical stability test after 500 runs of simulation are shown in Table 4.13. Mean values, standard deviations, and minimum and maximum values are given for dry matter intake, milk production and live weight gain. The analysis is made for every 50 runs as well as for all 500 runs. The simulated dry matter intake is very stable throughout the 500 runs. Milk production and live weight gain are stable through runs 1-300. Thereafter both these output variables seem to increase through runs 301-350 and then again stabilize at a slightly higher level. These trends are illustrated in figure 4.48. It is not tested if the model remains stable after more than 500 runs of simulation.

5 USE OF THE MODEL

The dynamic model has been developed to simulate a specific situation: a nonpregnant dairy cow at 44 days post partum fed ad libitum on a complete mixed diet of a given composition. A good model should be able to simulate situations different from those presumed in the definition of the model. Results of this kind of simulations are given in the present chapter. Firstly, the performance of the model cow is tested at different stages of lactation (section 5.1). Simulated effects of growth hormone administration on animal performance are referred to in section 5.2, and in section 5.3 results of an accomplished feeding trial are simulated. Finally, more detailed simulations of the regulation of gluconeogenesis are given in section 5.4.

5.1 Simulation of animal performance at different stages of lactation

Progressing lactation is characterized by a gradually changed nutrient partitioning in favour of body tissues. The nutrient partitioning during lactation is a homeorhetic adaptation controlled by hormonal factors (Bauman & Elliot 1983). These hormonal factors have not yet been completely identified or understood, but growth hormone, insulin and glucagon all seem to play an important role in determining milk yield capacity of cows (Hart et al. 1978, Thilsted 1980, Peel et al. 1981a, Danfær et al. 1988). The peripheral blood concentrations of these hormones are included in the model (see subsection 3.3.3) by means of the following equations:

$$GH = 16.7+0.04607*M-0.00964*B-0.00567*D$$

(conc. of growth hormone, ng/ml)

$$GLUCA = ALPHA+0.00514*M-0.00173*B+1.7*10^{-6}*B^2 +6.6*10^{-4}*D-1.2*10^{-6}*D^2$$

(conc. of glucagon, ng/ml)

$$INSUL = BETA-0.01106*M+6.7*10^{-4}*B+0.00134*D-3.0*10^{-6}*D^2$$

(conc. of insulin, ng/ml)

$$ALPHA = 0.793*R133/(2.2355+R133)+0.45$$

(ng(ml)

$$BETA = 0.86871*(R133+KCA*R40)/(15.0+R133+KCA*R40)+0.05*C24$$

(ng/ml)

R133 = absorption rate of propionate (mol C/h)

KCA*R40 = absorption rate of amino acids (mol C/h)

C24 = glucose pool size in extracellular fluid (mol C).

The parameters M, B and D are milk yield (kg/d), body weight (kg) and days after parturition, respectively, from the data of Herbein et al. (1985). In this way the hormone concentrations in the model are related to the stage of lactation. The rates of nutrient uptake and metabolism in different tissues are to some extent regulated by the hormone concentrations (see subsections 3.3.3 and 3.3.4).

Feed intake, digestion and metabolism of nutrients, as well as production of the model cow at different times during the lactational period can thus be simulated by changing a few parameter values in the model, namely D, M and B. It should be pointed out that M (milk yield) and B (body weight) represent the performance

of the cows in the study of Herbein et al. (1985) and not the performance of the model cow. The values of D, M and B used in the model during simulations of the lactational period are as follows:

Post partum interval, days	D	M	B
0-30	16	26.5	571
31-60	44	29.7	561
61-90	73	29.2	563
91-120	107	27.2	569
121-150	136	25.3	580
151-180	165	23.9	592
181-210	195	22.4	608
211-240	223	21.2	622
241-270	257	19.7	628
271-300	286	18.2	618

The values of B at D = 195 and of M at D = 223 are slightly changed from the data of Herbein et al. (1985).

The simulated results of animal performance (milk yield, live weight gain and body weight) at different stages of lactation are plotted in figure 5.1. Milk yield (kg 4% milk/d) and live weight gain (kg/d) are estimated directly by the model, while body weight (kg) is calculated from the rates of daily gain and a body weight of 600 kg at D = 44. The curves with filled symbols are from the model as presented in chapter 4, and the curves with open symbols are produced after further changes of some parameter values.

The shape of the lactation curve simulated by the original model is typical for high-yielding dairy cows (Bauman & Currie 1980, Goodall & Sprevak 1984, Bauman et al. 1985, Andries et al. 1988). Peak yield is 30.1 kg FCM/d at 44 days post partum and at the

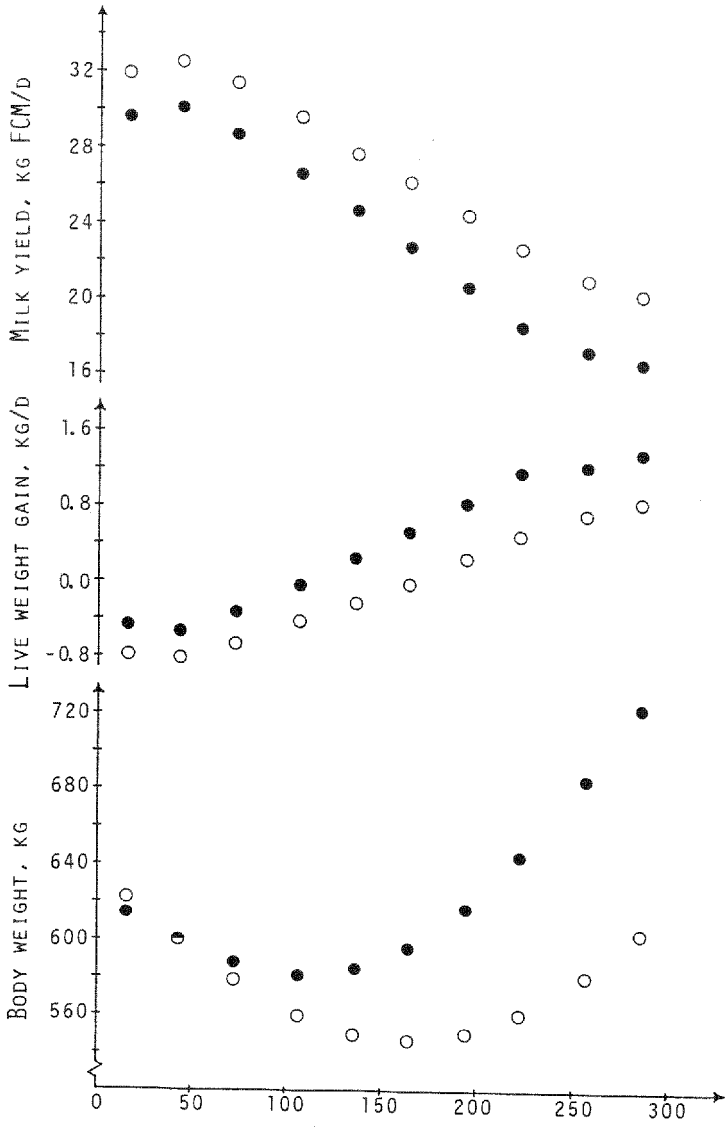


Figure 5.1. Simulated lactational performance of the model cow.
● With the original parameter values
○ After change of parameter values (see text).

latest stage of lactation (286 days post partum) the yield has declined to 16.7 kg FCM/d. The daily gain has its minimum, -0.53 kg, at 44 days, its maximum, 1.37 kg, at 286 days, and is zero at about 110 days post partum. Consequently, the body weight of the model cow is minimum at this time (16 weeks after calving). At the end of the simulated period (D = 286) the body weight has increased to 724 kg from 614 kg at the beginning (D = 16). The shape of the simulated weight curve is similar to that of the control cows in the experiment of Bauman et al. (1985). These cows weighed about 590 kg at 30 days, 545 kg (minimum weight) at 125 days, and 700 kg at 265 days post partum. The body weights of the model cow at corresponding lactational stages are 606, 582 and 696 kg, respectively. The apparently lower rate of weight loss in the model cow as compared to the cows in the experiment can be explained by the higher peak yield (about 40 kg/d) of these animals.

By changing the values of a few parameters (L156, M160, L51, M51, L195, M195, L197 and M197) in the model the performance of another cow with different tissue responsiveness to growth hormone and insulin can be simulated. The parameters are elements in the following equations:

```
R156 = K156*(C23/V4)          (acetate and ketone body uptake
                               in the mammary gland, mol C/h)

K156 = L156+M156*GH           (l/h)

R160 = R160M*C24/(K160+C24)   (glucose uptake in the
                               mammary gland, mol C/h)

R160M = L160+M160*GH          (mol C/h)

R51 = R51M*A16/(K51+A16)      (amino acid uptake in the
                               mammary gland, mol N/h)
```

R51M = L51+M51*GH (mol N/h)

R195 = R195M*C41/(K195+C41) (fat synthesis in adipose tissue, mol C/h)

R195M = L195+M195*INSUL (mol C/h)

R197 = R197M*C43/(K197+C43) (fat breakdown in adipose tissue, mol C/h)

R197M = L197-M197*INSUL (mol C/h).

The parameter values are changed in such a way that the milk production of the model cow will be about 3 kg/d higher than before at 44 days in lactation:

	Numerical value changed	
Parameter	from	to
L156	-441.730	-390.14
M160	0.8491	0.934
L51	- 1.4889	- 2.400
M51	0.1790	0.278
L195	0.0	0.587
M195	3.383	2.4816
L197	9.454	8.799
M197	11.375	9.732

The new parameter values imply that for given concentrations of growth hormone (GH) and insulin (INSUL) in the model more nutrients will be taken up by the mammary gland and less fat will be stored in adipose tissue. Hence, the performance of a cow with a higher potential for milk yield and a lower potential for body gain will be simulated.

After the parameters have been changed, the milk yield is 32.5 kg FCM/d at 44 days and 20.3 kg/d at 286 days post partum. The rate of body weight change is -0.8 kg/d in early lactation, it is zero at 165 days and 0.86 kg/d at 286 days from parturition. The resultant body weight is 622 kg at the beginning (D = 16) and only 604 kg at the end of the period (D = 286).

The differences between the two sets of simulated curves in figure 5.1 serve to illustrate how cows with different tissue sensitivity to metabolic hormones respond to the same feed during lactation. This could be part of the complex interactions of physiological factors which determine the genetic capacity for milk production.

5.2 Simulation of growth hormone treatments

It has been known for 40-50 years that extracts from the anterior pituitary stimulate milk production in cows (Asimov & Krouze 1937, Young 1947). Effects of growth hormone injections into dairy cows have been studied in many experiments in more recent years (Machlin 1973), especially after recombinant bovine growth hormone has become available (Bauman et al. 1982, Bauman et al. 1985, Soderholm et al. 1988, Elvinger et al. 1988).

Short-term administration of growth hormone by which feed intake is not increased (Peel et al. 1981a) can be simulated by the dynamic model. This is accomplished by changing the intercept value of the equation describing growth hormone concentration in blood plasma (ng/ml):

GH = 16.7+0.04607*M-0.00964*B-0.00567*D.

The simulations are performed at 2 lactational stages, 73 and 257 days after calving, with use of the intercept values listed below together with the resulting values of GH:

D = 73			D = 257		
Level of treatment	Inter-cept	GH	Level of treatment	Inter-cept	GH
0.0	16.7	12.20	0.0	16.7	10.10
0.8	17.5	13.00	0.65	17.35	10.75
1.6	18.3	13.80	1.3	18.0	11.40
2.5	19.2	14.70	1.8	18.5	11.90
			2.3	19.0	12.40

The doses of growth hormone administration are regarded as the increases of the intercept from the original value, 16.7. Results of the simulations are presented in figures 5.2-5.4. The milk yield is increased by increasing levels of treatment in the model, both in early and in late lactation. The absolute as well as the relative increases in milk yield are dependent on the level of treatment in a curvilinear fashion (figures 5.2 and 5.3) as found by Bauman et al. (1985) and Eppard et al. (1985). The relative response to increasing "doses" of growth hormone is much higher in late than in early lactation as shown by Peel et al. (1983), who examined the effects of growth hormone treatment 12 and 35 weeks post partum. The highest level of treatment results in 4.3 kg more milk per day in early lactation, which is of the same magnitude as found in several experiments (Peel et al. 1981a, Bauman et al. 1982, Peel et al. 1982a&b, Peel et al. 1983, Peel et al. 1985), but the corresponding increase in plasma growth hormone concentra-

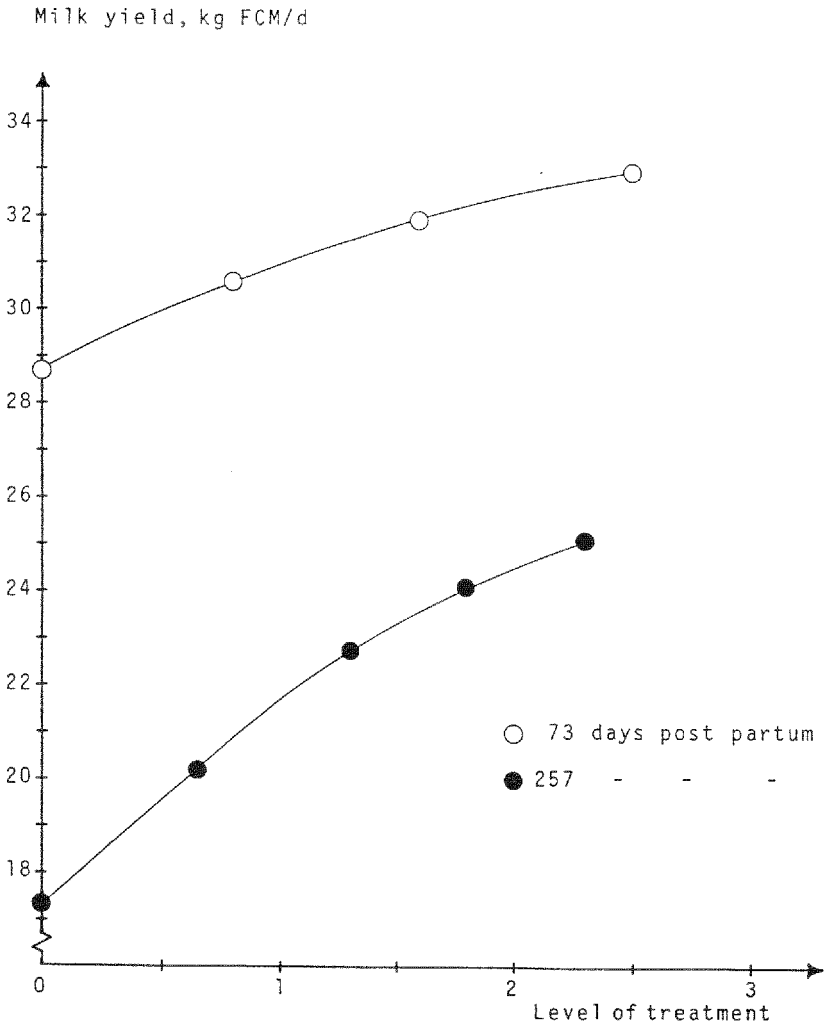


Figure 5.2. Simulated responses in milk yield to increasing doses of growth hormone treatment at 2 stages of lactation.

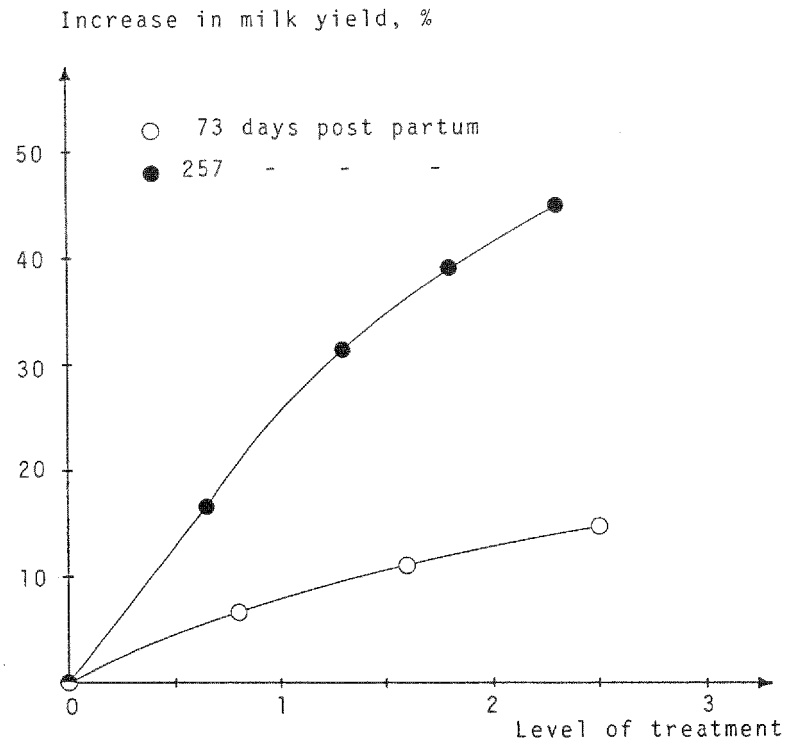


Figure 5.3. Simulated effects of increasing doses of growth hormone treatment on relative increases in milk yield at 2 stages of lactation.

tion in the model is much lower than observed in vivo. In late lactation the simulated response is higher than found in the study of Peel et al. (1983), but it is similar to the response reported by Eppard et al. (1985) in cows 192 days after calving.

The effects of growth hormone treatment on some other output variables in the model are: unchanged feed intake, decreased energy balance, decreased glucose and insulin plasma concentrations, and increased concentration of free fatty acids. It is generally observed in short-term experiments (10 days of growth hormone treatment) that feed intake is unaltered or slightly decreased, energy balance is decreased, free fatty acid levels are increased, but glucose and insulin concentrations are unaffected (Peel et al. 1981a, 1982a&b, 1983).

The efficiency of milk production can be expressed as kg milk per unit of net energy intake. This ratio can also be regarded as a measure of nutrient partitioning between the mammary gland and the body tissues. As both growth hormone and insulin are important factors in the regulation of nutrient partitioning, a relationship between the ratio of these two hormones and the efficiency of milk production could be expected. This relationship is illustrated in figure 5.4, where the simulated milk yield per feed unit (SFU) is plotted against the simulated ratio of growth hormone to insulin concentrations. A common relationship between these parameters for cows at different parities and lactational stages has been shown by Danfær et al. (1988). However, the two curves in figure 5.4 representing the two lactational stages (73 and 257 days post partum) do not seem to be parts of such a common relationship.

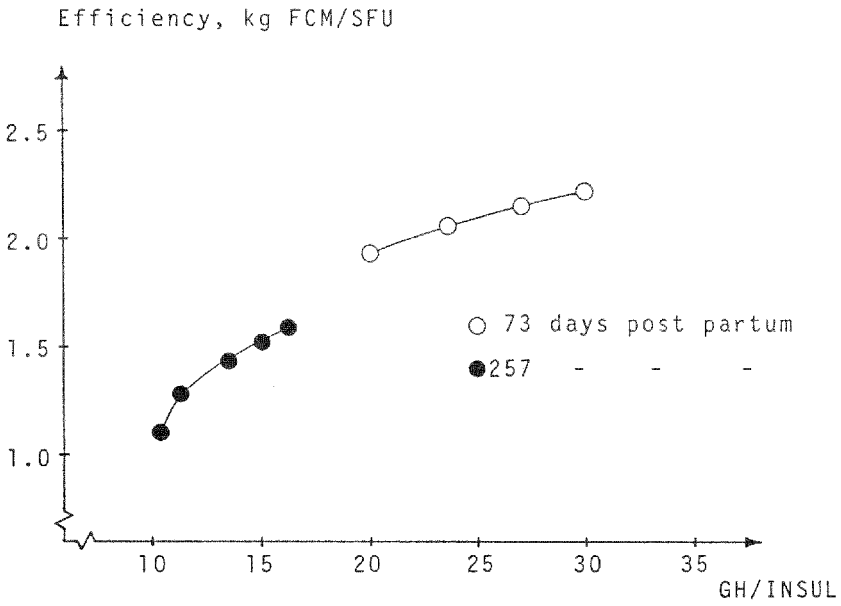


Figure 5.4. Simulated relationship between the ratio of growth hormone to insulin plasma concentrations and the efficiency of milk production at 2 stages of lactation.

5.3. Simulation of a feeding experiment

The use of the dynamic model has been evaluated so far by comparison of the simulated results with corresponding experimental data from different references. In this section the model is used to simulate the outcome of a single feeding experiment. Then the answer of the model can be tested against hard evidence from that experiment without any need for corrections or modifications because of different experimental conditions.

The experiment used for the simulation is a feeding trial in which cows were offered a total mixed diet ad libitum (Krohn & Konggaard 1987). The experimental period was 7.-28. week of lactation, but the results used here relate to a shorter period of the experiment, 15.-21. week of lactation. The average body weight of the cows was 580 kg. The composition of the feed is given in Table 5.1.

The results of 3 simulations are presented (Table 5.3). In the first simulation (A), the model is used with the original parameter values except for those concerned with feed composition, body weight and stage of lactation (Table 5.2). The second simulation (B) is performed with the parameter values changed in section 5.1 to simulate a different partitioning of nutrients. In the third simulation (C), more parameter values concerned with nutrient uptake and fat turnover in adipose tissue have been adjusted. The numerical values of all parameters that have been subjected to changes are listed in Table 5.2. The simulated results given in Table 5.3 are averages of runs 26 to 35.

Table 5.1. Composition of an experimental feed ration[1]) as used in the simulations.

Feedstuff	% af total dry matter
Concentrates	38.0
Fodder beets	39.6
Beet top silage	10.2
Straw	12.2
Nutrient	**g/kg dry matter**
Sugar	261.1
Starch	67.3
Cell wall carbohydrates	350.6
Crude fat	49.0
Crude protein	198.5
Ash	73.5

1) From Krohn & Konggaard (1987)

Table 5.2. Adjustments of parameter values during simulations of a feeding experiment[1].

Parameter	Symbol	Numerical value
Feed composition, kg/kg DM		
Sugar	KSU	0.2611
Starch	KST	0.0673
Cell wall carbohydrates	KCE	0.3506
Glycerol	KGL	0.0052
Fatty acids	KLI	0.0438
Concentrate protein	KC	0.1458
Roughage protein	KR	0.0527
Unfermentable fraction of concentrate protein	MC	0.10
Unfermentable fraction of roughage protein	MR	0.20
Body weight, kg	BW	580
Stage of lactation		
Days of lactation	D	136
Arbitrary body weight	B	580
Arbitrary milk yield	M	25.3

1) Krohn & Konggaard (1987)

(to be continued)

Table 5.2. (continued)

Parameter	Symbol	Numerical value in simulation A	B	C
Nutrient uptake				
Acetate and ketone bodies in mammary gland	L156	-441.730	-390.14*	-441.730
- -	M156	83.128	83.128	110.50*
Acetate and ketone bodies in muscle tissue	K157	99.555	99.555	350.0*
Acetate and ketone bodies in adipose tissue	M158	453.274	453.274	230.0*
Acetate and ketone bodies in other tissues	K159	175.805	175.805	450.0*
Glucose in mammary gland	L160	-6.4605	-6.4605	-4.8890*
- - - -	M160	0.8491	0.9340*	0.7900*
Glucose in muscle tissue	M161	1.3924	1.3924	1.2567*
Glucose in adipose tissue	M162	0.7331	0.7331	0.6595*
Lipid in mammary gland	M170A	2.2424	2.2424	2.150*
- - - -	M171A	1.3273	1.3273	1.300*
Lipid in adipose tissue	L170B	1.4913	1.4913	2.000*
- - - -	L171B	0.8826	0.8826	1.200*
Amino acids in mammary gland	L51	-1.4889	-2.400*	-1.4889
- - - -	M51	0.1790	0.2780*	0.1680*

A: Parameter values in the original model
B and C: Adjusted parameter values (see text)
*: Value changed

(to be continued)

Table 5.2. (continued)

Parameter	Symbol	Numerical value in simulation A	B	C
Adipose tissue metabolism				
Fat synthesis	L195	0.0	0.5870*	0.3106*
- -	M195	3.383	2.4816*	2.7775*
Lipolysis	L197	9.454	8.7990*	8.1432*
-	M197	11.375	9.7320*	8.8475*

A: Parameter values in the original model
B and C: Adjusted parameter values (see text)
*: Value changed

Table 5.3. Observed and simulated results of a feeding experiment[1].

Parameter	Observed results	Simulated results A	B	C
Dry matter intake, kg/d	**19.7**	19.87	19.85	19.85
Milk yield, kg/d	**28.1**	25.42	28.79	28.11
Milk fat yield, kg/d	**1.143**	1.040	1.238	1.142
Milk protein yield, kg/d	**0.892**	1.041	1.198	0.892
Live weight gain, kg/d	**0.329**	0.674	0.035	0.339
Net energy intake, MJ/d	**131.0**	137.3	135.4	131.3

1) Krohn & Konggaard (1987)
A: Simulated by the original model
B and C: Simulated after adjustment of parameter values (see Table 5.2)

The original model (A) gives almost the correct feed intake, but the milk yield is too low, and the live weight gain is too high compared to the experimental results. The milk protein yield is 17% too high. The model adjusted to simulate a different lactation curve (B) improves the prediction of milk yield, but live weight gain is underestimated, and milk protein yield is much too high. In the final simulation (C), the deviations from the experimental results are very small.

5.4 Simulated regulation of gluconeogenesis

The demand for glucose is high in lactating cows. The volume of milk produced is determined by the secreted amount of lactose, which is primarily synthesized from glucose. As the absorption of glucose is normally small, a high and constant rate of gluconeogenesis is crucial to a high milk yield.

Propionate and amino acids are the only substrates which can contribute to net synthesis of glucose. The quantitative importance of propionate is generally recognized (Elliot 1980), whereas the role of amino acids is more equivocal and debated (Black et al. 1968, Bruckental et al. 1980). If a significant proportion of gluconeogenesis has to be met by use of amino acids it could have a great impact on the protein requirement. The following questions are relevant to this problem:

- How much of the synthesized glucose is derived from propionate and from amino acids when different diets are fed?

- How are the contributions of propionate and amino acids to glu-

cose synthesis regulated?

The model can be used to elucidate these questions. For that purpose an experiment is simulated in which 3 different rations are fed to dairy cows in early lactation (44 days after calving). Parameters concerned with the following processes will be "recorded" in the experiment:

- feed intake, digestion and absorption
- liver metabolism
- animal production
- energy and protein utilization.

The experimental diets used in the simulations are characterized by a high starch content (HS), a high protein content (HP), and by a content of starch and protein protected against rumen fermentation (BSP). Their chemical composition is given in Table 5.4. The starch and protein contents are 346 and 124, 44 and 193, and 195 and 159 g per kg dry matter in rations HS, HP, and BSP, respectively. In ration BSP 20% of the starch and 57.5% of the concentrate protein (equivalent to 35.5% of total protein) are made unfermentable. All 3 diets contain the same amounts of cell wall carbohydrates (397-398 g/kg dry matter) and crude fat (45 g/kg dry matter).

Table 5.5 shows some of the simulation results. The rates of carbohydrate fermentation, microbial protein production, and propionate absorption are highest on diet HS with the high starch content, and lowest on diet BSP with protected starch and protein. The low fermentation rate of this diet reduces the feed intake by 3 kg dry matter/d compared to the other 2 diets. The rate of passage to the small intestine of undegraded feed protein is lowest

Table 5.4. Chemical composition (g/kg dry matter) of diets used in a simulated experiment on regulation of gluconeogenesis.

Nutrient	Ration HS (high starch)	HP (high protein)	BSP (bypass starch and protein)
Sugar	34	216	125
Starch	346	44	195*)
Cell wall carbohydrates	397	397	398
Crude fat	45	45	45
Crude protein	124	193	159**)
Ash	54	105	78
Total	1000	1000	1000

*) 20% of starch is unfermentable
**) 57.5% of concentrate protein is unfermentable

on diet HS and highest on diet BSP with protected protein. This results in almost the same rate of amino acid absorption from the 3 diets, although it is lowest from diet HS. The rate of glucose absorption is low on diets HS and HP, and about 5 times higher from diet BSP with protected starch.

In the model the blood plasma concentration of glucagon is increased by the rate of propionate absorption, and the concentration of insulin is increased by the propionate and amino acid absorption rates and by the size of the extracellular glucose pool (see subsection 3.3.3). The concentration of glucagon is therefore highest on diet HS and lowest on diet BSP, while the insulin concentration is highest on diet BSP and lowest on diet HP. The ratio of glucagon to insulin concentrations, which is regulating the processes of gluconeogenesis, is consequently highest on diet HP and lowest on diet BSP: 1.15 (HS), 1.21 (HP) and 0.99 (BSP).

The rate of gluconeogenesis is highest on diet HS (16 mol glucose/d) with the greatest availability of propionate, while it is lower (13.5 mol glucose/d) on the other 2 diets. The contributions of propionate and amino acids to glucose synthesis are regulated partly by the availability of the 2 substrates and partly by the ratio of glucagon to insulin concentrations. When this ratio increases, the rate of gluconeogenesis from amino acids is increased relatively more than that from propionate (see subsection 3.3.3). The result of these regulations is that the highest contribution of propionate (81%) and the lowest contribution of amino acids (3%) to glucose synthesis is seen with the high starch/low protein diet (HS), and that the highest contribution of amino acids (20%) is with the high protein/low starch diet (HP). The availability of propionate is higher on diet HP (25 mol/d) than on diet BSP (23 mol/d), but the rates of gluconeogenesis from propionate do not differ between the 2 diets. The availability of amino acids is

Table 5.5. Simulated effects of diet composition on absorption, gluconeogenesis and production in lactating cows.

Variable or Rate of process (d^{-1})	Ration HS (high starch)	HP (high protein)	BSP (bypass starch and protein)
Feed intake and digestion			
Dry matter intake, kg	18.64	18.60	15.62
Carbohydrate fermentation, mol C	391.4	307.3	270.0
Microbial protein production, mol N	26.1	20.8	18.2
Passage of undegraded dietary protein, mol N	9.3	13.8	16.6
Absorption of propionate, mol C	106.4	74.8	68.5
Absorption of glucose, mol C	5.0	4.6	24.5
Absorption of amino acids, mol N	26.6	28.5	27.9
Liver metabolism			
Glucagon:insulin	1.15	1.21	0.99
Glucose synthesis, mol C	96.3	81.1	80.5
from propionate, %	81.0	65.0	65.3
from amino acids, %	3.1	19.9	14.5

(to be continued)

Table 5.5. (continued)

Variable or Rate of process (d^{-1})	Ration HS (high starch)	HP (high protein)	BSP (bypass starch and protein)
Liver metabolism			
Propionate metabolism, mol C	106.4	74.8	68.5
gluconeogenesis, %	73.4	70.5	76.7
oxidation, %	26.6	29.5	23.3
Keto acid metabolism, mol C	24.4	26.8	21.3
gluconeogenesis, %	12.3	60.0	54.6
oxidation, %	87.7	40.0	45.4
Amino acid catabolism, mol N	6.43	7.06	5.61
Glucose available to peripheral tissues, mol C	101.3	85.7	105.0
Amino acids available to peripheral tissues, mol N	20.8	21.2	21.9
Production			
Milk yield, kg	33.70	29.93	34.95
Milk fat yield, kg	1.07	1.28	0.87
Milk protein yield, kg	0.98	1.03	1.02
Energy in milk, MJ	91.49	97.90	85.49

(to be continued)

Table 5.5. (continued)

Variable or Rate of process (d^{-1})	Ration HS (high starch)	HP (high protein)	BSP (bypass starch and protein)
Production			
Live weight gain, kg	-0.09	-0.46	-0.15
Energy balance, MJ	-2.23	-11.57	-3.87
Tissue protein balance, mol N	0.29	-0.48	0.62
Efficiency of utilization			
Energy[1)]	0.58	0.61	0.68
Protein[2)]	0.64	0.62	0.68

1) Net energy/metabolizable energy
2) Protein product/protein supply

about the same (21-22 mol/d) on diets HP and BSP, but the rate of gluconeogenesis from amino acids is 38% higher on diet HP than on diet BSP. These modifications of the relationship between substrate availability and process rate are due to the different ratios of glucagon to insulin simulated with the 2 diets: 1.21 (HP) and 0.99 (BSP).

The rate of amino acid deamination is not very different between diets, but it is highest (7.1 mol N/d) on diet HP and lowest (5.6 mol N/d) on diet BSP. In the model, propionate and deaminated amino acids are either used for gluconeogenesis or oxidation. The proportion converted to glucose is higher for propionate: 73% (HS), 71% (HP), and 77% (BSP) than for amino acids: 12% (HS), 60% (HP), and 55% (BSP).

The glucose flux rate is the sum of glucose absorption rate and glucose synthesis rate. It is higher on ration BSP (17.5 mol/d) and ration HS (16.9 mol/d) than on ration HP (14.3 mol/d) because of the high rate of gluconeogenesis (ration HS) and the high rate of glucose absorption (ration BSP). The availability of amino acids to the mammary gland and body tissues is almost the same with all 3 rations.

The yields of milk, milk fat, and milk protein are (kg/d): 33.7, 1.07 and 0.98; 29.9, 1.28 and 1.03; and 35.0, 0.87 and 1.02; on diets HS, HP and HSP, respectively. The differences in milk yield reflect differences in glucose flux rate. The relatively low milk fat yield with diet BSP is caused by several factors:

- the lower feed intake and hence, lower fat intake
- the lower fermentation rate and hence, lower microbial fat synthesis

- the higher insulin concentration in blood plasma.

The small differences in milk protein yield are determined by differences in amino acid availability and insulin concentration. The milk energy output is highest with diet HP and lowest with diet BSP. The tissue energy balance is accordingly lowest with diet HP (-11.6 MJ/d), but because of the lower energy intake on diet BSP the energy balance with this diet is lower (-3.9 MJ/d) than with diet HS (-2.2 MJ/d). Although negative energy balances are simulated with all diets, the tissue protein balance is negative only with diet HP.

The efficiency of energy utilization (calculated as the ratio of net energy to metabolizable energy) is higher with diet BSP (0.68) than with the other 2 diets (0.58-0.61). However, the efficiency of ration BSP is somewhat overestimated because the metabolizable energy is calculated as a constant fraction (0.84) of the digestible energy. This fraction is probably too small in the case of ration BSP because of a reduced methane energy loss during rumen fermentation. If the efficiency of energy utilization is instead expressed as the ratio of net energy to gross energy, the figures for rations HS, HP and BSP are 0.36, 0.36 and 0.41, respectively. The improved energy utilization obtained by protection of starch and protein against microbial breakdown is caused partly by a reduced energy loss in rumen fermentation and partly by lower rates of oxidation and heat production in the intermediary metabolism.

The efficiency of protein utilization (EPU) is calculated as the ratio of protein product to protein supply (Oldham 1978):

Protein product = milk protein-N + retained tissue protein-N (if positive)

Protein supply = protein product + catabolized amino acid-N.

Diet BSP has the highest tissue protein balance, the lowest rate of amino acid catabolism and hence, a better protein utilization (0.68) than simulated with the other 2 diets (0.62-0.64).

The simulations have shown that partly protection of dietary starch and protein against rumen fermentation increases the milk yield as well as the efficiency of energy and protein utilization. The final model simulations presented here will examine the ef- fects of a varying degree of dietary starch protection on feed in- take, nutrient absorption, and production. Five "experimental" diets are studied with 0, 15, 20, 25 and 35% of the starch made unfermentable. The total starch content is the same in all diets, 195 g/kg dry matter. The crude protein content is 159 g/kg dry matter, and 57.5% of the concentrate protein is unfermentable. Hence, the "20%" diet and the BSP diet in the previous simulations are identical. The main results are presented in figures 5.5-5.8.

The feed intake (kg dry matter/d) is decreasing with increasing levels of rumen bypass starch (figure 5.5). This is also the case for the absorption rates (mol/d) of propionate, amino acids and fatty acids (figure 5.5), while the absorption rate of glucose (mol/d) is increasing when more starch is made unfermentable (figure 5.6). The rate of glucose synthesis (mol/d) is decreasing, especially when the starch protection is enhanced from 25 to 35%, and the glucose flux rate is increased from 14.9 at 0 to 17.8 mol/d at 25% followed by a decrease to 16.4 mol/d at 35% protec- tion (figure 5.6).

The daily milk yield is increased from 30.4 to 35.4 kg at the 25% level and then decreased to 33.9 kg at the 35% level of starch

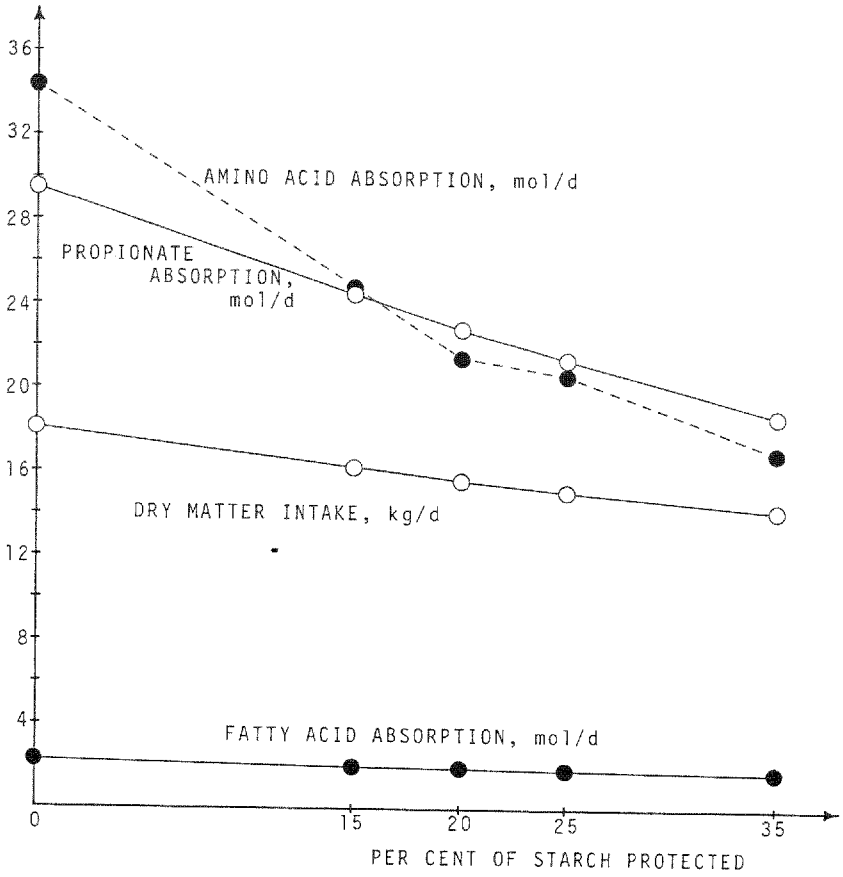


Figure 5.5. Simulated effects of unfermentable starch on dry matter intake, and absorption of propionate, amino acids and fatty acids.

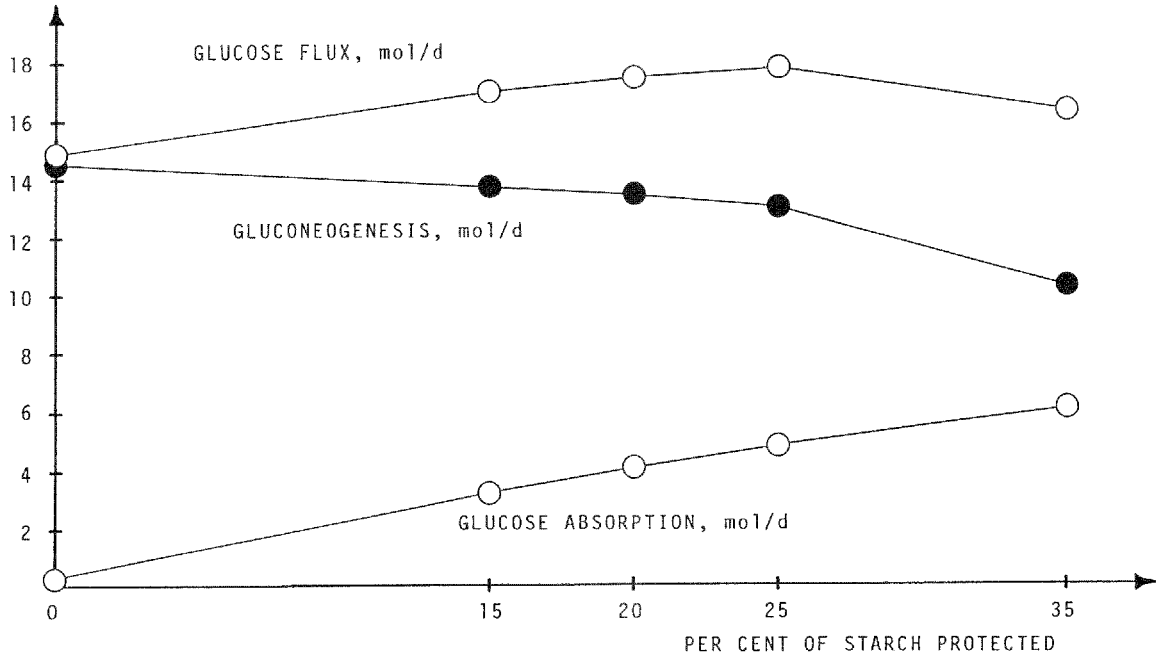


Figure 5.6. Simulated effects of unfermentable starch on glucose absorption, gluconeogenesis and glucose availability.

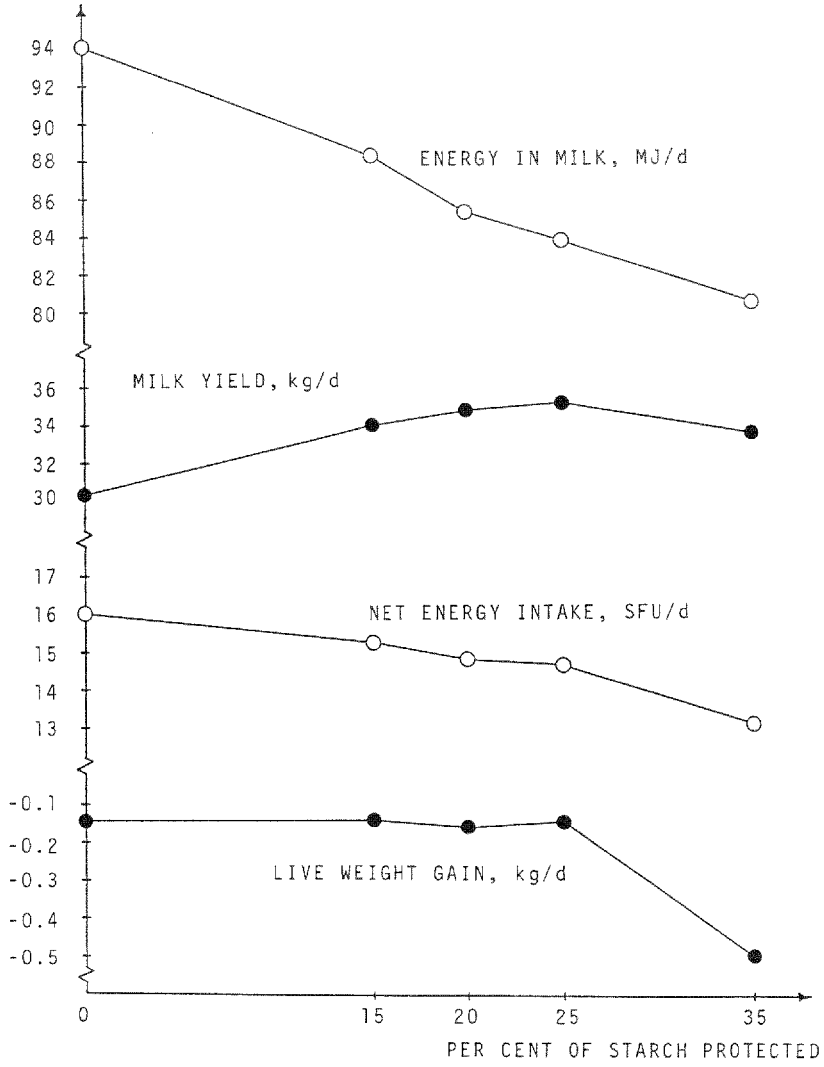


Figure 5.7. Simulated effects of unfermentable starch on net energy intake, milk yield and live weight gain.

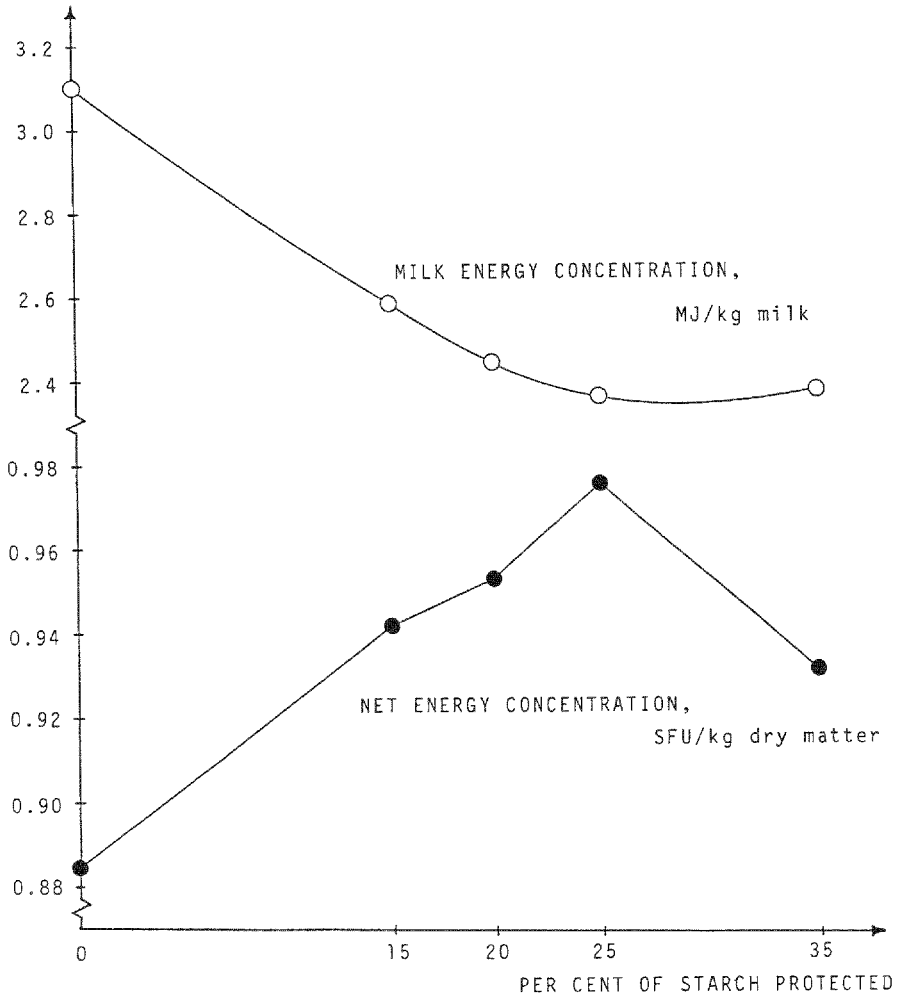


Figure 5.8. Simulated effects of unfermentable starch on energy concentration in milk and net energy concentration in the feed.

protection (figure 5.7). The energy output in milk (MJ/d) is on the other hand decreasing at all levels, and hence, the energy concentration in milk (MJ/kg) is lowest with the 25% diet (figure 5.8). Live weight gain is almost unchanged (about -0.15 kg/d) from 0 to 25%, but then it decreases to -0.49 kg/d on the 35% diet (figure 5.7). The reasons for this precipitous decrease in tissue energy balance are 1) lower availability of nutrients (see figures 5.5 and 5.6) and 2) lower insulin concentration in blood plasma at the 35% level of starch protection.

The net energy intake (Scand. feed units/d) is like the dry matter intake decreasing with increasing levels of unfermentable starch (figure 5.7). However, the 2 curves showing the intake of dry matter and net energy are not parallel. This means that the net energy content per kg dry matter of the same chemical composition (see Table 5.4) is not constant, which is clearly illustrated in figure 5.8. In all presently used energy evaluation systems (Van der Honing & Alderman 1988) the energy content of a feed is based upon its chemical composition. If in a given system the energy value of for example the 0% diet was estimated correctly, then this system would underestimate the energy value of the other diets by 5-10% according to the model simulations. This points towards the possibility of improving energy evaluation of feed rations by means of dynamic, mechanistic modelling of digestive and metabolic processes in the lactating cow.

6 DISCUSSION AND CONCLUSIONS

This final chapter is not intended to be an entirely detached evaluation of all details in the model. That would be beyond the ability of the author and beyond the interest of most readers. Instead the chapter will be devoted to a more general discussion of the objective and usefulness of the model: objectives and criteria for evaluation (section 6.1), evaluation (section 6.2), advantages and shortcomings (section 6.3), and future perspectives (section 6.4). In the last section (6.5) the general conclusions of the discussion are summarized.

6.1 Model objectives and evaluation criteria

The philosophy and methodology of modelling and basic principles in model evaluation have been excellently reviewed previously (Baldwin & Koong 1980, France & Thornley 1984, Sørensen & Kristensen 1988). Here only some important points about the definition of the purpose of the model and about the validation process will be stressed.

Clearly, the definition of the model's objective is important. The objective determines the type (e.g. static or dynamic) and the framework of the model and also the criteria for model validation. The system (e.g. a lactating cow) and the hierarchical level (e.g. different organs of the cow) to be studied are identified by the definition of the objective. When the system and the levels of de-

tail within the system are determined, the activity or the scientific purpose of the modelling should be defined, that is if the model should be used for prediction of animal performance, for evaluation of concepts and behaviour of subunits in the system, or for evaluation of hypotheses about regulations and interactions in nutrient metabolism.

The system is then described in a block diagram (figures 2.1-2.6, section 2.1), the transactions of matter is translated into mathematical equations, and the equation parameters are given numerical values (section 3.3). At this stage of the process the model can be tested according to the objective (see figure 6.1, Baldwin & Koong 1980).

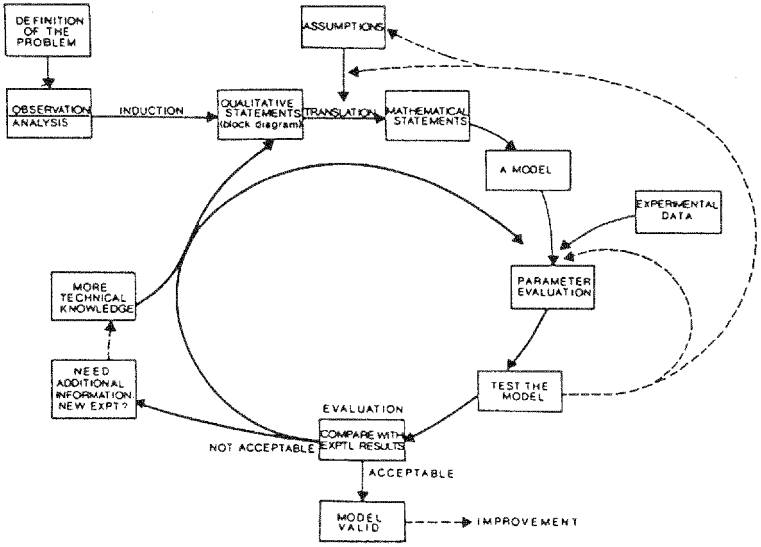


Figure 6.1. The modelling process (from Baldwin & Koong 1980).

The ideal validation procedure is to simulate the system behaviour under conditions not previously studied, and then testing the predictions by new experiments (Baldwin & Koong 1980). Often this ideal situation cannot be achieved and one has to use literature data. In this case, it is clearly important that the data used for model construction and parameter evaluation are independent from the data used for model testing. This can be secured, for instance, if physiological and biochemical data on subunits of the system are used for the model development, and empirical input-output data are used to test the simulated behaviour of the whole system.

If the result of the model validation comes out negatively, the modeller's scientific world do not fall apart. On the contrary, it can be fortified and developed by identification of critical questions leading to new experiments and improvements of the model. If the validation turns out to be positive, the model can be accepted (figure 6.1).

The choice of validation criteria is dependent on the modelling objective (Baldwin & Koong 1980):

(i) If the objective is to predict system behaviour for a given set of conditions, the model is accepted when the simulated results are within the confidence intervals for experimental data obtained under a corresponding set of conditions.

(ii) If the objective is evaluation of concepts about the subunits of the system, it can be concluded that the system is understood, when simulation results compare well with real life observations.

(iii) If the objective is to evaluate different hypotheses about the mechanistic behaviour of the system, this is achieved when the hypotheses have been "ranked" for probability and subjected to experimental testing.

France & Thornley (1984) make it a little more simple and separate the procedure for model validation into testing and evaluation. In their terminology testing means an objective check of the mathematical formulations for methodological correctness: definition of symbols and dimensions, and consistency and completeness of the equations in the model. Evaluation is carried out after the model has been tested. This is not a totally objective process, but it is dealing with judgements of the model behaviour in relation to the modelling objective as described above. In this sense, the structure of the model can only be evaluated and not tested. Therefore, in the following discussion of the present model the term evaluation is used according to the definition of France & Thornley (1984), and the word testing is avoided.

6.1.1 The objectives of the model

The main objective of the present model is to simulate the conversion of nutrients through digestive and metabolic processes in the lactating dairy cow into intermediate substances, and further into wastes and products of milk and body gain. Several minor objectives can be attained with such a general model. These are:

(i) Prediction of animal performance on diets of different composition and at different lactational stages.

(ii) Evaluation of current physiological and biochemical concepts causal to animal performance.

(iii) Evaluation of new hypotheses about the regulations of nutrient digestion and metabolism in the dairy cow. These hypotheses can either be part of the assumptions used in model construction, or some new ideas independent of the model itself.

To achieve these objectives the model has to be dynamic and mechanistic. Dynamic, because dynamic modelling is the only method to evaluate the quantitative impact of acute metabolic changes on whole animal performance - and mechanistic, because descriptions of causality are needed at the level of individual tissues. The most immediate objective of the dynamic modelling is:

(iv) Achievement of simulation results identical at all hierarchical levels to the static balance model based on the work of Hvelplund (1983) and Danfær (1983b).

6.1.2 Criteria for evaluation

Obviously, the model is evaluated in relation to objective (iv) by comparing the simulation results of the dynamic model to the solutions of the static model. The evaluation in relation to objective (i) must be performed by comparing the simulation results with a wide range of experimental data from feeding trials, digestibility studies, and studies of visceral and peripheral tissue metabolism. It is also important to evaluate the model in relation to objective (ii) by examining the underlying concepts of subunit behaviour

against qualitative and quantitative results from both in vivo and in vitro experiments on especially regulation of nutrient metabolism in individual tissues. When these minor objectives have been achieved, the main objective of the modelling can also be regarded as fulfilled. The usefulness of the model in relation to objective (iii) will increase as the model is developed towards achievement of the main objective.

6.2 Evaluation of the model

Some steps in the process of model evaluation have been performed by the simulations presented in chapters 4 and 5. These results are discussed here in context with their contributions to model evaluation.

6.2.1 Comparison with the static model

Simulation results concerning feed intake and whole animal performance, energy metabolism, and nutrient metabolism in the individual compartments obtained with the dynamic model are compared to results from the static model in Tables 4.1-4.9 (section 4.1). The differences between results from the 2 models are small and insignificant, and it can be concluded that the dynamic model is valid so far as it gives the same answers as the static model in terms of daily flux rates (objective iv).

6.6.2 Comparisons with literature data

In the following discussion where some simulation results are compared to in vivo data, the model is evaluated in relation to both its ability for prediction (objective i) and the validity of its concepts (objective ii).

The digestive tract

The simulated apparent digestibility of organic matter in the rumen of 48% (subsection 4.1.2) is within ranges of experimental results (43-56%) given by Klooster & Boekholt (1972) and Sutton (1980). Madsen (1986) found values from 42 to 47% with 4 diets of similar composition as that used in the model.

The simulated efficiency of microbial net growth (Y_{ATP}) in the rumen is 19.7 g cell dry matter per mol ATP at a rumen liquid dilution rate (K7) of 0.11 h^{-1}. This value is close to an average value of Y_{ATP} (19.9) calculated from Harrison & McAllan (1980) at dilution rates ranging from 0.10 to 0.12 h^{-1}. The net yield of ATP per mole of volatile fatty acids produced in the rumen is likely to be within the range of 2.0-2.8 moles (McMeniman et al. 1976). The corresponding simulated value is: 176 mol ATP/81.2 mol VFA = 2.2.

Values for the amount of microbial nitrogen leaving the rumen differ widely in the literature (Smith 1975, Stern & Hoover 1979). Calculated as g N per kg organic matter apparently fermented in the rumen, figures for cattle can vary from 17 to 44 g N/kg (Stern & Hoover 1979), and for lactating cows from 33 to 45 g N/kg (Madsen 1986). The estimates are somewhat dependent on the method used

for microbial protein determination (Smith et al. 1978). They are higher on roughage diets than on high-concentrate diets (McMeniman 1975, c.f. Harrison & McAllan 1980, Madsen 1986), and it is debatable whether they are increased by higher feed intake and rumen dilution rate (Sutton 1980, Madsen 1986). The amount of microbial N produced per kg organic matter truly fermented in the rumen can be estimated from literature data as:

20*19.9*7.7/100 = 30.6 g N/kg.

The values used in the calculation are: 20 mol ATP per kg organic matter truly fermented (Henderickx et al. 1972, McMeniman et al. 1976), 19.9 g microbial cell DM per mol ATP (Harrison & McAllan 1980), and 7.7% N in microbial cell DM (Henderickx et al. 1972, Hvelplund 1986).

The simulated microbial nitrogen outflow from the rumen is 36.4 g N per kg organic matter apparently fermented - corresponding to 27.4 g N per kg truly fermented organic matter as suggested by Miller (1973) and Thomas (1973) and also calculated by regression (Owens & Goetsch 1986).

The simulated rumen degradation rate of dietary protein (65%) is within a range of experimental values reported by Satter & Roffler (1975), Mercer & Annison (1976), Roy et al. (1977), and Madsen (1986).

The apparent digestibility of amino acids in the small intestine is about 70% (Klooster & Boekholt 1972, Armstrong et al. 1977), and the true digestibility is about 80% (Nolan 1975, Smith 1979). The corresponding simulated values are 71% and 79%, respectively.

The liver

The simulated contribution of propionate to glucose synthesis in the liver is 65.6% (subsection 4.1.3) corresponding to 63.0% of total glucose turnover rate. The latter value can be compared to an in vivo estimate of 61% (Wiltrout & Satter 1972). All other estimates in cows, which the author could find in the literature, are lower than that (e.g. Elliot 1980, Lomax & Baird 1983). The difference between the simulated and most literature values could be partly explained by the fact that the model does not allow for a possible conversion of some propionate to lactate in the rumen wall or in the liver (Young 1977). It is pertinent here to refer to Elliot (1980) who found it difficult to account for the required glucose precursors in high-yielding cows, if propionate does not contribute directly or indirectly to at least 60% of the glucose turnover. Lomax & Baird (1983) found that maximum 16.8% of glucose output from the liver could be derived from lactate and glycerol. The corresponding figure simulated by the model is a little lower than that (14.6%).

The literature data concerned with the contribution of amino acids to glucose synthesis in lactating cows can roughly be divided into 2 groups: one group suggesting that amino acids contribute significantly (>25% of glucose turnover), and one group suggesting that the contribution of amino acids is very small (<5% of glucose turnover).

Examples from the first group are data from Black et al. (1968) and from Lomax & Baird (1983). Using single intravenous injections of ^{14}C-labelled amino acids Black and coworkers estimated that 5 amino acids could provide for 30% of the glucose carbon and concluded that the total contribution of amino acids was more than 33% and maybe as much as 50% of glucose turnover. Lomax and Baird

calculated the maximum possible contribution of several substrates to glucose production in the liver. These substrates: propionate (46.0%), lactate, pyruvate, glycerol (17.4%) and four amino acids (8.6%) could account for 72% of glucose output. If it is assumed that the deficit of 28% is made up of amino acids other than those actually measured, the total contribution of amino acids would be 36.6% as a minimum, unless hepatic glycogenolysis had contributed significantly to glucose production.

The glucose turnover rate simulated by the model is: F130+F139 = 85.7 mol C/d, and the total amino acid catabolism in the liver is: F142+F143 = 26.9 mol C/d. If it is concluded from the references above, that 35% of the glucose turnover is derived from amino acids, then in case of the model there is not enough catabolized amino acids to cover the need for gluconeogenesis: 85.7*0.35 = 30.0 mol C/d. It should be noticed, however, that the estimate of Lomax and Baird for propionate contribution to glucose output (46%) is low compared to the 60% which might be expected from reasoning (Elliot 1980), from other experimental data (Wiltrout & Satter 1972), as well as from modelling. A correction of the estimated 46% to 60% of the glucose synthesized from propionate will accordingly decrease the contribution of amino acids from 36.6% to 21.6%, which is much closer to the simulated value.

Examples from the second group of literature data are papers of Boekholt (1976) and Bruckental et al. (1980). In none of these experiments was the transfer of amino acid-C to glucose-C actually measured. Boekholt infused glucose into the animals either through a duodenal fistula or into the peripheral circulation and measured the resultant change in the rate of urea excretion with the urine. As there were no significant decreases in urinary N excretion during periods of glucose infusion at milk yields of about 25 kg/d or lower, it was concluded that amino acids are not required for

gluconeogenesis at this production level.

This conclusion can be questioned for several reasons. Firstly, the results tell nothing about the actual contribution of amino acids to glucose synthesis, they can at most tell that the contribution is not changed by glucose infusion. Secondly, an unchanged rate of urea-N excretion could be explained by a decreased urea-N synthesis and a concomitant decrease in urea recycling to the digestive tract. Thirdly, an unchanged rate of amino acid catabolism and hence, urea-N synthesis, could be due to a decreased use of amino acids for gluconeogenesis and a concurrent increase in amino acid oxidation. In the same experiment the urinary-N excretion was decreased and the milk protein secretion increased during glucose infusion periods, when the milk yield was as high as 30 kg/d.

Bruckental and coworkers (1980) measured the rates of glucose and urea turnover in the blood plasma and calculated the proportion of glucose turnover derived from protein. The assumptions used in the calculations were: 1) 550 g glucose can be synthesized from 1 kg protein, 2) 35% of synthesized urea-N is derived from catabolized protein-N, and 3) 20% of catabolized protein-C is used for gluconeogenesis. The results based on these assumptions were that no more than 1-2% of the glucose flux rate was derived from protein.

The value of 550 g glucose/kg protein is widely and incorrectly used in the literature in estimations of amino acid contributions to gluconeogenesis. It is an empirical estimate of how much glucose can be synthesized from incremental supply of dietary protein (Krebs 1964). In the present calculations a factor for the conversion of glucogenic amino acids to glucose per se on a molar basis should be used instead. As all glucogenic amino acids, except for glycine, can contribute with 3 carbon atoms to the glucose molecu-

le, it is more correct to use a conversion factor of 2 mol amino acids per mol glucose. Hence, the corresponding value will be:

1 mol glucose = 180 g glucose
2 mol amino acids = 2*1.3*14.01*6.25/1000 = 0.228 kg protein
180/0.228 = 790 g glucose per kg protein,

which is 44% higher than the commonly used value.

The proportion of urea-N synthesis in the liver derived from catabolized amino acids (35%) was assumed on the basis of a model of N-metabolism in sheep fed at maintenance (Nolan 1975). This value is probably dependent on the level and degradability of dietary protein (Owens & Bergen 1983, Baldwin 1984). The proportion of catabolized amino acid-C converted to glucose-C (20%) was taken from a review of Lindsay (1976). However, in this paper Lindsay also refers to experiments with sheep by Wolff & Bergman (1972), who found that 62% of the amino acid net uptake in the liver was used for glucose synthesis. In the present model the simulated proportion of the net hepatic uptake of amino acid-C (= catabolized amino acid-C) converted to glucose-C is 60.4%.

If it is accepted that only 2% of the glucose turnover rate is derived from amino acids as estimated by Bruckental et al. (1980), then 98% of the glucose must be synthesized from substrates other than amino acids or must be absorbed from the digestive tract. The consequence of that in relation to the simulated results would be that:

(F130+F139)*0.98-F130 = 85.68*0.98-3.36 = 80.61 mol glucose-C/d

must be synthesized from 3-carbon precursors (propionate, lactate and glycerol). This means that 92% of these substrates available

in the liver should be used in gluconeogenesis. It is indeed a high proportion compared to the 20% of amino acids passing the glucose pool as assumed by Bruckental et al. (1980) - especially when it is considered that carbon from the major substrate, propionate, and carbon from glucogenic amino acids mix in the citric acid cycle and pass through the same regulatory steps in the gluconeogenic pathway (Lindsay 1970). Another point is that if nearly all propionate is used to produce glucose, then the liver may suffer from shortage of substrates for oxidation. The hepatic heat production in lactating cows is estimated by Smith & Baldwin (1974) as 18 MJ/d. If it is assumed (based on the above calculation) that 10% of available propionate is oxidized, that 2% of the glucose turnover rate is derived from amino acids representing 20% of the catabolized amino acids, and that the catabolized amino acid-C not used in gluconeogenesis is oxidized, then the heat produced in the liver can be calculated as 10.4 MJ/d - considerably lower than estimated by Smith & Baldwin (1974). On the other hand, the hepatic heat production simulated by the model where 27% of the propionate and 40% of the catabolized amino acids are oxidized, is 18.5 MJ/d in accordance with the finding of Smith & Baldwin.

From this discussion it is difficult to regard the conclusion of Oldham (1978) and Bruckental et al. (1980) that only 2% or less of the glucose turnover rate is derived from amino acids as a general one. It seems that this value depends on a number of factors, of which the availability of amino acids plays an important role. Nevertheless, it is an important question because it affects both the protein requirement and the glucose availability of the high-yielding dairy cow. Therefore more experimental work in this area is needed. The simulations presented in section 5.4 concerning the regulation of gluconeogenesis can give some idea of how different feed composition can be expected to influence glucose availability and the use of different substrates for glucose synthesis.

The simulated rate of urea-N synthesis is 24.7 mol/d equivalent to 2160 g crude protein/d. Bruckental et al. (1980) found that 16.0 mol urea-N equivalent to 1400 g crude protein/d was synthesized in cows having about the same milk yield, but consuming 850 g crude protein (9.7 mol N) less per day than the model cow. If the major part (e.g. 85%) of this extra dietary protein is absorbed as NH_3/NH_4^+ and amino acids and ultimately converted into urea, then the cows in the experiment would have synthesized: 16.0+9.7*0.85 = 24.3 mol urea-N/d - in much better agreement with the simulated value.

The mammary gland

The simulated rate of glucose uptake in the mammary gland is within a range of experimental results in the literature, whereas the simulated mammary uptake of acetate and ketone bodies is considerably higher than in vivo estimates (subsection 4.1.3). In a number of experiments where nutrient uptake in the udder is estimated by the A-V difference technique the rate of glucose uptake per kg milk produced is on average 2.4 mol C/kg (Annison et al. 1974, Bickerstaffe et al. 1974, Peeters et al. 1979, Williams & Elliot 1980, Rulquin 1981). The range of this value across the different experiments is 2.0-3.4 mol C/kg milk, where the highest estimate is from Rulquin (1981). The range for the other experiments is small (2.0-2.2 mol C/kg). The corresponding value simulated by the model is 2.3 mol C per kg milk in agreement with the literature data. The rate of acetate and ketone body mammary uptake in the same experiments is on average 1.4 mol C/kg milk (range 0.74-1.92 mol C/kg), but the simulated value is much higher than that, 2.74 mol C/kg milk.

The model is simulating that 24% of the glucose and 68% of the acetate and ketone bodies taken up by the mammary gland are oxidi-

zed. The figure for glucose is in agreement with estimates of Annison & Linzell (1964) and Smith (1971), but higher than values (4-17%) found by Bickerstaffe et al. (1974). The figure for acetate and ketone bodies is much higher than values for acetate alone (11-57%) found in the same study of Bickerstaffe and coworkers. The difference cannot be accounted for by oxidation of ketone bodies as this is low in fed animals (Smith et al. 1983).

It seems therefore that the model overestimates the uptake and oxidation rates of acetate and ketone bodies in the mammary gland. However, the validity of the literature data can be questioned when nutrient balances and heat production in the udder are considered. It can be calculated, that the daily energy uptake and heat production in the mammary gland will be 109.7 MJ and 9.6 MJ, respectively, when the average literature estimates are used for glucose uptake (2.4 mol C/kg milk), acetate and ketone body uptake (1.4 mol C/kg milk), glucose oxidation (11%), and acetate and ketone body oxidation (30%). The proportion of total energy uptake lost as heat is then: 9.6/109.7 = 0.09, which indicates an unrealistic high efficiency of the mammary gland. By using the highest literature estimates of mammary uptake and oxidation of these nutrients, the energy uptake and heat production can be calculated as 116.7 MJ/d and 21.6 MJ/d, respectively. This gives a higher proportion of heat energy: 21.6/116.7 = 0.19, but it is still lower than estimated by Linzell (1967) as well as by the present model (26%). Smith et al. (1983) concluded that the apparent deficit of substrates for oxidation could be made up by amino acids. However, this conclusion is not in accordance with arterio-venous difference studies showing that the secretion of carbon and nitrogen in milk protein is balanced by the net mammary uptake (Clark et al. 1978, Mepham 1982), thus indicating no net oxidation of amino acids in the udder.

It can be concluded that in vivo estimates of mammary glucose uptake are less variable and in better accordance with model simulations than in vivo estimates of acetate and ketone body uptake and oxidation, which in most cases seem to be too low.

Diurnal variations in output variables

The simulated pattern of feed intake with 8 distinct meals per day and a non-eating period of about 4 h in early morning (subsection 4.2.1, figure 4.1) is similar to experimental findings of Blum et al. (1985) and Krohn & Konggaard (1987). This pattern of diurnal variation is reflected in most of the state variables and rate variables in the model, markedly in the rumen and intestinal compartments and less clearly in the peripheral tissue compartments. Examples are the pool of fermentable carbohydrates in the rumen (figure 4.4), the intestinal absorption rate of amino acids (figure 4.25), and rates of lipid metabolism in adipose tissue (figure 4.46). The simulated diurnal variations in the blood plasma concentrations of insulin (figure 4.31), glucose, ketone bodies, lactate (figure 4.33), amino acids and urea (figure 4.39) are very similar to corresponding diurnal variations observed in vivo (Blum et al. 1985) in cows at the same lactational stage, and with the same feed intake and milk yield as the model cow. On the other hand the simulated blood plasma profile of free fatty acids (figure 4.36) show much less fluctuation than is normally seen in experiments (Bines et al. 1983, Blum et al. 1985). Although the course of the small diurnal variations in the plasma pool of free fatty acids are biologically reasonable, it seems that the model is inadequate in the simulation of fatty acid release from adipose tissue.

The discussion in this subsection can be summarized as follows:

A number of simulated processes in the digestive tract, the liver and the peripheral tissues are evaluated against literature data in anticipation of the objective of model prediction (objective i). Results of this evaluation are positive for the following processes:

- Apparent digestibility of organic matter and VFA production in the rumen.
- Microbial net growth and protein synthesis in the rumen.
- Degradability of dietary protein in the rumen.
- Digestibility of amino acids in the small intestine.
- Contribution of propionate and amino acids to glucose synthesis in the liver.
- Urea synthesis in the liver.
- Heat production in the liver.
- Glucose uptake and oxidation in the mammary gland.

It should be pointed out that the simulated contribution of amino acids to liver gluconeogenesis is much higher than the lowest values (Boekholt 1976, Bruckental et al. 1980) in a range of experimental data of which the simulated value lies in the middle. It is questioned, however, if these low estimates are generally applicable.

Negative results of the comparison with literature data are obtai-

ned for acetate and ketone body uptake and oxidation in the mammary gland. The simulated values are considerably higher than the experimental figures. However, the model is not necessarily wrong at this point because most of the in vivo measurements seem to underestimate the rates of acetate and ketone body uptake as well as acetate oxidation in the mammary gland.

The simulated diurnal variations of some output variables are evaluated in relation to concepts about the subunits used in the model (objective ii). The outcome of this evaluation is that daily variations in the rate of feed intake, and in the blood plasma concentrations of insulin, glucose, ketone bodies, lactate, amino acids and urea are simulated in a realistic way supporting the underlying physiological and biochemical concepts. On the other hand the course of the blood plasma profile of free fatty acids during the day shows that the model is somewhat insufficient in its concepts of free fatty acid release from the adipose tissue.

It can be concluded, that the dynamic model is able to give realistic quantitative predictions of important aspects of feed intake, of ruminal and intestinal digestion, and of liver and mammary gland metabolism. Concepts used in the model about the behaviour of subunits can be accepted to the extent that they are related to the diurnal pattern of the rate of feed intake and the blood plasma concentration of a number of metabolites - except free fatty acids.

In some areas of intermediary metabolism, notably amino acid contribution to gluconeogenesis and acetate metabolism in the mammary gland, where the model simulations are clearly different from literature data, more experimental work is needed.

6.2.3 Simulation of a feeding experiment

The model can be evaluated most objectively in relation to its purpose of prediction (objective i) when simulations are compared to results from a specific experiment carried out under the same conditions as assumed in the model. This is done in section 5.3 where the feed intake and productive performance of cows eating a complete diet ad libitum at 136 days post partum are simulated. The first simulation with the original parameter values failed to give accurate predictions of milk yield, milk protein content and live weight gain compared to the experimental results (Krohn & Konggaard 1987). Then the numerical values of 17 parameters concerning tissue nutrient uptake and metabolism were adjusted (Table 5.2), and the model was reevaluated according to the scheme in figure 6.1. After the adjustment of parameter values the simulated feed intake, milk yield, milk composition and live weight gain were the same as obtained in the experiment. Hence, it can be concluded that the adjusted model is able to predict the feed intake and productive performance of dairy cows under the specified conditions.

6.2.4 Simulation of animal performance during lactation

The discussion in this and the following subsection is concerned with evaluation of both quantitative (objective i) and qualitative (objective ii) aspects of model behaviour.

The simulated curves of milk yield and live weight gain during the lactational period are similar to in vivo observations (Bauman et al. 1985) as regards shape and magnitude of maxima and minima

(section 5.1, figure 5.1). The declining milk yield and increasing energy balance during lactation are results of an altered nutrient partitioning which in turn is believed to be regulated by metabolic hormones (Bauman & Elliot 1983). This concept is used in the model by means of equations describing the blood plasma concentrations of growth hormone, glucagon and insulin as well as equations describing hormonal regulation of nutrient uptake and metabolism in the mammary gland and body tissues. The simulation of 2 different lactation curves is an example of how the concept of hormonal regulation is expressed in the model. After a few changes of parameter values in some of the regulatory equations, the model can simulate an altered tissue responsiveness to growth hormone and insulin resulting in a higher milk yield and a lower live weight gain.

It seems fair to conclude that the model is able to simulate in a realistic way alterations in the rates of milk secretion and live weight gain during the lactational period. The ability of the model to simulate different lactational milk yields of cows having the same feed intake points to the possibility of using the model to make hypotheses about the physiological background for differences in the genetic capacity for milk yield.

6.2.5 Simulation of growth hormone treatments

The ability of the model to mimic hormonal regulation of the nutrient partitioning is also evaluated by simulation of the effects of short-term growth hormone treatment on animal performance (section 5.2, figures 5.2-5.4). This is done simply by increasing the intercept value in the equation for growth hormone concentration in blood plasma. The simulations are carried out both in early and

in late lactation (73 and 257 days, respectively, after calving). The simulated increases in milk yield in response to increasing "doses" of growth hormone are curvilinear both in early and late lactation as shown by Bauman et al. (1985) and Eppard et al. (1985). The relative increases are higher in late than in early lactation as shown by Peel et al. (1983), and the absolute increases are within the range of experimental observations at both lactational stages (Peel et al. 1983, Eppard et al. 1985). The simulated feed intake is unchanged, the energy balance is decreased, and the blood plasma concentration of free fatty acids is increased by the treatments as reported by Peel et al. 1981a, 1982a&b, Tyrrell et al. 1982b, Peel et al. 1983).

On the other hand the simulated increases in growth hormone concentration in response to "treatments" are much smaller than observed in vivo (Peel et al. 1981a, Peel et al. 1983, Eppard et al. 1985). The model predicts the plasma concentrations of glucose and insulin to decrease, but in most experiments these concentrations are unaffected by growth hormone treatment (e.g. Peel et al. 1981a, 1982a, 1983).

It can be concluded that treatment of lactating cows with increasing doses of growth hormone can be simulated satisfactorily by the model in terms of the effects on milk yield, feed intake, energy balance, and free fatty acid concentration in blood plasma. However, the model is not quite acceptable as regards the tissue sensitivity to growth hormone and the effects on glucose and insulin concentrations. Hence, the model can only be partly accepted in relation to its purpose of prediction (objective i) and of concept evaluation (objective ii) in these particular aspects of hormonal regulation.

6.2.6 Simulation of gluconeogenesis

The discussion in subsection 6.2.2 about the regulation of gluconeogenesis and the extent of amino acid contribution to glucose synthesis suggests that an experimental elucidation of the following questions is important:

- How much of the synthesized glucose is derived from propionate and from amino acids when different diets are fed?

- How are the contributions of propionate and amino acids to glucose synthesis regulated?

For that purpose the model can be used to simulate the outcome of experiments designed to answer these questions and to evaluate underlying concepts and hypotheses involved at the subunit level. Such simulations are presented in section 5.4.

In the first simulated experiment 3 different diets are used: a high starch diet (HS), a high protein diet (HP), and an intermediate diet with starch and protein protected against rumen fermentation (BSP). The main results of the simulations can be summarized as follows:

1) The rates of feed intake, carbohydrate and protein fermentation, microbial protein synthesis, and propionate absorption are decreased, while the rate of glucose absorption is markedly increased with the BSP diet.

2) The rate of glucose synthesis in the liver is higher with

diet HS than with either of the two other diets.

3) The proportion of the synthesized glucose derived from amino acids and the proportion of deaminated amino acids used for gluconeogenesis are very different with the 3 diets. Both proportions are lowest with diet HS and highest with diet HP.

4) As regards the volume of secreted milk the 3 diets are ranked (from highest to lowest): BSP, HS, HP - but as regards the secreted milk energy the diets are ranked oppositely. This means that the energy content (and fat content) per kg milk is highest with diet HP and lowest with diet BSP.

5) The efficiency of energy and protein utilization is highest with diet BSP.

Some of the simulated results with the BSP diet (decreased rumen digestibility of starch, decreased propionate production and microbial protein synthesis, as well as increased efficiency of protein utilization) are similar to corresponding data from experiments with lactating cows, where maize with low rumen degradability was compared to barley with high degradability (Oldham et al. 1979, Sutton et al. 1980).

The simulated contributions of the different glucogenic substrates to glucose synthesis are based on the hypothesis that the rate of gluconeogenesis is regulated by precursor availability and the ratio of glucagon to insulin concentrations. They are also based on the concept that the rate of glucose synthesis from amino acids is increased more than that from propionate, when the ratio of glucagon to insulin is increased (Brockman 1978a, Brockman 1979, Brockman & Greer 1980). This goes along with the hypothesis that the high-yielding dairy cow possesses an ability to utilize a relati-

vely high proportion (if needed) of the available amino acid-C for synthesis of glucose-C, as mobilized amino acids from body protein are the only source for an extra net glucose synthesis at a given feed intake. If these assumptions hold true, fully or partly, they may explain the differences in experimental estimates of amino acid contribution to gluconeogenesis (e.g. Bruckental et al. 1980, Lomax & Baird 1983). In fact, Lomax and Baird found that the proportion of synthesized glucose derived from amino acids was increased with fasting. It is also worth noting that the protein intake (2300 g/d) as well as the gluconeogenic contribution of amino acids (3% of glucose) simulated with the low protein diet (HS) are similar to the corresponding figures in the study of Bruckental and coworkers.

In the second simulated experiment 5 diets are used. These diets are identical in gross chemical composition, but 0-35% of the starch is unfermentable. In all diets the protein degradability is low. The results of the simulations regarding feed intake, nutrient absorption, gluconeogenesis, and production are given in figures 5.5-5.7. Attention should also be drawn to figure 5.8, which shows that the net energy content of the feed dry matter is very different in the 5 diets, even though they are of identical chemical composition. This is an important observation leading to the conclusion that a sufficiently realistic dynamic, mechanistic model could be the best tool above all to evaluate different feedstuffs and feed rations for lactating dairy cows.

The purpose of the simulations discussed in this subsection has been to demonstrate the model's ability for prediction (objective i), and for evaluation of concepts (objective ii) and hypotheses (objective iii). In context with the last mentioned objective it should be noticed that other hypotheses than those assumed can easily be incorporated in the model.

It can be concluded, that the model has at least partly served these objectives. However, as a general remark to the conclusions of subsections 6.2.2-6.2.6 it can be pointed out, that a good fit with a complex model such as the present one is not an irrefutable proof of validity, whereas a poor fit is a proof of incomplete validity of the model or erroneous experimental data. This means that further evaluations and adjustments of the model are required.

6.3 Advantages and drawbacks of the model

This section contains a discussion of some of the concepts used in the model and of some concepts which at present are not incorporated. The discussion can be regarded as the author's qualitative evaluation of merits and shortcomings of the model.

6.3.1 Advantages

A general advantage, which is not confined to the present model alone, is that with modelling it is possible to avoid a classical problem in animal science: that an object cannot be studied without disturbing the behaviour of the object. This means that the implementation of an experimental procedure will itself affect the environment and thereby the behaviour of animals, organs or cells. The less invasive the experimental procedure, the less detailed information about causal relationships can be obtained. With a whole animal model such as the present one the biological responses of the cow to different treatments can be studied at different

levels of organization (organs, cells etc.) without affecting any cow at all. However, a condition for gaining insight into biological phenomena by modelling is that the model is to a significant degree realistic - and a realistic model can hardly be made without using concepts and quantitative relationships based upon experimental results.

Another general quality confined to dynamic models only is that quantitative impacts of acute changes in metabolism on whole animal performance can be estimated. Examples of this from the present model are the effects of the distinct pattern of the rate of feed intake (figure 4.1) on rumen metabolism (e.g. figures 4.7 and 4.13), absorption of nutrients (e.g. figures 4.25 and 4.26), circulating nutrients and hormones (e.g. figures 4.31 and 4.33), tissue metabolism and milk secretion (e.g. figures 4.29, 4.35 and 4.43, section 4.2). The model can be used to simulate how the production of the cow is influenced via metabolic changes induced by a different pattern of feed intake or by different tissue sensitivity to regulating factors (specific nutrients, hormones etc.)

The presented model is, like other complex dynamic models, extremely flexible, because the regulation of most of the simulated processes can be easily changed by adjustment of existing parameter values or by introduction of new parameters. For example, the rate of feed intake can be modified by changing the non-eating period 1-5 hours a.m. into another time interval. Moreover the fixed rate of dry matter intake during eating periods can be changed to be a function of the content and the physical form of dietary fiber according to the principle of maximum chewing time (Nørgaard 1981). Other examples of easily adjustable transactions are:

Process	Model equations	Changeable parameters
From the rumen compartment:		
Interaction of carbohydrate fermentation	RSU106 = R106*X1*EXP(-G*X3) RST106 = R106*X2*EXP(-G*X3) RCE106 = R106*(1-EXP(-G*X3))	G
Maximal microbial protein synthesis	R9M = YATP*M9*(R108+R115) YATP = YATPM*A2*N1A/(KATP+A2*N1A)	M9 YATPM, KATP
From the liver and extracellular fluid compartments:		
Glucose synthesis from propionate	R136 = R136M*C14/(K136+C14) R136M = L136+M136*RATIO	K136 L136, M136
Acetate and ketone body synthesis	R149 = R149M*C19/(K149+C19) R149M = L149+M149*RATIO	K149 L149, M149
Glucose uptake in the mammary gland	R160 = R160M*C24/(K160+C24) R160M = L160+M160*GH	K160 L160, M160
Glucose uptake in adipose tissue	R162 = R162M*C24/(K162+C24) R162M = L162+M162*INSUL	K162 L162, M162
From the adipose tissue compartment:		
Fatty acid synthesis	R190 = R190M*C39/(K190+C39) R190M = L190+M190*INSUL	K190 L190, M190
Triglyceride synthesis	R195 = R195M*C41/(K195+C41) R195M = L195+M195*INSUL	K195 L195, M195

In addition to these examples all other rate equations in the model contain one or more fixed parameters, the value of which can easily be changed. All in all the numerous possibilities of parameter value adjustments provide the model with a great fitting power still keeping the numerical parameter values meaningful in a biological sense (although this is not completely true in the present version of the model, e.g. L156, L160 and L51, subsection 4.1.4).

A new method of simulation confined to metabolic regulation of pool sizes and rates of transaction is introduced in the model (see Appendix 2). The principle is described in section 2.3, and a few examples from the rumen and the liver compartments are given below:

Process	Mathematical formulation
Rumen compartment:	
Carbohydrate fermentation	R106 = R106M*C2/(K106+C2) IF (C2.LT.C2MX) GO TO 1 K106 = K106-0.1 GO TO 2 1 IF (C2.GT.C2MN) GO TO 2 K106 = K106+0.1 GO TO 2 2 CONTINUE
Dry matter intake	FT IF (UNFERM.LT.MAX) GO TO 12 FT = 0.0

```
      GO TO 13
12 IF (UNFERM.GT.MIN) GO TO 13
      FT = 3.3
      GO TO 13
13 CONTINUE
```

Liver compartment:

Glucose synthesis

```
R136 = R136M*C14/(K136+C14)
R142 = R142M*C17/(K142+C17)
R144 = R144M*C18/(K144+C18)
```

Glucose output

```
R139 = R139M*C16/(K139+C16)

   IF (C16.LT.C16MX) GO TO 32
      K136 = K136+0.0005
      K142 = K142+0.001
      K144 = K144+0.001
      GO TO 33
32 IF (C16.GT.C16MN) GO TO 33
      K136 = K136-0.0005
      K142 = K142-0.001
      K144 = K144-0.001
      GO TO 33
33 CONTINUE

   IF (C24.LT.C24MX) GO TO 36
      K139 = K139+0.005
      GO TO 37
36 IF (C24.GT.C24MN) GO TO 37
      K139 = K139-0.005
      GO TO 37
37 CONTINUE
```

The first example is regulation of the rumen pool size of fermentable carbohydrates (C2). When this pool reaches or exceeds a maximum value (C2MX), the affinity constant for carbohydrate fermentation (K106) is decreased by 0.1, and when C2 reaches or goes below a minimum value (C2MN), K106 is increased by 0.1. In this way the carbohydrate fermentation rate (R106) is regulated, and the substrate pool size (C2) cannot be infinitely large or small in spite of large diurnal fluctuations (see figure 4.4).

The second example is concerned with the physical regulation of feed intake. When the amount of unfermented organic matter in the rumen (UNFERM) is equal to or larger than a maximum value (MAX), which is dependent on the body weight of the cow, the feed intake stops (FT = 0.0). Otherwise the feed intake is 3.3 kg dry matter per h (see figure 4.1).

The last examples show how the rates of glucose synthesis (R136, R142 and R144) and glucose outflow from the liver (R139) are regulated by the pool sizes of liver glucose (C16) and blood plasma glucose (C24), respectively. The rates of gluconeogenesis are inhibited by an increase in C16 to or beyond a maximum value (C16MX) and are stimulated by a decrease in C16 to or below a minimum value (C16MN). In the same manner the rate of glucose outflow is inhibited and stimulated by large and small, respectively, values of C24 (see figures 4.27, 4.29 and 4.33). In this way the glucose synthesis rate is indirectly regulated by the glucose pool size in blood plasma.

The mutual regulation of substrate pool sizes and rates of transaction imitates allosteric enzyme regulation. An important biological phenomenon is thus induced in the model. In addition to this the regulations have a great stabilizing effect on the affected

pool sizes (e.g. C14 and C16, figure 4.27) as well as on the model as a whole (figure 4.48).

To the best of the author's knowledge this simple principle of metabolic regulation has not been used in other published models, but it is further developed in an unpublished model of pig growth (Danfær 1987).

The last merit which could be made of the model work is the rather comprehensive review of literature data in search for numerical values of biological relevance to apply to the state variables and the equation parameters (subsections 3.3.1-3.3.5).

6.3.2 Drawbacks

In this subsection some of the less attractive features about the model will be briefly discussed. These are related to the general structure of the model, the regulation of feed intake, microbial growth in the digestive tract, the regulation of hormone secretion, regulation of milk synthesis capacity within the mammary gland, and regulation of energy metabolism. The reader may think of something more.

General model structure

This is not completely satisfactory. Firstly, the emphasis put to the description of metabolism in the peripheral tissues (mammary gland and body tissues, subsection 3.3.4) seems to be too poor relative to the emphasis in description of processes in the visceral

tissues (rumen, intestines and liver, subsections 3.3.1-3.3.3). As an example, it can be illustrated by the number of descriptive equations in the liver compartment (43) compared to the number of descriptive equations in the mammary gland compartment (23).

The model is programmed in the CSMP III language which has a maximal capacity of 600 statement outputs (Speckhart & Green 1976). Although all the rates of transaction and all regulatory processes etc. are programmed in FORTRAN subroutines in order to save space (Appendix 2), the main CSMP programme containing all the differential and integration equations has utilized the available capacity and cannot be further enlarged. This means that new state variables cannot be introduced in the model unless by replacement of already existing ones. The problem of limited capacity is partly the explanation of the improper weighting between visceral and peripheral tissues mentioned above, and it is also the reason for most of the shortcomings discussed below.

In a few cases a state variable in the model represents more than one nutrient or metabolite (acetate + ketone bodies, lactate + glycerol). These pooled nutrients are partly metabolized in the same pathways, but the flexibility and the biological resemblance of the model are both suffering.

Because of the limited programming space already mentioned only 23 statements (equations) in the main programme can be reserved for the calculation of fluxes (F_i, F_j) by integration of the rates of transaction (R_i, R_j). This means that in order to calculate all fluxes the model must be run 10 times, each time with new integration equations in that specific part of the DYNAMIC segment in the programme (see Appendix 1, lines 4110-4360).

A disadvantage of a large and complex model as the present one is clearly, that it is very difficult to evaluate completely. For example, a satisfactory fit to experimental data at the whole animal level could be due to some errors counterbalancing each other at the subunit level. The consequence is that a thorough evaluation of the model will take a long time and require much work.

Feed intake

The rate of feed intake is regulated in the model by the physical capacity of the rumen only, and not by products of digestion and metabolism. In a review on metabolic control of food intake Forbes (1980) concluded that receptors in the digestive tract and the liver are sensitive to concentrations of digestion products such as acetate, propionate and lactate, and that signals from these areas are registered by the brain. After integration of the recieved impulses, the brain "decides" when feed intake is initiated or terminated. Free fatty acids and ketone bodies are also likely as candidates for metabolic regulation of feed intake (Rich et al. 1988). Models simulating both physical and metabolic control of food intake in sheep have been published (Forbes 1978, Fisher et al. 1987).

Differences in the capacity of feed intake at progressing lactation is not incorporated in the present model. It is well known that the voluntary energy intake of cows is lower in early lactation (especially just after calving) than in mid and later lactation (e.g. Bauman et al. 1985). Simulations of the feed intake at various parts of the lactational period would presumably be improved, if the model was supplemented with equations describing metabolic control and regulation by the volume of abdominal fat.

Rumen fermentation

The significance of feed particle size in relation to rate and pattern of rumen fermentation is not taken into account in the model. Neither is the fact that cell wall carbohydrates consist of several classes of chemical components (i.e. pectins, hemicelluloses, celluloses and lignins) each with different fermentation characteristics. These factors are included in other dynamic models of rumen digestion (Baldwin et al. 1977, Kristensen 1984, Murphy et al. 1986). However, the importance of feed particle size is doubtful according to some studies (Robinson et al. 1986, Nørgaard 1987).

In the present model the rate of microbial protein synthesis in the digestive tract is directly proportional to the rate of ATP synthesis during fermentation. This means that all available ATP is used for growth, and that the energy requirement for maintenance of the microbes is not considered. The simulated rate of net protein synthesis per day by rumen microbes is in agreement with experimental data (subsection 6.2.2), but at low feed intakes ignoring of the maintenance requirement could lead to significant errors (Baldwin & Koong 1980).

Regulation of hormone secretion

Blood plasma concentrations of the metabolic hormones, growth hormone, insulin and glucagon, are in the model related to the stage of lactation in a discrete manner based on findings of Herbein et al. (1985) and modified by absorbed nutrients. These hormones regulate the partitioning of nutrients as well as some important metabolic transactions, and therefore only discrete lactation curves can be simulated at present (see figure 5.1). An attractive model solution would be that the simulation of general trends in hormone

concentrations during the lactational period was based on intrinsic and mechanistic elements of the model. For example, growth hormone secretion could be stimulated by fasting and insufficient energy intake, and insulin secretion could be stimulated by high energy intake (Forbes 1980).

Regulation of milk synthesis capacity

The syntheses of milk components are in the model regulated only by the availability of nutrients within the mammary gland. Hence, the capacity for milk synthesis per se is not changed during the lactational period. In vivo, however, the declining milk yield with progressing lactation seems to be determined (apart from the nutrient availability) by a decreasing number of secretory cells as well as by a reduced activity of the synthetic and secretory machinery in the cells (Mepham 1983). Both these factors (cell number and activity per cell) may be controlled by growth hormone via somatomedins or other secondary hormones (Baumrucker 1986a&b, Nielsen 1988, Shamay et al. 1988). Regulations of this kind could easily be incorporated into a revised version of the model.

Regulation of energy metabolism

Maybe the most serious defect of the model is that rates of energy consuming, synthetic processes at the tissue level are not regulated by the availability of ATP and reducing cofactors produced by substrate oxidations. At the same time rates of substrate oxidation are not controlled by the requirement for energy in the synthetic pathways. In the static model (Danfær 1983b) account is made for both the synthesis and the consumption of high-energy phosphate bonds and reducing eqiuvalents in the stated pathways, and in all modelled tissues the available energy is in excess of that required for synthetic purposes. The defect of the dynamic model

will affect the simulation results, whenever the supply of energy is in shortage relative to the supply of substrates for synthetic pathways. This means that the dynamic model cannot be expected to cope well with situations such as fasting or very low feed intakes, where energy supply is the limiting factor. Rate equations for the production and the expenditure of ATP and reducing cofactors are included at the tissue level in other dynamic models, published (Gill et al. 1984, Baldwin et al. 1987b) and unpublished (Danfær 1987).

The last point to make here is related to the partition of energy lost in the urine and lost as heat. In the present model urinary energy (UE) is calculated by difference: digestible energy (DE)-metabolizable energy (ME)-energy in methane (MEE), where DE and MEE are obtained mechanistically from the dynamic simulations, and ME is determined empirically as DE*0.84 (subsection 3.3.5). Of course, this is an unsatisfactory solution in a model which is intended to be mechanistic. The flaw of the model is that urea is the only substance excreted in the urine. Therefore the energy loss in the urine would be underestimated and ME overestimated, if UE is calculated directly from the excreted urea. The total heat loss (HE) is calculated as the difference between ME and net energy for production (PRODE), where PRODE is the sum of milk energy and tissue energy balance. A mechanistic determination of HE based on fermentations and oxidations in the individual compartments would overestimate HE, because some of the organic substances oxidized should in fact be excreted in the urine. PRODE is calculated independently and mechanistically and is therefore not affected by the flaw.

6.4 Perspectives for use of the model

As stated previously the main objective of the presented work has been to develop a general model of the lactating cow, which is able to simulate the digestion and metabolism of nutrients in a realistic way. Such a model can be applied to different areas of scientific work:

1) Stimulation of thinking and formulation of hypotheses.

2) Prediction of performance at subunit as well as whole animal levels.

With regard to the first application the model needs not to be very realistic in all details, although the better the model the better possibilities to exclude false hypotheses. As to the second point there is practically no limitation in its application if the model is sufficiently precise in the simulation of in vivo behaviour.

The present version of the model can be used for formulation and evaluation of concepts and hypotheses about nutrient digestion, metabolism and interactions in the lactating dairy cow. It can also be used for prediction of real life situations in which the simulations are not considered to be influenced by the drawbacks of the model discussed in the preceding subsection.

As the model is hopefully improved by further evaluations and adjustments, the field of its application could be extended. In re-

lation to this it is pertinent to ask the following questions:

1) Which kind of experiments do we need to perform?

2) What can we learn from these experiments?

3) What are the expenses and technical limitations of these experiments?

4) How can use of models help to select the appropiate experiments, to supplement information from experiments, and to overcome limitations of experiments?

Answers to these questions could be a guide to find the most rational utilization of the model in the future. Here, attention is directed to a few examples:

In addition to formulation and evaluation of hypotheses the theoretical application could include an identification of lacking knowledge and also false knowledge originating from improper experiments or inadequate experimental techniques. The physiological and biochemical background of the genetic potential for high milk yield is a research area where knowledge is still lacking, and where solid hypotheses may be formulated by aid of the model.

In the more practical field of research the model could be a useful tool in screening of new feed rations for dairy cows, for finding the optimum composition of feed rations, and for development of a feed evaluation system. Screening of feed rations for their effects on animal performance would be a fast and inexpensive method to obtain useful information for farmers about new feeds. The

model could also be used in the opposite direction, namely to identify optimum diet compositions for desired levels and types of production.

The value of feedstuffs and feed rations is at present estimated by separate energy and protein evaluation systems (Van der Honing & Alderman 1988). Although the newer systems are based on more solid physiological concepts than the older ones, they are still static and to a great extent empirical and founded on defective concepts. Furthermore, none of the existing systems are able to describe metabolic interactions of absorbed nutrients. This problem has been of low priority in the past relative to the amount of time and work devoted to discussions and estimations of coefficients for degradability, digestion and utilization. It is the author's view that a proper feed evaluation system should be based on the rates of absorbed nutrients and their effects on metabolism and production for a wide range of different conditions. Dynamic, whole animal models based on established physiological and biochemical concepts and thoroughly evaluated would be perhaps the best tools in the development and operation of such a system. Of course, this idea could be extended to growing cattle and to other livestock species.

6.5 Conclusions

A dynamic, deterministic and mechanistic whole animal model has been developed and presented in accordance with its main objective: to simulate the conversion of nutrients through digestive and metabolic processes in the cow into intermediate substances, and further into waste products and products of milk and tissue constituents.

The model is based on a static model of nutrient digestion and metabolism in the lactating dairy cow (Hvelplund 1983, Danfær 1983b). In its present version the solutions of the dynamic model are the same as those of the static model with regard to daily feed intake, milk production, live weight loss, and to daily flux rates in all intermediate transactions.

Results of simulations at the subunit level of the model are compared to a range of independent literature data. These comparisons support the conclusion, that the model can give realistic predictions of a number of processes in the digestive tract, the liver and the mammary gland. Also simulations of the rate of feed intake and the dynamics of some extracellular nutrient and hormone pools are in fair agreement with in vivo observations.

In a few cases where the simulations differ significantly from some experimental results (i.e. gluconeogenesis from amino acids, mammary uptake and metabolism of acetate) it can be questioned if the experimental data have general validity. This conclusion is justified by the recognition that quantitative experimental results should be evaluated in view of the integrated nutrient metabolism in the animal.

The model's predictive ability of animal performance is evaluated against a specific feeding experiment (Krohn & Konggaard 1987). After adjustments of parameter values the simulated daily feed intake, milk yield and composition, as well as live weight gain are as observed in the experiment.

The model can simulate animal performance during the lactational period. Different lactation curves are obtained by adjustment of

parameters, simulating different tissue responsiveness to metabolic hormones.

The effects of growth hormone treatments on feed intake, milk yield, energy balance and blood plasma concentration of free fatty acids are simulated by the model in accordance with experimental results. However, the simulated increases in growth hormone plasma concentration elicited by the "treatments" are smaller than observed in vivo.

Two hypothetical experiments are performed by simulation. The results suggest that:

- The contribution of different substrates to glucose synthesis is regulated partly by substrate availability and partly by the ratio of glucagon to insulin concentrations in blood plasma.

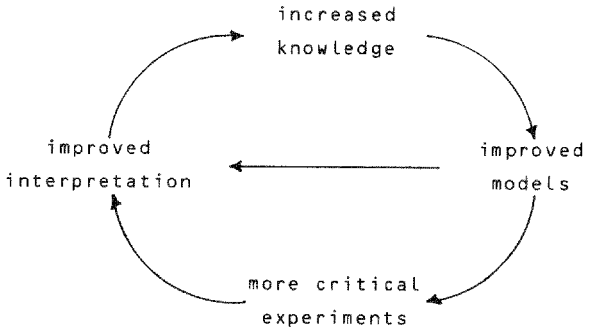
- Protection of dietary starch and protein against degradation in the rumen increases the efficiency of energy and protein utilization.

- Feed rations of identical chemical composition, but with different degradability of dietary starch, have different net energy values.

The model is very flexible, and possesses a new principle of modelling the regulation of pool sizes and rates of transaction. However, some concepts regarding the regulations of feed intake, microbial fermentation, hormone secretion, milk synthesis capacity, and energy metabolism should be improved. Therefore further

adjustments and evaluations are needed before the main objective of the model can be satisfactorily achieved.

In the future, use of the model can contribute to scientific progress within 2 areas: theoretical research (formulation and evaluation of concepts and hypotheses) and prediction of animal performance (experiment simulation, screening of rations, feed evaluation). The most rational and effective way to increase knowledge is to combine different experimental methods with modelling in a self-increasing process:



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APPENDIX 1: The CSMP program

```
//*       MOD(DYN1)                                                    0000070
//* 06/15/84 , 10:09:08        (AR10018)                               0000080
//* WHOLE ANIMAL MODEL                                                 0000090
// EXEC CSMP3X                                                       0000100
//FT15F001 DD DSN=&&DATA,DISP=(,PASS),                               0000110
// UNIT=SYSDA,SPACE=(TRK,(50,10)),                                   0000120
// DCB=(RECFM=VBS,LRECL=32756,BLKSIZE=4000)                          0000130
//SYSIN DD *                                                        0000140

INITIAL                                                              0000150
                                                                     0000160
PARAM K106I=2.50,K6I=.92361,K11I=.0632646,K20I=.00555038,K21I=2.723,... 0000170
      KCA=3.8,KATP=.07,YATPM=28.0,...                                0000180
                                                                     0000190
      K121I=.62684,K128I=.000001,K130I=.78593,K27I=6.578,K28I=2.731,... 0000200
      K34I=6.578,K38I=.0515,K40I=4.9427,...                          0000210
                                                                     0000220
      K136I=.1610,K137I=.0463,K139I=.575,K142I=.2315,K143I=.1155,...  0000230
      K144I=.194,K48I=.024,RUN=1                                     0000240
                                                                     0000250
                                                                     0000260
                                                                     0000270
                                                                     0000280
CONSTANT C1I=261.08,SU2I=3.8468,ST2I=.43363,CE2I=29.994,...          0000290
         C3I=19.765,AC4I=10.491,PR4I=6.6841,BU4I=3.8374,CH4I=.93307,... 0000300
         CO4I=2.0545,A1I=7.3081,A2I=2.1942,A3I=.001,A4I=11.252,...   0000310
         N1AI=.73488,N1BI=.11652,U1I=.21753,U4I=2.0479,...           0000320
                                                                     0000330
         C7I=29.578,C8I=.0745155,C9I=.91318,C10BI=56.65,C11I=.0143,... 0000340
         C12I=.0255599,C23I=.91920,A6I=1.5305,A7I=.85684,A8I=3.8248,... 0000350
         A10I=.077621,A11I=.28211,A12I=.9393,A13I=55.945,A16I=.50227,...0000360
         N2AI=.0585037,N2BI=.26074,U2I=.039282,...                   0000370
                                                                     0000380
         C14I=.18457,C16I=1.1542,C17I=.11677,C18I=.09737,C19I=.1684,... 0000390
         C20I=15.04,C21I=5.307,C22I=.03738,C24I=3.2518,...           0000400
         C25I=.25424,C26I=1.3553,C27I=.4959,C28I=.64867,...          0000410
         C38I=3.270,C41I=3.04,C44I=.046,...                          0000420
         A14I=.19935,A15I=19.819,A17I=.52259,A18I=.578,A20I=4.251,... 0000430
         A22I=2.817,N3I=.0483836,U3I=.35090,...                      0000440
                                                                     0000450
         C29I=.1485,C30I=.1782,C31I=.123,C33I=1.01,C34I=55.866,...   0000460
         C35I=1.55,C36I=1.860,C37I=.349,C39I=.221,C40I=.265,...      0000470
         C43I=3030.0,C45I=.200,C46I=.240,C47I=.045,...               0000480
         A19I=.232,A21I=498.0,A23I=330.0                             0000490
                                                                     0000500
```

```
                                                                    0000510
INCON BW=600,FT=3.3,L179=.06863                                     0000520
                                                                    0000530
K106=K106I                                                          0000540
K6=K6I                                                              0000550
K11=K11I                                                            0000560
K20=K20I                                                            0000570
K21=K21I                                                            0000580
                                                                    0000590
C1=C1I                                                              0000600
SU2=SU2I                                                            0000610
ST2=ST2I                                                            0000620
CE2=CE2I                                                            0000630
C3=C3I                                                              0000640
AC4=AC4I                                                            0000650
PR4=PR4I                                                            0000660
BU4=BU4I                                                            0000670
CH4=CH4I                                                            0000680
CO4=CO4I                                                            0000690
                                                                    0000700
A1=A1I                                                              0000710
A2=A2I                                                              0000720
A3=A3I                                                              0000730
A4=A4I                                                              0000740
N1A=N1AI                                                            0000750
N1B=N1BI                                                            0000760
U1=U1I                                                              0000770
U4=U4I                                                              0000780
                                                                    0000790
C2=SU2+ST2+CE2                                                      0000800
CA3=KCA*A3                                                          0000810
YATP=YATPM*A2*N1A/(KATP+A2*N1A)                                     0000820
X1=SU2/(SU2+ST2)                                                    0000830
X2=ST2/(SU2+ST2)                                                    0000840
X3=CE2/(SU2+ST2)                                                    0000850
                                                                    0000860
K121=K121I                                                          0000870
K128=K128I                                                          0000880
K130=K130I                                                          0000890
K27=K27I                                                            0000900
K28=K28I                                                            0000910
K34=K34I                                                            0000920
K38=K38I                                                            0000930
K40=K40I                                                            0000940
                                                                    0000950
C7=C7I                                                              0000960
C8=C8I                                                              0000970
C9=C9I                                                              0000980
C10B=C10BI                                                          0000990
C11=C11I                                                            0001000
C12=C12I                                                            0001010
C23=C23I                                                            0001020
                                                                    0001030
```

```
A6=A6I                                                          0001040
A7=A7I                                                          0001050
A8=A8I                                                          0001060
A10=A10I                                                        0001070
A11=A11I                                                        0001080
A12=A12I                                                        0001090
A13=A13I                                                        0001100
A16=A16I                                                        0001110
N2A=N2AI                                                        0001120
N2B=N2BI                                                        0001130
U2=U2I                                                          0001140
                                                                0001150
K136=K136I                                                      0001160
K137=K137I                                                      0001170
K139=K139I                                                      0001180
K142=K142I                                                      0001190
K143=K143I                                                      0001200
K144=K144I                                                      0001210
K48=K48I                                                        0001220
                                                                0001230
C14=C14I                                                        0001240
C16=C16I                                                        0001250
C17=C17I                                                        0001260
C18=C18I                                                        0001270
C19=C19I                                                        0001280
C20=C20I                                                        0001290
C21=C21I                                                        0001300
C22=C22I                                                        0001310
C24=C24I                                                        0001320
C25=C25I                                                        0001330
C26=C26I                                                        0001340
C27=C27I                                                        0001350
C28=C28I                                                        0001360
C38=C38I                                                        0001370
C41=C41I                                                        0001380
C44=C44I                                                        0001390
                                                                0001400
A14=A14I                                                        0001410
A15=A15I                                                        0001420
A17=A17I                                                        0001430
A18=A18I                                                        0001440
A20=A20I                                                        0001450
A22=A22I                                                        0001460
N3=N3I                                                          0001470
U3=U3I                                                          0001480
                                                                0001490
C29=C29I                                                        0001500
C30=C30I                                                        0001510
C31=C31I                                                        0001520
C33=C33I                                                        0001530
C34=C34I                                                        0001540
C35=C35I                                                        0001550
C36=C36I                                                        0001560
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C37=C37I                                                                0001570
C39=C39I                                                                0001580
C40=C40I                                                                0001590
C43=C43I                                                                0001600
C45=C45I                                                                0001610
C46=C46I                                                                0001620
C47=C47I                                                                0001630
                                                                        0001640
A19=A19I                                                                0001650
A21=A21I                                                                0001660
A23=A23I                                                                0001670
                                                                        0001680
CA20=KCA*A20                                                            0001690
                                                                        0001700
                                                                        0001710
DYNAMIC                                                                 0001720
                                                                        0001730
* SUBROUTINE RATE1  (RUMEN COMPARTMENT)                                 0001740
                                                                        0001750
  R100,RSU100,RST100,RCE100,RGL100,RLI100,R101,RSU101,RST101,RCE101,... 0001760
  RGL101,RLI101,R102,RSU102,RST102,RCE102,RLI102,R103,RSU103,RST103,... 0001770
  RCE103,RGL103,RLI103,R105,RSU105,RST105,RCE105,RLI105,R106,RSU106,... 0001780
  RST106,RCE106,R107,RSU107,RST107,RCE107,R108,R109,R110,RST110,...     0001790
  RCE110,RLI110,RAC,RPR,RBU,RCH,RCO,R111,RAC111,RPR111,RBU111,RCH111,...0001800
  RCO111,R112,R113,R114,R115,R0,R1,R2,R3,R4,R5,R6,R7,R8,R9,R10,R11,...   0001810
  R12,R13,R14,R15,R16,R17,R18,R19,R20,R21,R55,RGE = RATE1(FT,K106,...    0001820
  K6,K11,K20,K21,KCA,X1,X2,X3,YATP,C1,C2,C3,CA3,...                     0001830
  SU2,ST2,CE2,AC4,PR4,BU4,CH4,CO4,A1,A2,A3,A4,N1A,N1B,U1,U4)            0001840
                                                                        0001850
NOSORT                                                                  0001860
                                                                        0001870
DC1=R101-R103                                                           0001880
C1=C1I+INTGRL(0.0,DC1)                                                  0001890
DSU2=RSU102-RSU105-RSU106-RSU107                                        0001900
SU2=SU2I+INTGRL(0.0,DSU2)                                               0001910
DST2=RST102-RST105-RST106-RST107                                        0001920
ST2=ST2I+INTGRL(0.0,DST2)                                               0001930
DCE2=RCE102-RCE105-RCE106-RCE107                                        0001940
CE2=CE2I+INTGRL(0.0,DCE2)                                               0001950
DC3=R105+R113-R109-R110                                                 0001960
C3=C3I+INTGRL(0.0,DC3)                                                  0001970
DAC4=RAC-RAC111                                                         0001980
AC4=AC4I+INTGRL(0.0,DAC4)                                               0001990
DPR4=RPR-RPR111                                                         0002000
PR4=PR4I+INTGRL(0.0,DPR4)                                               0002010
DBU4=RBU-RBU111                                                         0002020
BU4=BU4I+INTGRL(0.0,DBU4)                                               0002030
DCH4=RCH-RCH111                                                         0002040
CH4=CH4I+INTGRL(0.0,DCH4)                                               0002050
DCO4=RCO-RCO111                                                         0002060
CO4=CO4I+INTGRL(0.0,DCO4)                                               0002070
                                                                        0002080
DA1=R1-R5                                                               0002090
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A1=A1I+INTGRL(0.0,DA1)                                                  0002100
DA2=R2+R8-R6-R7                                                         0002110
A2=A2I+INTGRL(0.0,DA2)                                                  0002120
DA3=R6+R12+R17-R8-R9-R10-R11                                            0002130
A3=A3I+INTGRL(0.0,DA3)                                                  0002140
DA4=R9-R12-R13                                                          0002150
A4=A4I+INTGRL(0.0,DA4)                                                  0002160
                                                                        0002170
DN1A=R3+R20+R21-R14-R15-R16                                             0002180
N1A=N1AI+INTGRL(0.0,DN1A)                                               0002190
DN1B=R11+R15-R17-R18-R20                                                0002200
N1B=N1BI+INTGRL(0.0,DN1B)                                               0002210
DU1=R4+R55-R21                                                          0002220
U1=U1I+INTGRL(0.0,DU1)                                                  0002230
                                                                        0002240
SORT                                                                    0002250
                                                                        0002260
* SUBROUTINE RATE2  (INTESTINAL COMPARTMENTS)                           0002270
                                                                        0002280
  R116,R117,R118,R119,R119F,R120,R120F,R121,R122,R123,R124,RAC124,...    0002290
  RPR124,RBU124,RCH124,RCO124,PRBC2,R125,R126,R127,R127A,R128,R129,...   0002300
  R130,R131,R132,R155,R22,R23,R24,R25,R26,R27,R28,R29,R30,R31,R32,...    0002310
  R33,R34,R35,R36,R37,R38,R39,R40,R41,R42,R50,R56,RFE =...               0002320
  RATE2(RSU103,RST103,RCE103,RGL103,RLI103,...                          0002330
  RSU107,RST107,RCE107,RST110,RCE110,RLI110,R5,R7,R10,R13,R14,R18,...   0002340
  K121,K128,K130,K27,K28,K34,K38,K40,YATPM,...                          0002350
  C7,C8,C9,C10B,C11,C12,C23,A6,A7,A8,A10,A11,A12,A13,A16,N2A,N2B,U2,U4) 0002360
                                                                        0002370
NOSORT                                                                  0002380
                                                                        0002390
DC7=R116-R119                                                           0002400
C7=C7I+INTGRL(0.0,DC7)                                                  0002410
DC8=R117-R120-R121                                                      0002420
C8=C8I+INTGRL(0.0,DC8)                                                  0002430
DC9=R118-R122-R123                                                      0002440
C9=C9I+INTGRL(0.0,DC9)                                                  0002450
DC10B=R119+R120+R122+R127+PRBC2-R119F-R120F-R126-R127A                  0002460
C10B=C10BI+INTGRL(0.0,DC10B)                                            0002470
DC11=R155-R128                                                          0002480
C11=C11I+INTGRL(0.0,DC11)                                               0002490
DC12=R121-R129-R130-R131                                                0002500
C12=C12I+INTGRL(0.0,DC12)                                               0002510
                                                                        0002520
DA6=R22-R25                                                             0002530
A6=A6I+INTGRL(0.0,DA6)                                                  0002540
DA7=R23-R26-R27                                                         0002550
A7=A7I+INTGRL(0.0,DA7)                                                  0002560
DA8=R25+R26+R32+R33+R36-R28-R29                                         0002570
A8=A8I+INTGRL(0.0,DA8)                                                  0002580
DA10=R30-R32                                                            0002590
A10=A10I+INTGRL(0.0,DA10)                                               0002600
DA11=R31-R33-R34                                                        0002610
A11=A11I+INTGRL(0.0,DA11)                                               0002620
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DA12=R27+R34+R42+R50-R39-R40                                          0002630
A12=A12I+INTGRL(0.0,DA12)                                             0002640
DA13=R39-R41-R42                                                      0002650
A13=A13I+INTGRL(0.0,DA13)                                             0002660
                                                                      0002670
DN2A=R24-R35                                                          0002680
N2A=N2AI+INTGRL(0.0,DN2A)                                             0002690
DN2B=R28+R38-R36-R37                                                  0002700
N2B=N2BI+INTGRL(0.0,DN2B)                                             0002710
DU2=R56-R38                                                           0002720
U2=U2I+INTGRL(0.0,DU2)                                                0002730
                                                                      0002740
SORT                                                                  0002750
                                                                      0002760
*  SUBROUTINE RATE3  (LIVER AND EXTRACELLULAR FLUID COMPARTMENTS)     0002770
                                                                      0002780
   R133,R134,R135,R136,R137,R138,R139,R140,R141,R142,R143,R144,R145,... 0002790
   R146,R147,R148,R149,R150,R151,R152,R153,R154,R156,R157,R158,...     0002800
   R159,R160,R161,R162,R163,R164,K165,R165,R166,R167,R168,R169,R170A,...0002810
   R170B,R171A,R171B,R172A,R172B,R173A,R173B,R189,R194,R199,R43,R44,... 0002820
   R45,R46,R47,R48,R49,R51,R52,R53,R54,R57,R58,R61,R64,DAYS,GH,GLUCA,...0002830
   INSUL,RATIO= RATE3(RAC111,RAC124,RPR111,RPR124,RBU111,RBU124,R132,...0002840
   R40,K136,K137,K139,K142,K143,K144,K48,C14,C16,C17,...               0002850
   C18,C19,C20,C21,C22,C23,C24,C25,C26,C27,C28,C38,C41,C44,...         0002860
   A14,A15,A16,A17,A18,A20,A22,N3,U3,U4)                              0002870
                                                                      0002880
NOSORT                                                                0002890
                                                                      0002900
DC14=R133-R136-R137                                                   0002910
C14=C14I+INTGRL(0.0,DC14)                                             0002920
DC16=R136+R142+R144-R139                                              0002930
C16=C16I+INTGRL(0.0,DC16)                                             0002940
DC17=R140-R141-R142-R143                                              0002950
C17=C17I+INTGRL(0.0,DC17)                                             0002960
DC18=R151+R164+R168-R144-R145-R146                                    0002970
C18=C18I+INTGRL(0.0,DC18)                                             0002980
DC19=R152+R165+R169-R147-R148-R149-R150                               0002990
C19=C19I+INTGRL(0.0,DC19)                                             0003000
DC20=R145+R147-R151-R152                                              0003010
C20=C20I+INTGRL(0.0,DC20)                                             0003020
DC21=R146+R148-R153                                                   0003030
C21=C21I+INTGRL(0.0,DC21)                                             0003040
DC22=R149-R154                                                        0003050
C22=C22I+INTGRL(0.0,DC22)                                             0003060
                                                                      0003070
DC23=R135+R154-R155-R156-R157-R158-R159                               0003080
C23=C23I+INTGRL(0.0,DC23)                                             0003090
DC24=R130+R139-R160-R161-R162-R163                                    0003100
C24=C24I+INTGRL(0.0,DC24)                                             0003110
DC25=R189+R199-R164                                                   0003120
C25=C25I+INTGRL(0.0,DC25)                                             0003130
DC26=R194-R165-R166-R167                                              0003140
C26=C26I+INTGRL(0.0,DC26)                                             0003150
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DC27=R132-R168-R169-R170A-R170B                                    0003160
C27=C27I+INTGRL(0.0,DC27)                                          0003170
DC28=R153-R171A-R171B                                              0003180
C28=C28I+INTGRL(0.0,DC28)                                          0003190
                                                                   0003200
DA14=R40+R46+R47+R54-R43-R44-R45                                   0003210
A14=A14I+INTGRL(0.0,DA14)                                          0003220
DA15=R43-R46                                                       0003230
A15=A15I+INTGRL(0.0,DA15)                                          0003240
                                                                   0003250
DA16=R44-R50-R51-R52-R53                                           0003260
A16=A16I+INTGRL(0.0,DA16)                                          0003270
DA17=R58+R61+R64-R54                                               0003280
A17=A17I+INTGRL(0.0,DA17)                                          0003290
                                                                   0003300
DN3=R16+R35+R37+R45-R47-R48                                        0003310
N3=N3I+INTGRL(0.0,DN3)                                             0003320
DU3=R48-R49                                                        0003330
U3=U3I+INTGRL(0.0,DU3)                                             0003340
DU4=R49-R55-R56-R57                                                0003350
U4=U4I+INTGRL(0.0,DU4)                                             0003360
                                                                   0003370
SORT                                                               0003380
                                                                   0003390
*  SUBROUTINE RATE4  (MAMMARY GLAND AND BODY TISSUE COMPARTMENTS)  0003400
                                                                   0003410
   R174,R175,R176,R177,R178,R179,R180,R181,R182,R183,...           0003420
   R184,R185,R186,R187,R188,R190,R191,R192,R193,R195,R196,R197,R198,... 0003430
   R200,R201,R202,...                                              0003440
   R59,R60,R62,R63,R65,R66=...                                     0003450
   RATE4(R172B,L179,INSUL,C29,C30,C31,C33,C34,CA20,C35,C36,C37,... 0003460
   C39,C40,C41,C43,C45,C46,C47,...                                 0003470
   A18,A19,A20,A21,A22,A23)                                        0003480
                                                                   0003490
NOSORT                                                             0003500
                                                                   0003510
DC29=R156-R174-R175                                                0003520
C29=C29I+INTGRL(0.0,DC29)                                          0003530
DC30=R160-R176-R177-R178                                           0003540
C30=C30I+INTGRL(0.0,DC30)                                          0003550
DC31=R172A+R174-R179-R180                                          0003560
C31=C31I+INTGRL(0.0,DC31)                                          0003570
DC33=R177-R182                                                     0003580
C33=C33I+INTGRL(0.0,DC33)                                          0003590
DC34=R179+R181-R183                                                0003600
C34=C34I+INTGRL(0.0,DC34)                                          0003610
                                                                   0003620
DA18=R51-R58-R59                                                   0003630
A18=A18I+INTGRL(0.0,DA18)                                          0003640
DA19=R59-R60                                                       0003650
A19=A19I+INTGRL(0.0,DA19)                                          0003660
                                                                   0003670
DC35=R157+R184-R185                                                0003680
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C35=C35I+INTGRL(0.0,DC35)                                          0003690
DC36=R161-R186-R187                                                0003700
C36=C36I+INTGRL(0.0,DC36)                                          0003710
DC37=R166-R188                                                     0003720
C37=C37I+INTGRL(0.0,DC37)                                          0003730
DC38=R186-R189                                                     0003740
C38=C38I+INTGRL(0.0,DC38)                                          0003750
                                                                   0003760
DA20=R52+R63-R61-R62                                               0003770
A20=A20I+INTGRL(0.0,DA20)                                          0003780
DA21=R62-R63                                                       0003790
A21=A21I+INTGRL(0.0,DA21)                                          0003800
                                                                   0003810
DC39=R158-R190-R191                                                0003820
C39=C39I+INTGRL(0.0,DC39)                                          0003830
DC40=R162-R192-R193                                                0003840
C40=C40I+INTGRL(0.0,DC40)                                          0003850
DC41=R173A+R190+R197-R194-R195                                     0003860
C41=C41I+INTGRL(0.0,DC41)                                          0003870
DC43=R195+R196-R197-R198                                           0003880
C43=C43I+INTGRL(0.0,DC43)                                          0003890
DC44=R173B+R198-R199                                               0003900
C44=C44I+INTGRL(0.0,DC44)                                          0003910
                                                                   0003920
DC45=R159-R200                                                     0003930
C45=C45I+INTGRL(0.0,DC45)                                          0003940
DC46=R163-R201                                                     0003950
C46=C46I+INTGRL(0.0,DC46)                                          0003960
DC47=R167-R202                                                     0003970
C47=C47I+INTGRL(0.0,DC47)                                          0003980
                                                                   0003990
DA22=R53+R66-R64-R65                                               0004000
A22=A22I+INTGRL(0.0,DA22)                                          0004010
DA23=R65-R66                                                       0004020
A23=A23I+INTGRL(0.0,DA23)                                          0004030
                                                                   0004040
                                                                   0004050
                                                                   0004060
                                                                   0004070
SORT                                                               0004080
                                                                   0004090
                                                                   0004100
F100=INTGRL(0.0,R100)                                              0004110
F103=INTGRL(0.0,R103)                                              0004120
F107=INTGRL(0.0,R107)                                              0004130
F109=INTGRL(0.0,R109)                                              0004140
F110=INTGRL(0.0,R110)                                              0004150
F111=INTGRL(0.0,R111)                                              0004160
F112=INTGRL(0.0,R112)                                              0004170
                                                                   0004180
F0=INTGRL(0.0,R0)                                                  0004190
F5=INTGRL(0.0,R5)                                                  0004200
F6=INTGRL(0.0,R6)                                                  0004210
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F7=INTGRL(0.0,R7)                                                       0004220
F10=INTGRL(0.0,R10)                                                     0004230
F11=INTGRL(0.0,R11)                                                     0004240
F13=INTGRL(0.0,R13)                                                     0004250
F14=INTGRL(0.0,R14)                                                     0004260
F15=INTGRL(0.0,R15)                                                     0004270
F16=INTGRL(0.0,R16)                                                     0004280
F17=INTGRL(0.0,R17)                                                     0004290
F18=INTGRL(0.0,R18)                                                     0004300
F20=INTGRL(0.0,R20)                                                     0004310
                                                                        0004320
F55=INTGRL(0.0,R55)                                                     0004330
                                                                        0004340
DIFFC1=F100+F112-F103-F107-F109-F110-F111                               0004350
DIFFA1=F0+F55-F5-F7-F10-F13-F14-F16-F18                                 0004360
                                                                        0004370
                                                                        0004380
                                                                        0004390
NOSORT                                                                  0004400
                                                                        0004410
     CALL POOL1(C1,AC4,PR4,BU4,CH4,C04,...                              0004420
                KATP,KCA,YATPM,...                                      0004430
                SU2,ST2,CE2,C3,A1,A2,A3,A4,N1A,N1B,U1,...               0004440
                C2,CA3,C4,UNFERM,X1,X2,X3,YATP)                         0004450
                                                                        0004460
NIGHT=STEP(1.)-STEP(5.)                                                 0004470
                                                                        0004480
     CALL REGUL1(C2,A2,A3,N1A,N1B,BW,NIGHT,UNFERM,...                   0004490
                 K106,K6,K11,K20,K21,FT)                                0004500
                                                                        0004510
     CALL POOL2(C8,C9,C11,C12,A6,A7,A8,A10,A11,A12,N2A,N2B,U2)          0004520
                                                                        0004530
     CALL REGUL2(C8,C11,C12,A7,A8,A11,A12,N2B,...                       0004540
                 K121,K128,K130,K27,K28,K34,K38,K40)                    0004550
                                                                        0004560
     CALL POOL3(C14,C16,C17,C18,C19,C20,C21,C22,C23,C24,C25,C26,C27,... 0004570
                C28,A14,A15,A16,A17,N3,U3,U4)                           0004580
                                                                        0004590
     CALL REGUL3(C14,C16,C17,C24,N3,...                                 0004600
                 K136,K137,K139,K142,K143,K144,K48)                     0004610
                                                                        0004620
     CALL POOL4(C29,C30,C31,C33,C34,C35,C36,C37,C38,...                 0004630
                C39,C40,C41,C43,C44,C45,C46,C47,...                     0004640
                A18,A19,A20,A21,A22,A23)                                0004650
                                                                        0004660
TERMINAL                                                                0004670
                                                                        0004680
RUN=RUN+1                                                               0004690
TIMER FINTIM=24.,PRDEL=24.,OUTDEL=.05,DELT=.05                          0004700
METHOD ADAMS                                                            0004710
IF(RUN.GT.35.) GO TO 50                                                 0004720
                                                                        0004730
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      CALL END1(C1,SU2,ST2,CE2,C3,AC4,PR4,BU4,CH4,C04,...                    0004740
                A1,A2,A3,A4,N1A,N1B,U1,U4,...                                0004750
                K106,K6,K11,K20,K21,...                                      0004760
                C1I,SU2I,ST2I,CE2I,C3I,AC4I,PR4I,BU4I,CH4I,C04I,...          0004770
                A1I,A2I,A3I,A4I,N1AI,N1BI,U1I,U4I,...                        0004780
                K106I,K6I,K11I,K20I,K21I)                                    0004790
                                                                             0004800
      CALL END2(C7,C8,C9,C10B,C11,C12,C23,...                                0004810
                A6,A7,A8,A10,A11,A12,A13,A16,N2A,N2B,U2,...                  0004820
                K121,K128,K130,K27,K28,K34,K38,K40,...                       0004830
                C7I,C8I,C9I,C10BI,C11I,C12I,C23I,...                         0004840
                A6I,A7I,A8I,A10I,A11I,A12I,A13I,A16I,N2AI,N2BI,U2I,...       0004850
                K121I,K128I,K130I,K27I,K28I,K34I,K38I,K40I)                  0004860
                                                                             0004870
      CALL END3(C14,C16,C17,C18,C19,C21,C22,C24,C25,C26,C27,C28,...          0004880
                C38,C41,C44,...                                              0004890
                A14,A15,A17,A18,A20,A22,N3,U3,...                            0004900
                K136,K137,K139,K142,K143,K144,K48,...                        0004910
                C14I,C16I,C17I,C18I,C19I,C21I,C22I,C24I,C25I,...             0004920
                C26I,C27I,C28I,C38I,C41I,C44I,...                            0004930
                A14I,A15I,A17I,A18I,A20I,A22I,N3I,U3I,...                    0004940
                K136I,K137I,K139I,K142I,K143I,K144I,K48I)                    0004950
                                                                             0004960
      CALL END4(C29,C30,C31,C33,C34,C35,C36,C37,...                          0004970
                C39,C40,C45,C46,C47,...                                      0004980
                A19,...                                                      0004990
                C29I,C30I,C31I,C33I,C34I,C35I,C36I,C37I,...                  0005000
                C39I,C40I,C45I,C46I,C47I,...                                 0005010
                A19I)                                                        0005020
                                                                             0005030
      CALL RERUN                                                             0005040
                                                                             0005050
50 CONTINUE                                                                  0005060
                                                                             0005070
                                                                             0005080
                                                                             0005090
                                                                             0005100
                                                                             0005110
PREPARE RUN,F100,F103,F106,F107,F109,F110,F111,F112,F0,F5,F6,F7,...           0005120
        F10,F11,F13,F14,F15,F16,F17,F18,F20,F55,...                          0005130
        DIFFC1,DIFFA1,...                                                    0005140
        C1,SU2,ST2,CE2,C3,AC4,PR4,BU4,CH4,C04,...                            0005150
        A1,A2,A3,A4,N1A,N1B,U1,N2A,N2B,U2,N3,U3,U4,...                       0005160
        K106,K6,K11,K20,K21,K28                                              0005170
                                                                             0005180
RANGE RUN,C1,SU2,ST2,CE2,C3,AC4,PR4,BU4,CH4,C04,...                          0005190
      A1,A2,A3,A4,N1A,N1B,U1,N2A,N2B,U2,N3,U3,U4,...                         0005200
      K106,K6,K11,K20,K21,K28,K38,K48                                        0005210
                                                                             0005220
END                                                                          0005230
STOP                                                                         0005240
                                                                             0005250
                                                                             0005260
```

APPENDIX 2: The FORTRAN subroutines

```
C      RUMEN COMPARTMENT                                                        0005270
                                                                                0005280
       SUBROUTINE RATE1(FT,K106,K6,K11,K20,K21,                                 0005290
      +                 KCA,X1,X2,X3,YATP,                                     0005300
      +                 C1,C2,C3,CA3,SU2,ST2,CE2,AC4,PR4,BU4,CH4,CO4,          0005310
      +                 A1,A2,A3,A4,N1A,N1B,U1,U4,                             0005320
      +                 R100,RSU100,RST100,RCE100,RGL100,RLI100,               0005330
      +                 R101,RSU101,RST101,RCE101,RGL101,RLI101,               0005340
      +                 R102,RSU102,RST102,RCE102,       RLI102,               0005350
      +                 R103,RSU103,RST103,RCE103,RGL103,RLI103,               0005360
      +                 R105,RSU105,RST105,RCE105,       RLI105,               0005370
      +                 R106,RSU106,RST106,RCE106,                             0005380
      +                 R107,RSU107,RST107,RCE107,R108,R109,                   0005390
      +                 R110,       RST110,RCE110,       RLI110,               0005400
      +                 RAC,RPR,RBU,RCH,RCO,                                   0005410
      +                 R111,RAC111,RPR111,RBU111,RCH111,RCO111,               0005420
      +                 R112,R113,R114,R115,                                   0005430
      +                 RO,R1,R2,R3,R4,R5,R6,R7,R8,R9,R10,R11,R12,R13,         0005440
      +                 R14,R15,R16,R17,R18,R19,R20,R21,R55,RGE)               0005450
                                                                                0005460
       REAL KSU,LSU,MSU,KST,LST,MST,KCE,LCE,MCE,KGL,LGL,KLI,LLI,MLI             0005470
       REAL K103,K105,K106,L106,K107,KCA,K110,L110,M110,N110                    0005480
       REAL KAC111,KPR111,KBU111,KCH111,KCO111,K112,K                           0005490
       REAL KC,LC,MC,KR,LR,MR,M3,M4,K5,K6,K7,K8,M9,K9,K10,K11,K12,K13           0005500
       REAL K14,K15,K16,K17,K18,K20,K21,K55                                     0005510
       REAL N1A,N1B                                                             0005520
                                                                                0005530
       DATA KSU,LSU,MSU,KST,LST,MST/.2235,35.087,.0,.0313,37.037,.0/            0005540
       DATA KCE,LCE,MCE/.4268,37.037,.4/                                        0005550
       DATA KGL,LGL,KLI,LLI,MLI/.0047,32.573,.04,62.402,.9/                     0005560
       DATA K103,K105,L106,K107/.025,.073,1.0534,.043/                          0005570
       DATA K110,L110,M110,N110/.08,.08,.44,.48/                                0005580
       DATA KAC111,KPR111,KBU111/.4483,.4605,.4540/                             0005590
       DATA KCH111,KCO111,K112,K/1.,1.187,.090,.75/                             0005600
       DATA KC,LC,MC,KR,LR,MR/.100,11.423,.2788,.0788,11.423,.1/                0005610
       DATA M3,M4,K5,K7,K8,K9,M9/.0,.0,.043,.11005,.0415,.001,5.735E-3/         0005620
       DATA K12,K15,K16,K17,K55,G/.02,.189,18.385,.0097,16.687,.0006/           0005630
                                                                                0005640
       DATA R112M,R6M,R8M,R11M,R15M/3.0,1.685,.157,1.737,.6/                    0005650
       DATA R17M,R20M,R21M/1.51,1.04,2.463/                                     0005660
                                                                                0005670
       DATA ACSU,PRSU,BUSU,CHSU,COSU/.36036,.13514,.21622,.1045,.18378/         0005680
       DATA ATPSU/.76937/                                                       0005690
       DATA ACST,PRST,BUST,CHST,COST/.38667,.26833,.1000,.08667,.15833/         0005700
       DATA ATPST/.75333/                                                       0005710
       DATA ACCE,PRCE,BUCE,CHCE,COCE/.36264,.36265,.06165,.0680,.14506/         0005720
```

```
DATA ATPCE/.70354/                                                      0005730
DATA AC,PR,BU,BC,CH,CO/.29749,.1373,.09153,.16476,.14874,.16018/        0005740
DATA ATPPR/.0/                                                          0005750
                                                                        0005760
DATA V1,V4/74.,150./                                                    0005770
                                                                        0005780
DATA CSU,CST,CCE,CLI,CPR/16.6,17.6,18.8,39.75,23.93/                    0005790
                                                                        0005800
    K10=K110                                                            0005810
    K13=K110                                                            0005820
    K14=K7                                                              0005830
    K18=K110                                                            0005840
                                                                        0005850
    RSU100=FT*KSU*LSU                                                   0005860
    RST100=FT*KST*LST                                                   0005870
    RCE100=FT*KCE*LCE                                                   0005880
    RGL100=FT*KGL*LGL                                                   0005890
    RLI100=FT*KLI*LLI                                                   0005900
    R100=RSU100+RST100+RCE100+RGL100+RLI100                             0005910
    RSU101=MSU*RSU100                                                   0005920
    RST101=MST*RST100                                                   0005930
    RCE101=MCE*RCE100                                                   0005940
    RGL101=MSU*RGL100                                                   0005950
    RLI101=MLI*RLI100                                                   0005960
    R101=RSU101+RST101+RCE101+RGL101+RLI101                             0005970
    RSU102=(1-MSU)*(RSU100+RGL100)                                      0005980
    RST102=(1-MST)*RST100                                               0005990
    RCE102=(1-MCE)*RCE100                                               0006000
    RLI102=(1-MLI)*RLI100                                               0006010
    R102=RSU102+RST102+RCE102+RLI102                                    0006020
    R103=K103*C1                                                        0006030
    S=MSU*(KSU*LSU+KGL*LGL)+MST*KST*LST+MCE*KCE*LCE+MLI*KLI*LLI         0006040
    RSU103=R103*MSU*KSU*LSU/S                                           0006050
    RST103=R103*MST*KST*LST/S                                           0006060
    RCE103=R103*MCE*KCE*LCE/S                                           0006070
    RGL103=R103*MSU*KGL*LGL/S                                           0006080
    RLI103=R103*MLI*KLI*LLI/S                                           0006090
    RSU105=K105*SU2                                                     0006100
    RST105=K105*ST2                                                     0006110
    RCE105=K105*CE2                                                     0006120
    RLI105=RLI102                                                       0006130
    R105=RSU105+RST105+RCE105+RLI105                                    0006140
    R106M=L106*A4                                                       0006150
    R106=R106M*C2/(K106+C2)                                             0006160
    RSU106=R106*X1*EXP(-G*X3)                                           0006170
    RST106=R106*X2*EXP(-G*X3)                                           0006180
    RCE106=R106*(1-EXP(-G*X3))                                          0006190
                                                                        0006200
    SUAC1=ACSU*RSU106                                                   0006210
    SUPR1=PRSU*RSU106                                                   0006220
    SUBU1=BUSU*RSU106                                                   0006230
    SUCH1=CHSU*RSU106                                                   0006240
    SUCO1=COSU*RSU106                                                   0006250
```

```
SUATP1=ATPSU*RSU106                                                    0006260
STAC1=ACST*RST106                                                      0006270
STPR1=PRST*RST106                                                      0006280
STBU1=BUST*RST106                                                      0006290
STCH1=CHST*RST106                                                      0006300
STCO1=COST*RST106                                                      0006310
STATP1=ATPST*RST106                                                    0006320
CEAC1=ACCE*RCE106                                                      0006330
CEPR1=PRCE*RCE106                                                      0006340
CEBU1=BUCE*RCE106                                                      0006350
CECH1=CHCE*RCE106                                                      0006360
CECO1=COCE*RCE106                                                      0006370
CEATP1=ATPCE*RCE106                                                    0006380
                                                                       0006390
RSU107=K107*SU2                                                        0006400
RST107=K107*ST2                                                        0006410
RCE107=K107*CE2                                                        0006420
R107=RSU107+RST107+RCE107                                              0006430
R108=SUATP1+STATP1+CEATP1                                              0006440
R110=K110*C3                                                           0006450
RST110=L110*R110                                                       0006460
RCE110=M110*R110                                                       0006470
RLI110=N110*R110                                                       0006480
RAC111=KAC111*AC4                                                      0006490
RPR111=KPR111*PR4                                                      0006500
RBU111=KBU111*BU4                                                      0006510
RCH111=KCH111*CH4                                                      0006520
RCO111=KCO111*CO4                                                      0006530
R111=RAC111+RPR111+RBU111+RCH111+RCO111                                0006540
R112=R112M*CA3/(K112+CA3)                                              0006550
                                                                       0006560
PRAC1=AC*R112                                                          0006570
PRPR1=PR*R112                                                          0006580
PRBU1=BU*R112                                                          0006590
PRBC1=BC*R112                                                          0006600
PRCH1=CH*R112                                                          0006610
PRCO1=CO*R112                                                          0006620
PRATP1=ATPPR*R112                                                      0006630
                                                                       0006640
RAC=SUAC1+STAC1+CEAC1+PRAC1                                            0006650
RPR=SUPR1+STPR1+CEPR1+PRPR1                                            0006660
RBU=SUBU1+STBU1+CEBU1+PRBU1                                            0006670
RCH=K*(SUCH1+STCH1+CECH1+PRCH1)                                        0006680
RCO=SUCO1+STCO1+CECO1+PRCO1-RCH*(1-1/K)                                0006690
                                                                       0006700
R113=PRBC1                                                             0006710
R114=R112-R113                                                         0006720
R115=PRATP1                                                            0006730
                                                                       0006740
RCO=FT*KC*LC                                                           0006750
RRO=FT*KR*LR                                                           0006760
RO=RCO+RRO                                                             0006770
R1=MC*RCO+MR*RRO                                                       0006780
```

```
      R3=M3*R0                                                          00067
      R4=M4*R0                                                          0006
      R2=R0-R1-R3-R4                                                    0006
      R5=K5*A1                                                          0006
      R6=R6M*A2/(K6+A2)                                                 0006
      R7=K7*A2                                                          00068
      R8=R8M*A3/(K8+A3)                                                 00068
      R9M=YATP*M9*(R108+R115)                                           00068
      R9=R9M*A3/(K9+A3)                                                 00068
      R10=K10*A3                                                        00068
      R11=R11M*A3/(K11+A3)                                              00068
      R12=K12*A4                                                        00069
      R13=K13*A4                                                        0006
      R14=K14*N1A                                                       0006
      R15=R15M*N1A/(K15+N1A)                                            0006
      R16=K16*(N1A/V1)                                                  0006
      R17=R17M*N1B/(K17+N1B)                                            0006
                                                                        0006
      R109=R112-KCA*(R11-R17)                                           0006
                                                                        0006
      R18=K18*N1B                                                       0006
      R19=R10+R13+R18                                                   0007
      R20=R20M*N1B/(K20+N1B)                                            0007
      R21=R21M*U1/(K21+U1)                                              00070
      R55=K55*(U4/V4-U1/V1)                                             00070
                                                                        00070
      ESU100=(RSU100/LSU)*CSU                                           00070
      EST100=(RST100/LST)*CST                                           00070
      ECE100=(RCE100/LCE)*CCE                                           00070
      ELI100=(RGL100*(1/LGL-18.02/1000)+RLI100/LLI)*CLI                 00070
      EPR0=((R1+R2)/LC)*CPR                                             00070
      RGE=ESU100+EST100+ECE100+ELI100+EPR0                              00071
                                                                        00071
      RETURN                                                            00071
      END                                                               00071
                                                                        00071
                                                                        00071
C     INTESTINAL COMPARTMENTS                                           00071
                                                                        00071
      SUBROUTINE RATE2(RSU103,RST103,RCE103,RGL103,RLI103,              00071
     +                 RSU107,RST107,RCE107,RST110,RCE110,RLI110,       00071
     +                 R5,R7,R10,R13,R14,R18,                           00072
     +                 K121,K128,K130,K27,K28,K34,K38,K40,YATPM,        00072
     +                 C7,C8,C9,C10B,C11,C12,C23,                       00072
     +                 A6,A7,A8,A10,A11,A12,A13,A16,N2A,N2B,U2,U4,      00072
     +                 R116,R117,R118,R119,R119F,R120,R120F,R121,R122,   00072
     +                 R123,R124,RAC124,RPR124,RBU124,RCH124,RCO124,     00072
     +                 PRBC2,R125,R126,R127,R127A,R128,R129,R130,R131,   00072
     +                 R132,R155,                                       00072
     +                 R22,R23,R24,R25,R26,R27,R28,R29,R30,R31,R32,R33,  00072
     +                 R34,R35,R36,R37,R38,R39,R40,R41,R42,R50,R56,RFE)  00072
                                                                        00073
```

```
REAL K116,K119,L119,K120,L120,K121,K122,K123,K126,K127A,K128,K129 0007310
REAL K130,K131,K155,K,KCA,LCE,LC,M9                              0007320
REAL K23,L23,M23,N23,K25,K26,K27,K28,K29,K31,L31,K32,K33         0007330
REAL K34,K35,K36,L36,K37,K38,K39,K40,K41,L41,K42,K50,K56         0007340
REAL N2A,N2B                                                     0007350
                                                                 0007360
DATA K116,K119,L119,L120,K123/.0833,.240,.220,1.00,2.1617/       0007370
DATA K126,K127A,K129,K131,K155/.115,.13692,.0677,.0625,110.55/   0007380
DATA K23,L23,M23,N23/.80,1.00,.70,1.00/                          0007390
DATA K31,L31,K35,K36,K37/.97554,.97554,33.4009,.06371,18.495/    0007400
DATA K39,K41,L41,K42/.30691,26.330,.0380,.002282/                0007410
DATA K50,K56,K,KCA,M9/8.763,16.727,.75,3.8,5.735E-3/             0007420
                                                                 0007430
DATA R121M,R128M,R129M,R130M/1.667,.7145,.0160,1.667/             0007440
DATA R27M,R28M,R34M,R38M/6.98,.630,6.98,.403/                    0007450
DATA R39M,R40M,R50M/.676,6.98,6.98/                              0007460
                                                                 0007470
DATA ACST,PRST,BUST,CHST,COST/.38667,.26833,.1000,.08667,.15833/ 0007480
DATA ATPST/.75333/                                               0007490
DATA ACCE,PRCE,BUCE,CHCE,COCE/.36264,.36265,.06165,.0680,.14506/ 0007500
DATA ATPCE/.70354/                                               0007510
DATA AC,PR,BU,BC,CH,CO/.29749,.1373,.09153,.16476,.14874,.16018/ 0007520
                                                                 0007530
DATA V2A,V2B,VD,V4/21.3,12.1,12.3,150./                          0007540
                                                                 0007550
DATA LCE,CCE,CFA,CGLU/37.037,18.8,10.027,2.805/                  0007560
DATA CKA,CBC,CAA,LC/19.4,3.497,23.4,11.423/                      0007570
                                                                 0007580
    K120=K119                                                    0007590
    K122=K119                                                    0007600
    K25=K119                                                     0007610
    K26=K119                                                     0007620
    K29=K126                                                     0007630
    K32=K119                                                     0007640
    K33=K119                                                     0007650
                                                                 0007660
    L36=YATPM*M9                                                 0007670
                                                                 0007680
    R116=RCE103+RCE107+RCE110+K116*(RLI103+RLI110*48/51)         0007690
    R117=RSU103+RST103+RGL103+RSU107+RST107+RST110+RLI110*3/51    0007700
    R118=(1-K116)*(RLI103+RLI110*48/51)                          0007710
    R119=K119*C7                                                 0007720
    R119F=L119*R119                                              0007730
    R120=K120*C8                                                 0007740
    R120F=L120*R120                                              0007750
    R121=R121M*C8/(K121+C8)                                      0007760
    R122=K122*C9                                                 0007770
    R123=K123*C9                                                 0007780
                                                                 0007790
    STAC2=ACST*R120F                                             0007800
    STPR2=PRST*R120F                                             0007810
    STBU2=BUST*R120F                                             0007820
    STCH2=CHST*R120F                                             0007830
```

```
STCO2=COST*R120F                                                    0007840
STATP2=ATPST*R120F                                                  0007850
CEAC2=ACCE*R119F                                                    0007860
CEPR2=PRCE*R119F                                                    0007870
CEBU2=BUCE*R119F                                                    0007880
CECH2=CHCE*R119F                                                    0007890
CECO2=COCE*R119F                                                    0007900
CEATP2=ATPCE*R119F                                                  0007910
                                                                    0007920
R125=STATP2+CEATP2                                                  0007930
R126=K126*C10B                                                      0007940
R128=R128M*C11/(K128+C11)                                           0007950
R129=R129M*C12/(K129+C12)                                           0007960
R130=R130M*C12/(K130+C12)                                           0007970
R131=K131*R123                                                      0007980
R132=R123+R131                                                      0007990
R155=K155*(C23/V4)                                                  0008000
                                                                    0008010
R22=(1-K23*L23)*(R5+R7)+(1-M23*N23)*(R10+R13)                       0008020
R23=K23*L23*(R5+R7)+M23*N23*(R10+R13)                               0008030
R24=R14+R18                                                         0008040
R25=K25*A6                                                          0008050
R26=K26*A7                                                          0008060
R27=R27M*A7/(K27+A7)                                                0008070
R28=R28M*A8/(K28+A8)                                                0008080
R29=K29*A8                                                          0008090
R32=K32*A10                                                         0008100
R33=K33*A11                                                         0008110
R34=R34M*A11/(K34+A11)                                              0008120
R35=K35*(N2A/V2A)                                                   0008130
R36M=L36*R125                                                       0008140
R36=R36M*N2B/(K36+N2B)                                              0008150
                                                                    0008160
R127=KCA*(R28-R36)                                                  0008170
R127A=K127A*R127                                                    0008180
                                                                    0008190
PRAC2=AC*R127A                                                      0008200
PRPR2=PR*R127A                                                      0008210
PRBU2=BU*R127A                                                      0008220
PRBC2=BC*R127A                                                      0008230
PRCH2=CH*R127A                                                      0008240
PRCO2=CO*R127A                                                      0008250
                                                                    0008260
RAC124=STAC2+CEAC2+PRAC2                                            0008270
RPR124=STPR2+CEPR2+PRPR2                                            0008280
RBU124=STBU2+CEBU2+PRBU2                                            0008290
RCH124=K*(STCH2+CECH2+PRCH2)                                        0008300
RCO124=STCO2+CECO2+PRCO2-RCH124*(1-1/K)                             0008310
R124=RAC124+RPR124+RBU124+RCH124+RCO124                             0008320
                                                                    0008330
R37=K37*(N2B/V2B)                                                   0008340
R38=R38M*U2/(K38+U2)                                                0008350
R39=R39M*A12/(K39+A12)                                              0008360
```

```
      R40=R40M*A12/(K40+A12)                                            0008370
      R41M=L41*(R116+R117+R118+KCA*(R22+R23))                           0008380
      R41=R41M*A13/(K41+A13)                                            0008390
      R30=(1-K31*L31)*R41                                               0008400
      R31=K31*L31*R41                                                   0008410
      R42=K42*A13                                                       0008420
      R50=R50M*A16/(K50+A16)                                            0008430
      R56=K56*(U4/V4-U2/V2B)                                            0008440
                                                                        0008450
      CE=R119*((RCE103+RCE107+RCE110)/R116-L119)                        0008460
      ECE126=(CE/LCE)*CCE                                               0008470
      ELI126=(R119*(1-L119)-CE+R122)*CFA/16                             0008480
      ESU126=(R120*(1-L120))*CGLU/6                                     0008490
      EKA126=(R127*(1-K127A)/KCA)*CKA/LC                                0008500
      EBC126=PRBC2*CBC/6                                                0008510
      EPR29=R29*CAA/LC                                                  0008520
      RFE=ECE126+ELI126+ESU126+EKA126+EBC126+EPR29                      0008530
                                                                        0008540
      RETURN                                                            0008550
      END                                                               0008560
                                                                        0008570
                                                                        0008580
C     LIVER AND EXTRACELLULAR FLUID COMPARTMENTS                        0008590
                                                                        0008600
      SUBROUTINE RATE3(RAC111,RAC124,RPR111,RPR124,RBU111,RBU124,R132,  0008610
     +                 R40,                                             0008620
     +                 K136,K137,K139,K142,K143,K144,K48,               0008630
     +                 C14,C16,C17,C18,C19,C20,C21,C22,C23,C24,         0008640
     +                 C25,C26,C27,C28,C38,C41,C44,                     0008650
     +                 A14,A15,A16,A17,A18,A20,A22,N3,U3,U4,            0008660
     +                 R133,R134,R135,R136,R137,R138,R139,R140,R141,    0008670
     +                 R142,R143,R144,R145,R146,R147,R148,R149,         0008680
     +                 R150,R151,R152,R153,R154,R156,R157,R158,R159,    0008690
     +                 R160,R161,R162,R163,R164,K165,R165,R166,R167,    0008700
     +                 R168,R169,R170A,R170B,R171A,R171B,               0008710
     +                 R172A,R172B,R173A,R173B,                         0008720
     +                 R189,R194,R199,                                  0008730
     +                 R43,R44,R45,R46,R47,R48,R49,R51,R52,R53,         0008740
     +                 R54,R57,R58,R61,R64,DAYS,GH,GLUCA,INSUL,RATIO)   0008750
                                                                        0008760
      REAL K134,K136,L136,M136,K137,K139,K142,L142,M142                 0008770
      REAL K143,K144,L144,M144,K145,K146,K147,K148,K149,L149,M149       0008780
      REAL K150,L150,M150,K151,K152,K153,K154,K156,L156,M156,K157       0008790
      REAL K158,L158,M158,K159,K160,L160,M160,K161,L161,M161            0008800
      REAL K162,L162,M162,K163,K164,K165,L165,M165,K166,K167,K168,K169  0008810
      REAL K170A,L170A,M170A,K170B,L170B,M170B,K171A,L171A,M171A        0008820
      REAL K171B,L171B,M171B,K172,K173,K189,K194,K199                   0008830
      REAL K43,K44,K45,L45,M45,K46,L46,M46,K47,K48,K49                  0008840
      REAL K51,L51,M51,K52,L52,M52,K53,K54,L54,M54,K57,K58,K61,K64      0008850
      REAL INSUL,KCA,M,N3                                               0008860
                                                                        0008870
      DATA K134,L136,M136,L142,M142/.10,3.950,1.05,.15,1.505/           0008880
      DATA L144,M144,K145,K147/.15,1.107,.0625,1.391/                   0008890
```

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DATA K148,K149,L149,M149,K150/.03862,.513,1.200,1.025,.1430/                    0008900
DATA L150,M150,K152,K153,K154/1.809,1.333,1.555,1.308,16.150/                   0008910
DATA L156,M156,K157/-441.730,83.128,99.555/                                     0008920
DATA L158,M158,K159/.0,453.274,175.805/                                         0008930
DATA K160,L160,M160/1.153,-6.4605,.8491/                                        0008940
DATA K161,L161,M161/1.830,.0,1.3924/                                            0008950
DATA K162,L162,M162,K163/2.747,.0,.7331,1.4553/                                 0008960
DATA K164,L165,M165/.16665,149.5,67.75/                                         0008970
DATA K166,K167,K169/60.700,20.230,.1485/                                        0008980
DATA K170A,L170A,M170A/.1464,2.9865,2.2424/                                     0008990
DATA K170B,L170B,M170B/.4640,1.4913,1.210/                                      0009000
DATA K171A,L171A,M171A/.1980,1.7666,1.3273/                                     0009010
DATA K171B,L171B,M171B/.6040,.8826,.2028/                                       0009020
DATA K189,K194,K199/.1252,.5296,2.370/                                          0009030
                                                                                0009040
DATA K43,K44,K45,L45,M45/.010558,.5975,.0655,.0,.3703/                          0009050
DATA L46,M46,K47,K49/5.05E-4,2.245,.05755,16.788/                               0009060
DATA K51,L51,M51/.30118,-1.4889,.1790/                                          0009070
DATA K52,L52,M52,K53/.4145,.0,.6524,.336/                                       0009080
DATA K54,L54,M54/5.5477,.0,3.85965/                                             0009090
DATA K57,K58,K61,K64/47.765,.0,2.834,1.878/                                     0009100
DATA B,D,M,KCA/561.,44.,29.7,3.80/                                              0009110
                                                                                0009120
DATA R137M,R139M,R143M,R147M,R148M/1.180,5.7113,.8912,.289,1.0834/               0009130
DATA R152M,R153M,R163M,R164M,R169M/.1285,1.1511,.1309,.8638,.6513/               0009140
DATA R43M,R44M,R47M,R48M/.1755,4.8887,.1050,1.4714/                             0009150
DATA R53M,R58M,R61M,R64M/.3208,.0,.342,.339/                                    0009160
                                                                                0009170
DATA V3,V4/6.0,150.0/                                                           0009180
                                                                                0009190
    K146=K145                                                                   0009200
    K151=K145                                                                   0009210
    K168=K145                                                                   0009220
    K172=K145                                                                   0009230
    K173=K145                                                                   0009240
                                                                                0009250
    R133=RPR111+RPR124                                                          0009260
    DAYS=D                                                                      0009270
                                                                                0009280
    GH=16.7+.04607*M-.00964*B-.00567*D                                          0009290
    ALPHA=.793*R133/(2.2355+R133)+.45                                           0009300
    BETA=.86871*(R133+KCA*R40)/(15.+R133+KCA*R40)+.05*C24                       0009310
    GLUCA=ALPHA+.00514*M-.00173*B+1.7E-6*B**2+6.6E-4*D-1.2E-6*D**2              0009320
    INSUL=BETA-.01106*M+6.7E-4*B+.00134*D-3.E-6*D**2                            0009330
    RATIO=GLUCA/INSUL                                                           0009340
                                                                                0009350
    R134=K134*(RBU111+RBU124)                                                   0009360
    R135=(1-K134)*(RBU111+RBU124)+RAC111+RAC124                                 0009370
    R136M=L136+M136*RATIO                                                       0009380
    R136=R136M*C14/(K136+C14)                                                   0009390
    R137=R137M*C14/(K137+C14)                                                   0009400
    R138=R134                                                                   0009410
    R139=R139M*C16/(K139+C16)                                                   0009420
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R142M=L142+M142*RATIO                                    0009430
R142=R142M*C17/(K142+C17)                                0009440
R143=R143M*C17/(K143+C17)                                0009450
R144M=L144+M144*RATIO                                    0009460
R144=R144M*C18/(K144+C18)                                0009470
R147=R147M*C19/(K147+C19)                                0009480
R148=R148M*C19/(K148+C19)                                0009490
R145=K145*R147                                           0009500
R146=K146*R148                                           0009510
R149M=L149+M149*RATIO                                    0009520
R149=R149M*C19/(K149+C19)                                0009530
R150M=L150-M150*RATIO                                    0009540
R150=R150M*C19/(K150+C19)                                0009550
R152=R152M*C20/(K152+C20)                                0009560
R151=K151*R152                                           0009570
R153=R153M*C21/(K153+C21)                                0009580
R154=K154*C22                                            0009590
K156=L156+M156*GH                                        0009600
R156=K156*(C23/V4)                                       0009610
R157=K157*(C23/V4)                                       0009620
K158=L158+M158*INSUL                                     0009630
R158=K158*(C23/V4)                                       0009640
R159=K159*(C23/V4)                                       0009650
R160M=L160+M160*GH                                       0009660
R160=R160M*C24/(K160+C24)                                0009670
R161M=L161+M161*INSUL                                    0009680
R161=R161M*C24/(K161+C24)                                0009690
R162M=L162+M162*INSUL                                    0009700
R162=R162M*C24/(K162+C24)                                0009710
R163=R163M*C24/(K163+C24)                                0009720
R164=R164M*C25/(K164+C25)                                0009730
K165=L165-M165*INSUL                                     0009740
R165=K165*C26/V4                                         0009750
R166=K166*C26/V4                                         0009760
R167=K167*C26/V4                                         0009770
R169=R169M*C27/(K169+C27)                                0009780
R168=K168*R169                                           0009790
R170AM=L170A-M170A*INSUL                                 0009800
R170A=R170AM*C27/(K170A+C27)                             0009810
R170BM=EXP(M170B*INSUL)-L170B                            0009820
R170B=R170BM*C27/(K170B+C27)                             0009830
R171AM=L171A-M171A*INSUL                                 0009840
R171A=R171AM*C28/(K171A+C28)                             0009850
R171BM=EXP(M171B*INSUL)-L171B                            0009860
R171B=R171BM*C28/(K171B+C28)                             0009870
                                                         0009880
R172=R170A+R171A                                         0009890
R172A=R172/(1+K172)                                      0009900
R172B=K172*R172A                                         0009910
R173=R170B+R171B                                         0009920
R173A=R173/(1+K173)                                      0009930
R173B=K173*R173A                                         0009940
                                                         0009950
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      R189=K189*C38                                                    0009960
      R194=K194*C41                                                    0009970
      R199=K199*C44                                                    0009980
                                                                       0009990
      R43=R43M*A14/(K43+A14)                                           00010000
      R44=R44M*A14/(K44+A14)                                           00010010
      R45M=L45+M45*RATIO                                               00010020
      R45=R45M*A14/(K45+A14)                                           00010030
      K46=L46*EXP(M46*RATIO)                                           00010040
      R46=K46*A15                                                      00010050
      R47=R47M*N3/(K47+N3)                                             00010060
                                                                       00010070
      R140=KCA*R45                                                     00010080
      R141=KCA*R47                                                     00010090
                                                                       00010100
      R48=R48M*N3/(K48+N3)                                             00010110
      R49=K49*(U3/V3)                                                  00010120
      R51M=L51+M51*GH                                                  00010130
      R51=R51M*A16/(K51+A16)                                           00010140
      R52M=L52+M52*INSUL                                               00010150
      R52=R52M*A16/(K52+A16)                                           00010160
      R53=R53M*A16/(K53+A16)                                           00010170
      R54M=L54+M54*RATIO                                               00010180
      R54=R54M*A17/(K54+A17)                                           00010190
      R57=K57*U4/V4                                                    00010200
      R58=R58M*A18/(K58+A18)                                           00010210
      R61=R61M*A20/(K61+A20)                                           00010220
      R64=R64M*A22/(K64+A22)                                           00010230
                                                                       00010240
      RETURN                                                           00010250
      END                                                              00010260
                                                                       00010270
                                                                       00010280
C     MAMMARY GLAND AND BODY TISSUE COMPARTMENTS                       00010290
                                                                       00010300
      SUBROUTINE RATE4(R172B,L179,INSUL,C29,C30,C31,C33,C34,           00010310
     +                 CA20,C35,C36,C37,C39,C40,C41,                   00010320
     +                 C43,C45,C46,C47,                                00010330
     +                 A18,A19,A20,A21,A22,A23,                        00010340
     +                 R174,R175,R176,R177,R178,R179,                  00010350
     +                 R180,R181,R182,R183,R184,R185,                  00010360
     +                 R186,R187,R188,R190,R191,R192,                  00010370
     +                 R193,R195,R196,R197,R198,                       00010380
     +                 R200,R201,R202,                                 00010390
     +                 R59,R60,R62,R63,R65,R66)                        00010400
                                                                       00010410
      REAL K174,K175,K177,K178,K179,L179,K180,K182,K183                00010420
      REAL K184,K185,K186,K187,K188                                    00010430
      REAL K190,L190,M190,K191,K193,K195,L195,M195,K196                00010440
      REAL K197,L197,M197,K198,K200,K201,K202                          00010450
      REAL K59,K60,K62,L62,M62,K63,K65,K66                             00010460
      REAL INSUL                                                       00010470
                                                                       00010480
```

```
DATA K174,K175,K177,K178/.0604,.0886,.308,.0953/                        00010490
DATA K179,K180,K182,K183/.2273,4.385,2.084,.056/                        00010500
DATA K184,K185,K186,K187,K188/1.984,4.089,5.582,.2232,14.259/           00010510
DATA K190,L190,M190,K191,K193/.0376,.0,1.500,.2256,.1775/               00010520
DATA K195,L195,M195,K196/3.659,.0,3.383,.0625/                          00010530
DATA K197,L197,M197/4292.0,9.454,11.375/                                00010540
DATA K200,K201,K202/.1332,.0449,1.839/                                  00010550
DATA K59,K60,K62,L62,M62/.578,1.976,.4723,.0,.399/                      00010560
DATA K63,K65,K66/4.1E-4,.313,6.2E-4/                                    00010570
                                                                        00010580
DATA R174M,R175M,R177M,R178M/1.550,3.704,5.732,1.040/                   00010590
DATA R179M,R180M/8.407,6.843/                                           00010600
DATA R184M,R185M,R186M,R187M,R188M/.1594,2.616,1.639,.028,20.928/       00010610
DATA R191M,R193M/1.435,.235/                                            00010620
DATA R200M,R201M,R202M/1.699,.101,6.978/                                00010630
DATA R59M,R65M/.917,.214/                                               00010640
                                                                        00010650
DATA V5,V6,V7,V8/14.85,155.0,4.42,20.0/                                 00010660
                                                                        00010670
    K198=K196                                                           00010680
                                                                        00010690
    R174=R174M*C29/(K174+C29)                                           00010700
    R175=R175M*C29/(K175+C29)                                           00010710
    R177=R177M*C30/(K177+C30)                                           00010720
    R178=R178M*C30/(K178+C30)                                           00010730
    R179=R179M*C31/(K179+C31)                                           00010740
    R180=R180M*C31/(K180+C31)                                           00010750
    R181=L179*R179                                                      00010760
    R176=R181-R172B                                                     00010770
    R182=K182*C33                                                       00010780
    R183=K183*C34                                                       00010790
                                                                        00010800
    R59=R59M*A18/(K59+A18)                                              00010810
    R60=K60*A19                                                         00010820
                                                                        00010830
                                                                        00010840
    R184=R184M*CA20/(K184+CA20)                                         00010850
    R185=R185M*C35/(K185+C35)                                           00010860
    R186=R186M*C36/(K186+C36)                                           00010870
    R187=R187M*C36/(K187+C36)                                           00010880
    R188=R188M*C37/(K188+C37)                                           00010890
                                                                        00010900
    R62M=L62+M62*INSUL                                                  00010910
    R62=R62M*A20/(K62+A20)                                              00010920
    R63=K63*A21                                                         00010930
                                                                        00010940
                                                                        00010950
    R190M=L190+M190*INSUL                                               00010960
    R190=R190M*C39/(K190+C39)                                           00010970
    R191=R191M*C39/(K191+C39)                                           00010980
    R193=R193M*C40/(K193+C40)                                           00010990
    R195M=L195+M195*INSUL                                               00011000
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      R195=R195M*C41/(K195+C41)                                         00011010
      R196=K196*R195                                                    00011020
      R192=R196                                                         00011030
      R197M=L197-M197*INSUL                                             00011040
      R197=R197M*C43/(K197+C43)                                         00011050
      R198=K198*R197                                                    00011060
                                                                        00011070
                                                                        00011080
      R200=R200M*C45/(K200+C45)                                         00011090
      R201=R201M*C46/(K201+C46)                                         00011100
      R202=R202M*C47/(K202+C47)                                         00011110
                                                                        00011120
      R65=R65M*A22/(K65+A22)                                            00011130
      R66=K66*A23                                                       00011140
                                                                        00011150
  RETURN                                                                00011160
  END                                                                   00011170
                                                                        00011180
                                                                        00011190
  SUBROUTINE POOL1(C1,AC4,PR4,BU4,CH4,CO4,                              00011200
 +                 KATP,KCA,YATPM,                                    00011210
 +                 SU2,ST2,CE2,C3,                                    00011220
 +                 A1,A2,A3,A4,N1A,N1B,U1,                            00011230
 +                 C2,CA3,C4,                                         00011240
 +                 UNFERM,X1,X2,X3,YATP)                              00011250
                                                                        00011260
  REAL KCA,KATP,N1A,N1B                                                 00011270
                                                                        00011280
  DATA A,C/.25,.30/                                                     00011290
                                                                        00011300
      IF(SU2.LT.0.01) SU2=0.01                                          00011310
      IF(ST2.LT.0.001) ST2=0.001                                        00011320
      IF(CE2.LT.0.1) CE2=0.1                                            00011330
      IF(C3.LT.0.1) C3=0.1                                              00011340
      IF(A1.LT.0.01) A1=0.01                                            00011350
      IF(A2.LT.0.01) A2=0.01                                            00011360
      IF(A3.LT.0.001) A3=0.001                                          00011370
      IF(A4.LT.0.1) A4=0.1                                              00011380
      IF(N1A.LT.0.001) N1A=0.001                                        00011390
      IF(N1B.LT.0.0001) N1B=0.0001                                      00011400
      IF(U1.LT.0.001) U1=0.001                                          00011410
                                                                        00011420
      C2=SU2+ST2+CE2                                                    00011430
      C4=AC4+PR4+BU4+CH4+CO4                                            00011440
      CA3=KCA*A3                                                        00011450
      YATP=YATPM*A2*N1A/(KATP+A2*N1A)                                   00011460
      UNFERM=A1+A*A2+C1+C*C2                                            00011470
      X1=SU2/(SU2+ST2)                                                  00011480
      X2=ST2/(SU2+ST2)                                                  00011490
      X3=CE2/(SU2+ST2)                                                  00011500
                                                                        00011510
  RETURN                                                                00011520
  END                                                                   00011530
```

```
      SUBROUTINE REGUL1(C2,A2,A3,N1A,N1B,BW,NIGHT,UNFERM,                00011540
     +                  K106,K6,K11,K20,K21,FT)                          00011550
                                                                         00011560
      REAL K106,K6,K11,K20,K21                                           00011570
      REAL N1A,N1B,NIGHT                                                 00011580
      REAL MAX,MIN,N1AMX,N1AMN,N1BMX,N1BMN                               00011590
                                                                         00011600
      DATA C2MX,C2MN/42.,30.25/                                          00011610
      DATA A2MX,A2MN,A3MX,A3MN/2.65,1.45,.20,.05/                        00011620
      DATA N1AMX,N1AMN,N1BMX,N1BMN/2.37,.30,.05,.0175/                   00011630
      DATA Y1,Y2,Y3,Y4/198.,.15,178.,.15/                                00011640
                                                                         00011650
          MAX=Y1+Y2*BW                                                   00011660
          MIN=Y3+Y4*BW                                                   00011670
                                                                         00011680
          IF(C2.LT.C2MX) GO TO 1                                         00011690
            K106=K106-0.1                                                00011700
            GO TO 2                                                      00011710
    1     IF(C2.GT.C2MN) GO TO 2                                         00011720
            K106=K106+0.1                                                00011730
            GO TO 2                                                      00011740
    2     CONTINUE                                                       00011750
          IF(A2.LT.A2MX) GO TO 3                                         00011760
            K6=K6-0.01                                                   00011770
            GO TO 4                                                      00011780
    3     IF(A2.GT.A2MN) GO TO 4                                         00011790
            K6=K6+0.01                                                   00011800
            GO TO 4                                                      00011810
    4     CONTINUE                                                       00011820
          IF(A3.LT.A3MX) GO TO 5                                         00011830
            K11=K11-0.0001                                               00011840
            GO TO 6                                                      00011850
    5     IF(A3.GT.A3MN) GO TO 6                                         00011860
            K11=K11+0.0001                                               00011870
            GO TO 6                                                      00011880
    6     CONTINUE                                                       00011890
          IF(N1B.LT.N1BMX) GO TO 7                                       00011900
            K20=K20-0.00001                                              00011910
            GO TO 8                                                      00011920
    7     IF(N1B.GT.N1BMN) GO TO 8                                       00011930
            K20=K20+0.00001                                              00011940
            GO TO 8                                                      00011950
    8     CONTINUE                                                       00011960
          IF(N1A.LT.N1AMX) GO TO 9                                       00011970
            K21=K21+0.01                                                 00011980
            GO TO 10                                                     00011990
    9     IF(N1A.GT.N1AMN) GO TO 10                                      00012000
            K21=K21-0.01                                                 00012010
            GO TO 10                                                     00012020
   10     CONTINUE                                                       00012030
          IF(NIGHT.EQ.0.) GO TO 11                                       00012040
                                                                         00012050
                                                                         00012060
```

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          FT=0.0                                                        00012070
          GO TO 13                                                      00012080
11      IF(UNFERM.LT.MAX) GO TO 12                                      00012090
          FT=0.0                                                        00012100
          GO TO 13                                                      00012110
12      IF(UNFERM.GT.MIN) GO TO 13                                      00012120
          FT=3.3                                                        00012130
          GO TO 13                                                      00012140
13      CONTINUE                                                        00012150
                                                                        00012160
        IF(K106.LT.0.00001) K106=0.00001                                00012170
        IF(K6.LT.0.000001) K6=0.000001                                  00012180
        IF(K11.LT.0.000001) K11=0.000001                                00012190
        IF(K20.LT.0.000001) K20=0.000001                                00012200
        IF(K21.LT.0.00001) K21=0.00001                                  00012210
                                                                        00012220
      RETURN                                                            00012230
      END                                                               00012240
                                                                        00012250
                                                                        00012260
      SUBROUTINE POOL2(C8,C9,C11,C12,                                   00012270
     +                 A6,A7,A8,A10,A11,A12,N2A,N2B,U2)                 00012280
                                                                        00012290
      REAL N2A,N2B                                                      00012300
                                                                        00012310
          IF(C8.LT.0.01) C8=0.01                                        00012320
          IF(C9.LT.0.01) C9=0.01                                        00012330
          IF(C11.LT.0.0001) C11=0.0001                                  00012340
          IF(C12.LT.0.001) C12=0.001                                    00012350
          IF(A6.LT.0.01) A6=0.01                                        00012360
          IF(A7.LT.0.01) A7=0.01                                        00012370
          IF(A8.LT.0.1) A8=0.1                                          00012380
          IF(A10.LT.0.01) A10=0.01                                      00012390
          IF(A11.LT.0.01) A11=0.01                                      00012400
          IF(A12.LT.0.01) A12=0.01                                      00012410
          IF(N2A.LT.0.001) N2A=0.001                                    00012420
          IF(N2B.LT.0.005) N2B=0.005                                    00012430
          IF(U2.LT.0.001) U2=0.001                                      00012440
                                                                        00012450
      RETURN                                                            00012460
      END                                                               00012470
                                                                        00012480
                                                                        00012490
      SUBROUTINE REGUL2(C8,C11,C12,A7,A8,A11,A12,N2B,                   00012500
     +                  K121,K128,K130,K27,K28,K34,K38,K40)             00012510
                                                                        00012520
      REAL K121,K128,K130,K27,K28,K34,K38,K40                           00012530
      REAL N2B,N2BMX,N2BMN                                              00012540
                                                                        00012550
      DATA C8MX,C8MN,C11MX,C11MN/.195,.064,.0286,.002/                  00012560
      DATA C12MX,C12MN/.136,.02/                                        00012570
      DATA A7MX,A7MN,A8MX,A8MN/1.10,.63,4.0,3.5/                        00012580
      DATA A11MX,A11MN,A12MX,A12MN/.37,.21,1.0,.65/                     00012590
```

```
   DATA N2BMX,N2BMN/.30,.20/                                        00012600
                                                                    00012610
        IF(C8.LT.C8MX) GO TO 14                                     00012620
          K121=K121-0.01                                            00012630
          GO TO 15                                                  00012640
14      IF(C8.GT.C8MN) GO TO 15                                     00012650
          K121=K121+0.01                                            00012660
          GO TO 15                                                  00012670
15      CONTINUE                                                    00012680
        IF(C11.LT.C11MX) GO TO 16                                   00012690
          K128=K128-0.00001                                         00012700
          GO TO 17                                                  00012710
16      IF(C11.GT.C11MN) GO TO 17                                   00012720
          K128=K128+0.00001                                         00012730
          GO TO 17                                                  00012740
17      CONTINUE                                                    00012750
        IF(C12.LT.C12MX) GO TO 18                                   00012760
          K130=K130-0.001                                           00012770
          GO TO 19                                                  00012780
18      IF(C12.GT.C12MN) GO TO 19                                   00012790
          K130=K130+0.001                                           00012800
          GO TO 19                                                  00012810
19      CONTINUE                                                    00012820
        IF(A7.LT.A7MX) GO TO 20                                     00012830
          K27=K27-0.1                                               00012840
          GO TO 21                                                  00012850
20      IF(A7.GT.A7MN) GO TO 21                                     00012860
          K27=K27+0.1                                               00012870
          GO TO 21                                                  00012880
21      CONTINUE                                                    00012890
        IF(A8.LT.A8MX) GO TO 22                                     00012900
          K28=K28-0.01                                              00012910
          GO TO 23                                                  00012920
22      IF(A8.GT.A8MN) GO TO 23                                     00012930
          K28=K28+0.01                                              00012940
          GO TO 23                                                  00012950
23      CONTINUE                                                    00012960
        IF(A11.LT.A11MX) GO TO 24                                   00012970
          K34=K34-0.1                                               00012980
          GO TO 25                                                  00012990
24      IF(A11.GT.A11MN) GO TO 25                                   00013000
          K34=K34+0.1                                               00013010
          GO TO 25                                                  00013020
25      CONTINUE                                                    00013030
        IF(A12.LT.A12MX) GO TO 26                                   00013040
          K40=K40-0.01                                              00013050
          GO TO 27                                                  00013060
26      IF(A12.GT.A12MN) GO TO 27                                   00013070
          K40=K40+0.01                                              00013080
          GO TO 27                                                  00013090
27      CONTINUE                                                    00013100
        IF(N2B.LT.N2BMX) GO TO 28                                   00013110
          K38=K38+0.001                                             00013120
```

```
        GO TO 29                                                        00013130
28      IF(N2B.GT.N2BMN) GO TO 29                                       00013140
          K38=K38-0.001                                                 00013150
          GO TO 29                                                      00013160
29      CONTINUE                                                        00013170
                                                                        00013180
        IF(K121.LT.0.00001) K121=0.00001                                00013190
        IF(K128.LT.0.000001) K128=0.000001                              00013200
        IF(K130.LT.0.000001) K130=0.000001                              00013210
        IF(K27.LT.0.0001) K27=0.0001                                    00013220
        IF(K28.LT.0.00001) K28=0.00001                                  00013230
        IF(K34.LT.0.0001) K34=0.0001                                    00013240
        IF(K38.LT.0.000001) K38=0.000001                                00013250
        IF(K40.LT.0.00001) K40=0.00001                                  00013260
                                                                        00013270
      RETURN                                                            00013280
      END                                                               00013290
                                                                        00013300
                                                                        00013310
      SUBROUTINE POOL3(C14,C16,C17,C18,C19,C20,C21,C22,C23,C24,         00013320
     +                 C25,C26,C27,C28,                                 00013330
     +                 A14,A15,A16,A17,N3,U3,U4)                        00013340
                                                                        00013350
      REAL N3                                                           00013360
                                                                        00013370
          IF(C14.LT.0.0001) C14=0.0001                                  00013380
          IF(C16.LT.0.001) C16=0.001                                    00013390
          IF(C17.LT.0.0001) C17=0.0001                                  00013400
          IF(C18.LT.0.001) C18=0.001                                    00013410
          IF(C19.LT.0.0001) C19=0.0001                                  00013420
          IF(C20.LT.0.1) C20=0.1                                        00013430
          IF(C21.LT.0.01) C21=0.01                                      00013440
          IF(C22.LT.0.0001) C22=0.0001                                  00013450
          IF(C23.LT.0.01) C23=0.01                                      00013460
          IF(C24.LT.0.01) C24=0.01                                      00013470
          IF(C25.LT.0.001) C25=0.001                                    00013480
          IF(C26.LT.0.01) C26=0.01                                      00013490
          IF(C27.LT.0.001) C27=0.001                                    00013500
          IF(C28.LT.0.01) C28=0.01                                      00013510
          IF(A14.LT.0.001) A14=0.001                                    00013520
          IF(A15.LT.0.1) A15=0.1                                        00013530
          IF(A16.LT.0.001) A16=0.001                                    00013540
          IF(A17.LT.0.001) A17=0.001                                    00013550
          IF(N3.LT.0.00001) N3=0.00001                                  00013560
          IF(U3.LT.0.001) U3=0.001                                      00013570
          IF(U4.LT.0.01) U4=0.01                                        00013580
                                                                        00013590
      RETURN                                                            00013600
      END                                                               00013610
                                                                        00013620
                                                                        00013630
```

```
      SUBROUTINE REGUL3(C14,C16,C17,C24,N3,                             00013640
     +                  K136,K137,K139,K142,K143,K144,K48)              00013650
                                                                        00013660
      REAL K136,K137,K139,K142,K143,K144,K48                            00013670
      REAL N3,N3MX,N3MN                                                 00013680
                                                                        00013690
      DATA C14MX,C14MN,C16MX,C16MN/.1980,.0195,1.45,.25/                00013700
      DATA C17MX,C17MN,C24MX,C24MN/.200,.02,6.50,.85/                   00013710
      DATA N3MX,N3MN/.175,.01/                                          00013720
                                                                        00013730
          IF(C14.LT.C14MX) GO TO 30                                     00013740
            K137=K137-0.0005                                            00013750
            GO TO 31                                                    00013760
   30     IF(C14.GT.C14MN) GO TO 31                                     00013770
            K137=K137+0.0005                                            00013780
            GO TO 31                                                    00013790
   31     CONTINUE                                                      00013800
          IF(C16.LT.C16MX) GO TO 32                                     00013810
            K136=K136+0.0005                                            00013820
            K142=K142+0.001                                             00013830
            K144=K144+0.001                                             00013840
            GO TO 33                                                    00013850
   32     IF(C16.GT.C16MN) GO TO 33                                     00013860
            K136=K136-0.0005                                            00013870
            K142=K142-0.001                                             00013880
            K144=K144-0.001                                             00013890
            GO TO 33                                                    00013900
   33     CONTINUE                                                      00013910
          IF(C17.LT.C17MX) GO TO 34                                     00013920
            K143=K143-0.0005                                            00013930
            GO TO 35                                                    00013940
   34     IF(C17.GT.C17MN) GO TO 35                                     00013950
            K143=K143+0.0005                                            00013960
            GO TO 35                                                    00013970
   35     CONTINUE                                                      00013980
          IF(C24.LT.C24MX) GO TO 36                                     00013990
            K139=K139+0.005                                             00014000
            GO TO 37                                                    00014010
   36     IF(C24.GT.C24MN) GO TO 37                                     00014020
            K139=K139-0.005                                             00014030
            GO TO 37                                                    00014040
   37     CONTINUE                                                      00014050
          IF(N3.LT.N3MX) GO TO 38                                       00014060
            K48=K48-0.0001                                              00014070
            GO TO 39                                                    00014080
   38     IF(N3.GT.N3MN) GO TO 39                                       00014090
            K48=K48+0.0001                                              00014100
            GO TO 39                                                    00014110
   39     CONTINUE                                                      00014120
                                                                        00014130
          IF(K136.LT.0.000001) K136=0.000001                            00014140
          IF(K137.LT.0.000001) K137=0.000001                            00014150
          IF(K139.LT.0.0001) K139=0.0001                                00014160
```

```
      IF(K142.LT.0.000001) K142=0.000001                                00014170
      IF(K143.LT.0.000001) K143=0.000001                                00014180
      IF(K144.LT.0.00001) K144=0.00001                                  00014190
      IF(K48.LT.0.0000001) K48=0.0000001                                00014200
                                                                        00014210
      RETURN                                                            00014220
      END                                                               00014230
                                                                        00014240
                                                                        00014250
      SUBROUTINE POOL4(C29,C30,C31,C33,C34,C35,C36,C37,C38,             00014260
     +                 C39,C40,C41,C43,C44,C45,C46,C47,                 00014270
     +                 A18,A19,A20,A21,A22,A23)                         00014280
                                                                        00014290
      IF(C29.LT.0.001) C29=0.001                                        00014300
      IF(C30.LT.0.001) C30=0.001                                        00014310
      IF(C31.LT.0.001) C31=0.001                                        00014320
      IF(C33.LT.0.001) C33=0.001                                        00014330
      IF(C34.LT.0.01) C34=0.01                                          00014340
      IF(C35.LT.0.001) C35=0.001                                        00014350
      IF(C36.LT.0.001) C36=0.001                                        00014360
      IF(C37.LT.0.001) C37=0.001                                        00014370
      IF(C38.LT.0.001) C38=0.001                                        00014380
      IF(C39.LT.0.0001) C39=0.0001                                      00014390
      IF(C40.LT.0.0001) C40=0.0001                                      00014400
      IF(C41.LT.0.001) C41=0.001                                        00014410
      IF(C43.LT.1.0) C43=1.0                                            00014420
      IF(C44.LT.0.0001) C44=0.0001                                      00014430
      IF(C45.LT.0.0001) C45=0.0001                                      00014440
      IF(C46.LT.0.0001) C46=0.0001                                      00014450
      IF(C47.LT.0.0001) C47=0.0001                                      00014460
      IF(A18.LT.0.0001) A18=0.0001                                      00014470
      IF(A19.LT.0.001) A19=0.001                                        00014480
      IF(A20.LT.0.001) A20=0.001                                        00014490
      IF(A21.LT.1.0) A21=1.0                                            00014500
      IF(A22.LT.0.0001) A22=0.0001                                      00014510
      IF(A23.LT.1.0) A23=1.0                                            00014520
                                                                        00014530
      RETURN                                                            00014540
      END                                                               00014550
                                                                        00014560
                                                                        00014570
      SUBROUTINE END1(C1,SU2,ST2,CE2,C3,AC4,PR4,BU4,CH4,CO4,            00014580
     +                A1,A2,A3,A4,N1A,N1B,U1,U4,                        00014590
     +                K106,K6,K11,K20,K21,                              00014600
     +                C1I,SU2I,ST2I,CE2I,C3I,AC4I,PR4I,BU4I,CH4I,CO4I,  00014610
     +                A1I,A2I,A3I,A4I,N1AI,N1BI,U1I,U4I,                00014620
     +                K106I,K6I,K11I,K20I,K21I)                         00014630
                                                                        00014640
      REAL K106,K6,K11,K20,K21                                          00014650
      REAL N1A,N1B                                                      00014660
      REAL K106I,K6I,K11I,K20I,K21I                                     00014670
      REAL N1AI,N1BI                                                    00014680
                                                                        00014690
```

```
      C1I=C1                                                            00014700
      SU2I=SU2                                                          00014710
      ST2I=ST2                                                          00014720
      CE2I=CE2                                                          00014730
      C3I=C3                                                            00014740
      AC4I=AC4                                                          00014750
      PR4I=PR4                                                          00014760
      BU4I=BU4                                                          00014770
      CH4I=CH4                                                          00014780
      CO4I=CO4                                                          00014790
                                                                        00014800
      A1I=A1                                                            00014810
      A2I=A2                                                            00014820
      A3I=A3                                                            00014830
      A4I=A4                                                            00014840
      N1AI=N1A                                                          00014850
      N1BI=N1B                                                          00014860
      U1I=U1                                                            00014870
      U4I=U4                                                            00014880
                                                                        00014890
      K106I=K106                                                        00014900
      K6I=K6                                                            00014910
      K11I=K11                                                          00014920
      K20I=K20                                                          00014930
      K21I=K21                                                          00014940
                                                                        00014950
  RETURN                                                                00014960
  END                                                                   00014970
                                                                        00014980
                                                                        00014990
  SUBROUTINE END2(C7,C8,C9,C10B,C11,C12,C23,                            00015000
 +                A6,A7,A8,A10,A11,A12,A13,A16,N2A,N2B,U2,             00015010
 +                K121,K128,K130,K27,K28,K34,K38,K40,                  00015020
 +                C7I,C8I,C9I,C10BI,C11I,C12I,C23I,                    00015030
 +                A6I,A7I,A8I,A10I,A11I,A12I,A13I,A16I,                00015040
 +                N2AI,N2BI,U2I,                                       00015050
 +                K121I,K128I,K130I,K27I,K28I,K34I,K38I,K40I)          00015060
                                                                        00015070
  REAL K121,K128,K130,K27,K28,K34,K38,K40                               00015080
  REAL N2A,N2B                                                          00015090
  REAL K121I,K128I,K130I,K27I,K28I,K34I,K38I,K40I                       00015100
  REAL N2AI,N2BI                                                        00015110
                                                                        00015120
      C7I=C7                                                            00015130
      C8I=C8                                                            00015140
      C9I=C9                                                            00015150
      C10BI=C10B                                                        00015160
      C11I=C11                                                          00015170
      C12I=C12                                                          00015180
      C23I=C23                                                          00015190
                                                                        00015200
      A6I=A6                                                            00015210
      A7I=A7                                                            00015220
```

```
      A8I=A8                                                            00015230
      A10I=A10                                                          00015240
      A11I=A11                                                          00015250
      A12I=A12                                                          00015260
      A13I=A13                                                          00015270
      A16I=A16                                                          00015280
      N2AI=N2A                                                          00015290
      N2BI=N2B                                                          00015300
      U2I=U2                                                            00015310
                                                                        00015320
      K121I=K121                                                        00015330
      K128I=K128                                                        00015340
      K130I=K130                                                        00015350
      K27I=K27                                                          00015360
      K28I=K28                                                          00015370
      K34I=K34                                                          00015380
      K38I=K38                                                          00015390
      K40I=K40                                                          00015400
                                                                        00015410
      RETURN                                                            00015420
      END                                                               00015430
                                                                        00015440
                                                                        00015450
      SUBROUTINE END3(C14,C16,C17,C18,C19,C21,C22,C24,                  00015460
     +                C25,C26,C27,C28,C38,C41,C44,                      00015470
     +                A14,A15,A17,A18,A20,A22,N3,U3,                    00015480
     +                K136,K137,K139,K142,K143,K144,K48,                00015490
     +                C14I,C16I,C17I,C18I,C19I,C21I,C22I,C24I,          00015500
     +                C25I,C26I,C27I,C28I,C38I,C41I,C44I,               00015510
     +                A14I,A15I,A17I,A18I,A20I,A22I,N3I,U3I,            00015520
     +                K136I,K137I,K139I,K142I,K143I,K144I,K48I)         00015530
                                                                        00015540
      REAL K136,K137,K139,K142,K143,K144,K48                            00015550
      REAL N3                                                           00015560
      REAL K136I,K137I,K139I,K142I,K143I,K144I,K48I                     00015570
      REAL N3I                                                          00015580
                                                                        00015590
          C14I=C14                                                      00015600
          C16I=C16                                                      00015610
          C17I=C17                                                      00015620
          C18I=C18                                                      00015630
          C19I=C19                                                      00015640
          C21I=C21                                                      00015650
          C22I=C22                                                      00015660
          C24I=C24                                                      00015670
          C25I=C25                                                      00015680
          C26I=C26                                                      00015690
          C27I=C27                                                      00015700
          C28I=C28                                                      00015710
          C38I=C38                                                      00015720
          C41I=C41                                                      00015730
          C44I=C44                                                      00015740
                                                                        00015750
```

```
      A14I=A14                                                          00015760
      A15I=A15                                                          00015770
      A17I=A17                                                          00015780
      A18I=A18                                                          00015790
      A20I=A20                                                          00015800
      A22I=A22                                                          00015810
      N3I=N3                                                            00015820
      U3I=U3                                                            00015830
                                                                        00015840
      K136I=K136                                                        00015850
      K137I=K137                                                        00015860
      K139I=K139                                                        00015870
      K142I=K142                                                        00015880
      K143I=K143                                                        00015890
      K144I=K144                                                        00015900
      K48I=K48                                                          00015910
                                                                        00015920
      RETURN                                                            00015930
      END                                                               00015940
                                                                        00015950
                                                                        00015960
      SUBROUTINE END4(C29,C30,C31,C33,C34,C35,C36,C37,                  00015970
     +                C39,C40,C45,C46,C47,                              00015980
     +                A19,                                              00015990
     +                C29I,C30I,C31I,C33I,C34I,C35I,C36I,C37I,          00016000
     +                C39I,C40I,C45I,C46I,C47I,                         00016010
     +                A19I)                                             00016020
                                                                        00016030
      C29I=C29                                                          00016040
      C30I=C30                                                          00016050
      C31I=C31                                                          00016060
      C33I=C33                                                          00016070
      C34I=C34                                                          00016080
      C35I=C35                                                          00016090
      C36I=C36                                                          00016100
      C37I=C37                                                          00016110
      C39I=C39                                                          00016120
      C40I=C40                                                          00016130
      C45I=C45                                                          00016140
      C46I=C46                                                          00016150
      C47I=C47                                                          00016160
                                                                        00016170
      A19I=A19                                                          00016180
                                                                        00016190
      RETURN                                                            00016200
      END                                                               00016210
                                                                        00016220
                                                                        00016230
ENDJOB                                                                  00016240
                                                                        00016250
                                                                        00016260
                                                                        00016270
```

APPENDIX 3: The SAS program creating a data set

```
// EXEC SAS                                                              00016280
//CSMP DD DSN=AR10018.CSMP.SAS,DISP=OLD                                  00016290
//CSMPDATA DD DSN=&&DATA,DISP=(OLD,DELETE)                               00016300
//PROG DD UNIT=SYSDA,SPACE=(TRK,10),DCB=CARD                             00016310
//SYSIN DD *                                                            00016320


DATA _NULL_; INFILE CSMPDATA;                                            00016330
INPUT; INPUT; INPUT;                                                     00016340
FILE PROG ;                                                              00016350
PUT 'INPUT Ø1 (' Ø;                                                      00016360
INPUT VAR Ø12. Ø;                                                        00016370
DO  WHILE(VAR>'  '); PUT VAR Ø9. Ø; INPUT VAR Ø Ø;  END; INPUT;          00016380
PUT ') (RB4.);';                                                         00016390
STOP;                                                                    00016400
DATA CSMP.TEST;                                                          00016410
INFILE CSMPDATA;                                                         00016420
LENGTH DEFAULT=4;                                                        00016430
DROP _I_ X;                                                              00016440
IF _N_=1 THEN DO _I_=1 TO 9; INPUT; RERUN=1; END;                        00016450
INPUT X Ø4. Ø;                                                           00016460
IF X='ENDS' THEN DO; RERUN+1; RETURN; END;                               00016470
IF X='ENDJ' OR X='ENDF' THEN STOP;                                       00016480
%INCLUDE PROG / SOURCE2 S2=80;                                           00016490
OUTPUT;                                                                  00016500
```

APPENDIX 4: The SAS program performing statistical calculations

```
//*       JOB(SAS1)                                                    00000060
//* 04/26/85 , 10:44:56        (AR10018)                               00000070
//* MEAN OF RUNS                                                       00000080
// EXEC SAS                                                          00000090
//CSMP DD DSN=AR10018.CSMP.SAS,DISP=OLD                              00000100
//SYSIN DD *                                                         00000110


PROC PRINT DATA=CSMP.TEST; BY RERUN;                                  00000120
DATA; SET CSMP.TEST;                                                  00000130
IF 26 <= RERUN <= 35;                                                 00000140
IF TIME = 24.;                                                        00000150
LACT=F182*28.525;                                                     00000160
MILK=LACT/48.0;                                                       00000170
FAT=F183*(16.174+L179*12.682)/(1+L179);                               00000180
CFAT=FAT/MILK;                                                        00000190
PRO=F60*89.384;                                                       00000200
CPRO=PRO/MILK;                                                        00000210
EBAL=(F147-F152+F195-F197)*10.027/16+                                 00000220
     (F145-F151+F196-F198)*1.660/3+(F43-F46+F62-F63+F65-F66)*2.065;   00000230
GAIN=EBAL/25.0;                                                       00000240
MAIN=.53*(.90*(BW+GAIN/2))**.67;                                      00000250
MILKE=(LACT*16.527+FAT*38.116+PRO*24.518)/1000;                       00000260
                                                                      00000270
GE=FGE;                                                               00000280
FE=FFE;                                                               00000290
DE=GE-FE;                                                             00000300
ME=DE*.84;                                                            00000310
MEE=(FCH111+FCH124)*.89;                                              00000320
UE=DE-ME-MEE;                                                         00000330
PRODE=MILKE+EBAL;                                                     00000340
HE=ME-PRODE;                                                          00000350
NE=MAIN+PRODE;                                                        00000360
SFU=NE/7.89;                                                          00000370
                                                                      00000380
FEPCT=100*FE/GE;                                                      00000390
DEPCT=100*DE/GE;                                                      00000400
MEEPCT=100*MEE/GE;                                                    00000410
UEPCT=100*UE/GE;                                                      00000420
MEPCT=100*ME/GE;                                                      00000430
HEPCT=100*HE/GE;                                                      00000440
PRODEP=100*PRODE/GE;                                                  00000450
NEPCT=100*NE/GE;                                                      00000460
                                                                      00000470
PROC MEANS;                                                           00000480
```

APPENDIX 5: Numerical values of state variables and equation parameters in the rumen compartment

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Rate of feed intake	FT	kg DM/h	3.3	3.3
Sugar content in feed	KSU	kg/kg DM	0.2235	0.2235
Carbon content in sugar	LSU	mol C/kg	35.087	35.087
Unfermentable fraction of sugar and glycerol	MSU		0.0	0.0
Starch content in feed	KST	kg/kg DM	0.0313	0.0313
Carbon content in starch	LST	mol C/kg	37.037	37.037
Unfermentable fraction of starch	MST		0.0	0.0
Cell wall carbohydrates in feed	KCE	kg/kg DM	0.4268	0.4268
Carbon content in cell wall carbohydrates	LCE	mol C/kg	37.037	37.037
Unfermentable fraction of cell wall carbohydrates	MCE		0.40	0.40
Glycerol content in feed	KGL	kg/kg DM	0.0047	0.0047
Carbon content in glycerol	LGL	mol C/kg	32.573	32.573
Fatty acid content in feed	KLI	kg/kg DM	0.04	0.04
Carbon content in fatty acids	LLI	mol C/kg	62.402	62.402
Unfermentable fraction of fatty acids	MLI		0.90	0.90

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations

(to be continued)

Appendix 5 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Rate constant for unfermentable carbohydrate and lipid outflow	K103	h^{-1}	0.025	0.025
Unfermentable carbohydrates and lipids	C1	mol C	255.6	261.08*)
Rate constant for microbial uptake of carbohydrates	K105	h^{-1}	0.070	0.073
Fermentable sugar	SU2	mol C	2.93	3.8468*)
Fermentable starch	ST2	mol C	0.49	0.4336*)
Fermentable cell wall carbohydrates	CE2	mol C	33.66	29.994*)
Affinity constant for carbohydrate fermentation	K106	mol C	9.270	2.50*)
Maximal fermentation rate factor	L106	mol C/(molN*h)	1.218	1.0534
Cell wall carbohydrate fermentation rate factor	G		0.04	0.0006
Acetate from sugar	ACSU	mol C/mol C	0.36036	0.36036
Propionate from sugar	PRSU	mol C/mol C	0.13514	0.13514
Butyrate from sugar	BUSU	mol C/mol C	0.21622	0.21622
Methane from sugar	CHSU	mol C/mol C	0.1045	0.1045
Carbon dioxide from sugar	COSU	mol C/mol C	0.18378	0.18378
ATP from sugar	ATPSU	mol ATP/mol C	0.76937	0.76937

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 5 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1)]	Final[2)]
Acetate from starch	ACST	mol C/mol C	0.38667	0.38667
Propionate from starch	PRST	mol C/mol C	0.26833	0.26833
Butyrate from starch	BUST	mol C/mol C	0.1000	0.1000
Methane from starch	CHST	mol C/mol C	0.08667	0.08667
Carbon dioxide from starch	COST	mol C/mol C	0.15833	0.15833
ATP from starch	ATPST	mol ATP/mol C	0.75333	0.75333
Acetate from cell wall carbohydrates	ACCE	mol C/mol C	0.36264	0.36264
Propionate from cell wall carbohydrates	PRCE	mol C/mol C	0.36265	0.36265
Butyrate from cell wall carbohydrates	BUCE	mol C/mol C	0.06165	0.06165
Methane from cell wall carbohydrates	CHCE	mol C/mol C	0.0680	0.0680
Carbon dioxide from cell wall carbohydrates	COCE	mol C/mol C	0.14506	0.14506
ATP from cell wall carbohydrates	ATPCE	mol ATP/mol C	0.70354	0.70354
Rate constant for fermentable carbohydrate outflow	K107	h^{-1}	0.041	0.043
Rate constant for microbial outflow	K110,K10 K13,K18	h^{-1}	0.0828	0.08
Microbial carbohydrates and lipids	C3	mol C	17.59	19.765*)

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 5 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1)]	Final[2)]
Fraction of microbial starch	L110		0.08	0.08
Fraction of microbial cell wall carbohydrates	M110		0.44	0.44
Fraction of microbial lipids	N110		0.48	0.48
Rate constant for acetate outflow	KAC111	h^{-1}	0.4504	0.4483
Rate constant for propionate outflow	KPR111	h^{-1}	0.4627	0.4605
Rate constant for butyrate outflow	KBU111	h^{-1}	0.4561	0.4540
Rate constant for methane outflow	KCH111	h^{-1}	1.000	1.00
Rate constant for carbon dioxide outflow	KCO111	h^{-1}	1.263	1.187
Ruminal acetate	AC4	mol C	9.385	10.491*)
Ruminal propionate	PR4	mol C	5.401	6.6841*)
Ruminal butyrate	BU4	mol C	3.755	3.8374*)
Ruminal methane	CH4	mol C	0.917	0.9331*)
Ruminal carbon dioxide	CO4	mol C	1.834	2.0545*)
Affinity constant for protein fermentation	K112	mol C	0.0939	0.090

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 5 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Max. rate of protein fermentation	R112M	mol C/h	2.66	3.00
Carbon:nitrogen ratio in protein	KCA	mol C/mol N	3.8	3.8
Microbial amino acids and peptides	CA3	mol C	0.532	0.0038*)
Acetate from protein	AC	mol C/mol C	0.29749	0.29749
Propionate from protein	PR	mol C/mol C	0.13730	0.1373
Butyrate from protein	BU	mol C/mol C	0.09153	0.09153
Branched chain fatty acids from protein	BC	mol C/mol C	0.16476	0.16476
Methane from protein	CH	mol C/mol C	0.14874	0.14874
Carbon dioxide from protein	CO	mol C/mol C	0.16018	0.16018
ATP from protein	ATPPR	mol ATP/mol C	0.0	0.0
Reduction factor for methane	K		0.75	0.75
Concentrate protein content in feed	KC	kg/kg DM	0.100	0.100
Nitrogen content in concentrate protein	LC	mol N/kg	11.423	11.423
Unfermentable fraction of concentrate protein	MC		0.2788	0.2788

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 5 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Roughage protein content in feed	KR	kg/kg DM	0.0788	0.0788
Nitrogen content in roughage protein	LR	mol N/kg	11.423	11.423
Unfermentable fraction of roughage protein	MR		0.10	0.10
Rate constant for unfermentable protein outflow	K5	h^{-1}	0.043	0.043
Unfermentable protein	A1	mol N	7.061	7.3081*)
Affinity constant for microbial uptake of amino acids and peptides	K6	mol N	0.890	0.9236*)
Max. rate of microbial amino acid and peptide uptake	R6M	mol N/h	1.572	1.685
Fermentable protein, peptides and amino acids	A2	mol N	2.077	2.1942*)
Rate constant for fermentable protein outflow	K7	h^{-1}	0.11	0.1101
Affinity constant for microbial excretion of amino acids	K8	mol N	0.06	0.0415
Max. rate of microbial amino acid excretion	R8M	mol N/h	0.157	0.157
Microbial amino acids and peptides	A3	mol N	0.140	0.001*)

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 5 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1)]	Final[2)]
Affinity constant for microbial protein synthesis	K9	mol N	0.0068	0.001
Nitrogen content in microbes	M9	mol N/g DM	$5.742*10^{-3}$	$5.735*10^{-3}$
Max. efficiency of microbial growth	YATPM	g DM/mol ATP	28.0	28.0
Affinity constant	KATP	$(\text{mol N})^2$	0.1483	0.07
Affinity constant for degradation of microbial amino acids	K11	mol N	0.06	0.0633*)
Max. rate of microbial amino acid degradation	R11M	mol N/h	1.432	1.737
Rate constant for degradation of microbial protein	K12	h^{-1}	0.0207	0.02
Microbial protein and nucleic acids	A4	mol N	10.04	11.252*)
Rate constant for NH_3/NH_4^+ outflow	K14	h^{-1}	0.11	0.1101
Ruminal NH_3/NH_4^+	N1A	mol N	0.928	0.7349*)
Affinity constant for microbial uptake of NH_3/NH_4^+	K15	mol N	0.002	0.189
Max. rate of microbial NH_3/NH_4^+ uptake	R15M	mol N/h	0.493	0.6

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 5 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Rate constant for NH_3/NH_4^+ absorption	K16	l/h	18.154	18.385
Rumen fluid volume	V1	l	74.0	74.0
Affinity constant for microbial amino acid synthesis	K17	mol N	0.0182	0.0097
Max. rate of microbial amino acid synthesis	R17M	mol N/h	1.454	1.51
Microbial NH_3/NH_4^+	N1B	mol N	0.026	0.1165*)
Affinity constant for microbial excretion of NH_3/NH_4^+	K20	mol N	0.0046	0.0056*)
Max. rate of microbial NH_3/NH_4^+ excretion	R20M	mol N/h	0.749	1.04
Affinity constant for hydrolysis of urea	K21	mol N	2.743	2.723*)
Max. rate of hydrolysis of urea	R21M	mol N/h	2.463	2.463
Ruminal urea	U1	mol N	0.222	0.2175*)
Rate constant for urea uptake	K55	l/h	16.765	16.687
Blood urea	U4	mol N	2.1	2.0479*)
Extracellular fluid volume	V4	l	150.0	150.0

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 5 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Energy content in sugar	CSU	MJ/kg	16.6	16.6
Energy content in starch	CST	MJ/kg	17.6	17.6
Energy content in cell wall carbohydrates	CCE	MJ/kg	18.8	18.8
Energy content in lipid	CLI	MJ/kg	39.75	39.75
Energy content in protein	CPR	MJ/kg	23.93	23.93

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations

APPENDIX 6: Numerical values of state variables and equation parameters in the intestinal compartments

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Indigestible fraction of fatty acids	K116		0.0745	0.0833
Rate constant for digesta flow in small intestine	K119,K120, K122	h^{-1}	0.24	0.240
Fermented fraction of cell wall carbohydrates	L119		0.22	0.220
Indigestible carbohydrates and lipids in small intestine	C7	mol C	28.80	29.578*)
Digestible carbohydrates and glycerol in small intestine	C8	mol C	0.123	0.0745*)
Fermented fraction of starch	L120		1.00	1.00
Affinity constant for glucose uptake from the lumen	K121	mol C	0.6515	0.6268*)
Max. rate of glucose uptake from the lumen	R121M	mol C/h	1.667	1.667
Digestible fatty acids in small intestine	C9	mol C	0.899	0.9132*)
Rate constant for fatty acid uptake from the lumen	K123	h^{-1}	2.160	2.1617

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 6 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Reduction factor for methane	K		0.75	0.75
Rate constant for faecal excretion	K126,K29	h^{-1}	0.114	0.115
Undigested carbohydrates and lipids in the hind gut	C10B	mol C	55.756	56.65*)
Carbon:nitrogen ratio in protein	KCA	mol C/mol N	3.8	3.8
Fermented fraction of deaminated amino acids	K127A		0.1361	0.13692
Affinity constant for acetate and ketone body oxidation	K128	mol C	0.0016	$1*10^{-6}$*)
Max. rate of acetate and ketone body oxidation	R128M	mol C/h	0.713	0.7145
Acetate and ketone bodies in intestinal wall	C11	mol C	0.014	0.0143*)
Affinity constant for glucose oxidation	K129	mol C	0.086	0.0677
Max. rate of glucose oxidation	R129M	mol C/h	0.0144	0.0160
Glucose in intestinal wall	C12	mol C	0.086	0.0256*)

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 6 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Affinity constant for glucose absorption	K130	mol C	0.9665	0.7859*)
Max. rate of glucose absorption	R130M	mol C/h	1.667	1.667
Glycerol esterification of fatty acids	K131	mol C/mol C	0.0625	0.0625
Rate constant for uptake of acetate and ketone bodies from the blood	K155	l/h	110.60	110.55
Acetate and ketone bodies in extracellular fluid	C23	mol C	0.87	0.9192*)
Extracellular fluid volume	V4	l	150.0	150.0
Fraction of amino acids in unfermented feed protein	K23		0.80	0.80
Digestible fraction of amino acids in unfermented feed protein	L23		1.00	1.00
Fraction of amino acids in microbial protein	M23		0.70	0.70
Digestible fraction of amino acids in microbial protein	N23		1.00	1.00

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 6 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Rate constant for digesta flow in small intestine	K25,K26, K32,K33	h^{-1}	0.24	0.240
Indigestible protein in small intestine	A6	mol N	1.500	1.5305*)
Digestible protein in small intestine	A7	mol N	0.863	0.8568*)
Affinity constant for amino acid uptake from the lumen	K27	mol N	6.581	6.578*)
Max. rate of amino acid uptake from the lumen	R27M	mol N/h	6.98	6.98
Affinity constant for hind gut protein degradation	K28	mol N	1.616	2.731*)
Max. rate of protein degradation in the hind gut	R28M	mol N/h	0.5205	0.630
Undigested protein in the hind gut	A8	mol N	3.77	3.8248*)
Fraction of amino acids in endogenous protein	K31		0.9756	0.9755
Digestible fraction of amino acids in endogenous protein	L31		0.9756	0.9755
Indigestible endogenous protein	A10	mol N	0.076	0.0776*)

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 6 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1)]	Final[2)]
Digestible endogenous protein	A11	mol N	0.287	0.2821*)
Affinity constant for endogenous amino acid uptake from the lumen	K34	mol N	6.581	6.578*)
Max. rate of endogenous amino acid uptake from the lumen	R34M	mol N/h	6.98	6.98
Rate constant for NH_3/NH_4^+ absorption from small intestine	K35	l/h	33.142	33.4009
NH_3/NH_4^+ in small intestine	N2A	mol N	0.067	0.0585*)
Small intestinal fluid volume	V2A	l	21.3	21.3
Affinity constant for microbial amino acid synthesis	K36	mol N	0.0621	0.0637
Nitrogen content in microbes	M9	mol N/g DM	$5.742*10^{-3}$	$5.735*10^{-3}$
Max. efficiency of microbial growth	YATPM	g DM/mol ATP	28.0	28.0
NH_3/NH_4^+ in the hind gut	N2B	mol N	0.262	0.2607*)

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 6 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Rate constant for NH_3/NH_4^+ absorption from the hind gut	K37	l/h	18.154	18.495
Hind gut fluid volume	V2B	l	12.1	12.1
Affinity constant for hydrolysis of urea	K38	mol N	0.0629	0.0515*)
Max. rate of hydrolysis of urea	R38M	mol N/h	0.403	0.403
Urea in the hind gut	U2	mol N	0.0462	0.0393*)
Affinity constant for intestinal protein synthesis	K39	mol N	0.3076	0.3069
Max. rate of intestinal protein synthesis	R39M	mol N/h	0.676	0.676
Amino acids in intestinal tissue	A12	mol N	0.930	0.9393*)
Affinity constant for amino acid absorption	K40	mol N	4.9666	4.9427*)
Max. rate of intestinal amino acid absorption	R40M	mol N/h	6.98	6.98
Affinity constant for endogenous protein secretion	K41	mol N	26.622	26.330

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 6 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Factor for endogenous protein secretion	L41	mol N/mol C	0.0383	0.0380
Protein in intestinal tissue	A13	mol N	56.0	55.945*)
Rate constant for degradation of intestinal protein	K42	h^{-1}	0.0023	0.0023
Affinity constant for amino acid uptake from the blood	K50	mol N	8.7832	8.763
Max. rate of amino acid uptake from the blood	R50M	mol N/h	6.98	6.98
Amino acids in extracellular fluid	A16	mol N	0.504	0.5023*)
Rate constant for urea uptake	K56	l/h	16.765	16.727
Urea in extracellular fluid	U4	mol N	2.1	2.0479*)

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 6 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Carbon content of cell wall carbohydrates	LCE	mol C/kg	37.037	37.037
Energy content of cell wall carbohydrates	CCE	MJ/kg	18.8	18.8
Energy content of fatty acids	CFA	MJ/mol	10.027	10.027
Energy content of glucose	CGLU	MJ/mol	2.805	2.805
Energy content of metabolized protein	CKA	MJ/kg	19.4	19.4
Nitrogen content of protein	LC	mol N/kg	11.423	11.423
Energy content of branched fatty acids	CBC	MJ/mol	3.497	3.497
Energy content of protein	CAA	MJ/kg	23.4	23.4

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations

PPENDIX 7: Numerical values of state variables and equation parameters in the liver and extracellular fluid compartments

arameter or state ariable	Symbol	Unit	Numerical value Original[1]	Final[2]
arbon:nitrogen ratio n protein	KCA	mol C/mol N	3.8	3.8
raction of butyrate aken up by the liver	K134		0.10	0.10
ffinity constant for lucose synthesis from ropionate	K136	mol C	0.032	0.1610*)
ndependent part of max. ate of glucose synthesis rom propionate	L136	mol C/h	3.981	3.950
ependent part of max. ate of glucose synthesis rom propionate	M136	mol C/h	1.356	1.05
ropionate in liver issue	C14	mol C	0.021	0.1846*)
ffinity constant for ropionate oxidation	K137	mol C	0.008	0.0463*)
ax. rate of propionate xidation	R137M	mol C/h	1.133	1.180
ffinity constant for lucose outflow	K139	mol C	0.5772	0.575*)
ax. rate of glucose utflow	R139M	mol C/h	5.718	5.7113

) Assumed or estimated from the literature
) Finally adjusted after repeated simulations
) Initial value at the beginning of the run

(to be continued)

Appendix 7 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Glucose in liver tissue	C16	mol C	0.866	1.1542*)
Affinity constant for glucose synthesis from keto acids	K142	mol C	0.0467	0.2315*)
Independent part of max. rate of glucose synthesis from keto acids	L142	mol C/h	0.150	0.15
Dependent part of max. rate of glucose synthesis from keto acids	M142	mol C/h	1.677	1.505
Keto acids in liver tissue	C17	mol C	0.02	0.1168*)
Affinity constant for keto acid oxidation	K143	mol C	0.02	0.1155*)
Max. rate of keto acid oxidation	R143M	mol C/h	0.860	0.8912
Affinity constant for glucose synthesis from glycerol and lactate	K144	mol C	0.206	0.194*)
Independent part of max. rate of glucose synthesis from glycerol and lactate	L144	mol C/h	0.15	0.15
Dependent part of max. rate of glucose synthesis from glycerol and lactate	M144	mol C/h	1.073	1.107
Glycerol and lactate in liver tissue	C18	mol C	0.103	0.0974*)

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 7 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Affinity constant for liver fat synthesis	K147	mol C	0.270	1.391
Max. rate of liver fat synthesis	R147M	mol C/h	0.289	0.289
Free fatty acids in liver tissue	C19	mol C	0.030	0.1684*)
Affinity constant for lipoprotein synthesis	K148	mol C	0.0075	0.0386
Max. rate of lipoprotein synthesis	R148M	mol C/h	1.084	1.0834
Glycerol esterification of fatty acids	K145, K146, K151, K168, K172, K173	mol C/mol C	0.0625	0.0625
Affinity constant for acetate and ketone body synthesis	K149	mol C	0.10	0.513
Independent part of max. rate of acetate and ketone body synthesis	L149	mol C/h	1.234	1.200
Dependent part of max. rate of acetate and ketone body synthesis	M149	mol C/h	1.0	1.025
Affinity constant for fatty acid oxidation	K150	mol C	0.02	0.1430
Independent part of max. rate of fatty acid oxidation	L150	mol C/h	1.809	1.809

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 7 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Dependent part of max. rate of fatty acid oxidation	M150	mol C/h	1.34	1.333
Affinity constant for liver fat breakdown	K152	mol C	1.659	1.555
Max. rate of liver fat breakdown	R152M	mol C/h	0.129	0.1285
Depot fat in liver tissue	C20	mol C	14.80	15.04*)
Affinity constant for lipoprotein secretion	K153	mol C	1.279	1.308
Max. rate of lipoprotein secretion	R153M	mol C/h	1.152	1.1511
Lipoproteins in liver tissue	C21	mol C	5.10	5.307*)
Rate constant for acetate and ketone body secretion	K154	h^{-1}	15.97	16.150
Acetate and ketone bodies in liver tissue	C22	mol C	0.036	0.0374*)
Independent part of rate constant for acetate and ketone body uptake in the mammary gland	L156	l/h	0.0	-441.730
Dependent part of rate constant for acetate and ketone body uptake in the mammary gland	M156	$l^2/(h*ug)$	47.538	83.128

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 7 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Acetate and ketone bodies in extracellular fluid	C23	mol C	0.87	0.9192*)
Extracellular fluid volume	V4	l	150.0	150.0
Rate constant for acetate and ketone body uptake in muscle tissue	K157	l/h	99.48	99.555
Independent part of rate constant for acetate and ketone body uptake in adipose tissue	L158	l/h	0.0	0.0
Dependent part of rate constant for acetate and ketone body uptake in adipose tissue	M158	$l^2/(h*ug)$	456.5	453.274
Rate constant for acetate and ketone body uptake in other tissues	K159	l/h	175.7	175.805
Affinity constant for glucose uptake in the mammary gland	K160	mol C	1.1567	1.153
Independent part of max. rate of glucose uptake in the mammary gland	L160	mol C/h	0.0	-6.4605
Dependent part of max. rate of glucose uptake in the mammary gland	M160	mol C*l/(h*ug)	0.3288	0.8491
Glucose in extracellular fluid	C24	mol C	2.700	3.2518*)

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 7 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original [1]	Final [2]
Affinity constant for glucose uptake in muscle tissue	K161	mol C	1.799	1.830
Independent part of max. rate of glucose uptake in muscle tissue	L161	mol C/h	0.0	0.0
Dependent part of max. rate of glucose uptake in muscle tissue	M161	mol C*l/(h*ug)	1.392	1.3924
Affinity constant for glucose uptake in adipose tissue	K162	mol C	2.70	2.747
Independent part of max. rate of glucose uptake in adipose tissue	L162	mol C/h	0.0	0.0
Dependent part of max. rate of glucose uptake in adipose tissue	M162	mol C*l/(h*ug)	0.7346	0.7331
Affinity constant for glucose uptake in other tissues	K163	mol C	1.444	1.4553
Max. rate of glucose uptake in other tissues	R163M	mol C/h	0.132	0.1309
Affinity constant for glycerol and lactate uptake in the liver	K164	mol C	0.175	0.1667
Max. rate of glycerol and lactate uptake in the liver	R164M	mol C/h	0.864	0.8638

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations

(to be continued)

Appendix 7 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Glycerol and lactate in extracellular fluid	C25	mol C	0.263	0.2542*)
Independent part of rate constant for free fatty acid uptake in the liver	L165	l/h	150.0	149.5
Dependent part of rate constant for free fatty acid uptake in the liver	M165	$l^2/(h*ug)$	69.073	67.750
Free fatty acids in extracellular fluid	C26	mol C	1.241	1.3553*)
Rate constant for free fatty acid uptake in muscle tissue	K166	l/h	60.459	60.700
Rate constant for free fatty acid uptake in other tissues	K167	l/h	20.153	20.230
Affinity constant for fatty acid uptake in the liver from chylomicrons	K169	mol C	0.123	0.1485
Max. rate of fatty acid uptake in the liver from chylomicrons	R169M	mol C/h	0.647	0.6513
Triglyceride in circulating chylomicrons	C27	mol C	0.367	0.4959*)

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 7 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Affinity constant for fatty acid and glycerol uptake in the mammary gland from chylomicrons	K170A	mol C	0.122	0.1464
Independent part of max. rate of fatty acid and glycerol uptake in the mammary gland from chylomicrons	L170A	mol C/h	3.144	2.9865
Dependent part of max. rate of fatty acid and glycerol uptake in the mammary gland from chylomicrons	M170A	mol C*l/(h*ug)	2.518	2.2424
Affinity constant for fatty acid and glycerol uptake in adipose tissue from chylomicrons	K170B	mol C	0.369	0.4640
Independent part of max. rate of fatty acid and glycerol uptake in adipose tissue from chylomicrons	L170B	mol C/h	1.503	1.4913
Dependent part of max. rate of fatty acid and glycerol uptake in adipose tissue from chylomicrons	M170B	ml/ng	1.224	1.210
Affinity constant for fatty acid and glycerol uptake in the mammary gland from lipoproteins	K171A	mol C	0.242	0.1980

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations

(to be continued)

Appendix 7 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Independent part of max. rate of fatty acid and glycerol uptake in the mammary gland from lipoproteins	L171A	mol C/h	1.880	1.7666
Dependent part of max. rate of fatty acid and glycerol uptake in the mammary gland from lipoproteins	M171A	mol C*l/(h*ug)	1.550	1.3273
Triglyceride in circulating lipoproteins	C28	mol C	0.727	0.6487*)
Affinity constant for fatty acid and glycerol uptake in adipose tissue from lipoproteins	K171B	mol C	0.727	0.6040
Independent part of max. rate of fatty acid and glycerol uptake in adipose tissue from lipoproteins	L171B	mol C/h	1.369	0.8826
Dependent part of max. rate of fatty acid and glycerol uptake in adipose tissue from lipoproteins	M171B	ml/ng	0.903	0.2028
Rate constant for outflow of lactate from muscle tissue	K189	h^{-1}	0.1252	0.1252
Lactate in muscle tissue	C38	mol C	3.270	3.270*)

1) Assumed or estimated from literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 7 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Rate constant for outflow of fatty acids from adipose tissue	K194	h^{-1}	0.5296	0.5296
Free fatty acids in adipose tissue	C41	mol C	3.04	3.04*)
Rate constant for outflow of glycerol from adipose tissue	K199	h^{-1}	2.370	2.370
Glycerol in adipose tissue	C44	mol C	0.046	0.046*)
Affinity constant for liver protein synthesis	K43	mol N	0.0099	0.01056
Max. rate of liver protein synthesis	R43M	mol N/h	0.172	0.1755
Amino acids in liver tissue	A14	mol N	0.203	0.19935*)
Affinity constant for amino acid outflow	K44	mol N	0.609	0.5975
Max. rate of amino acid outflow	R44M	mol N/h	4.867	4.8887
Affinity constant for amino acid deamination	K45	mol N	0.0202	0.0655
Independent part of max. rate of amino acid deamination	L45	mol N/h	0.0	0.0
Dependent part of max. rate of amino acid deamination	M45	mol N/h	0.300	0.3703

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 7 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Independent part of rate constant for liver protein breakdown	L46	h^{-1}	0.0005	$5.05*10^{-4}$
Dependent part of rate constant for liver protein breakdown	M46		2.233	2.245
Liver protein	A15	mol N	19.643	19.819*)
Affinity constant for amino acid synthesis	K47	mol N	0.00032	0.05755
Max. rate of amino acid synthesis	R47M	mol N/h	0.079	0.1050
NH_3/NH_4^+ in liver tissue	N3	mol N	0.0006	0.04838*)
Affinity constant for urea synthesis	K48	mol N	0.00027	0.024*)
Max. rate of urea synthesis	R48M	mol N/h	1.476	1.4714
Rate constant for urea outflow	K49	l/h	16.765	16.788
Urea in liver tissue	U3	mol N	0.364	0.3509*)
Volume of liver tissue fluid	V3	l	6.0	6.0
Rate constant for urea excretion in urine	K57	l/h	47.256	47.765
Urea in extracellular fluid	U4	mol N	2.1	2.0479*)

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 7 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Affinity constant for amino acid uptake in the mammary gland	K51	mol N	0.2954	0.30118
Independent part of max. rate of amino acid uptake in the mammary gland	L51	mol N/h	0.0	-1.4889
Dependent part of max. rate of amino acid uptake in the mammary gland	M51	mol N*l/(h*ug)	0.059	0.1790
Amino acids in extracellular fluid	A16	mol N	0.504	0.50227*)
Affinity constant for amino acid uptake in muscle tissue	K52	mol N	0.4124	0.4145
Independent part of max. rate of amino acid uptake in muscle tissue	L52	mol N/h	0.0	0.0
Dependent part of max. rate of amino acid uptake in muscle tissue	M52	mol N*l/(h*ug)	0.653	0.6524
Affinity constant for amino acid uptake in other tissues	K53	mol N	0.336	0.336
Max. rate of amino acid uptake in other tissues	R53M	mol N/h	0.321	0.3208
Affinity constant for amino acid uptake in the liver	K54	mol N	5.503	5.5477

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 7 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Independent part of max. rate of amino acid uptake in the liver	L54	mol N/h	0.0	0.0
Dependent part of max. rate of amino acid uptake in the liver	M54	mol N/h	3.869	3.8597
Amino acids in liver artery	A17	mol N	0.504	0.52259*)
Affinity constant for amino acid outflow from muscle tissue	K61	mol N	2.834	2.834
Max. rate of amino acid outflow from muscle tissue	R61M	mol N/h	0.342	0.342
Amino acids in muscle tissue	A20	mol N	4.251	4.251*)
Affinity constant for amino acid outflow from other tissues	K64	mol N	1.878	1.878
Max. rate of amino acid outflow from other tissues	R64M	mol N/h	0.339	0.339
Amino acids in other tissues	A22	mol N	2.817	2.817*)

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

APPENDIX 8: **Numerical values of state variables and equation parameters in the mammary gland and body tissue compartments**

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Mammary gland				
Volume of mammary tissue fluid	V5	l	14.85	14.85
Affinity constant for fatty acid synthesis	K174	mol C	0.0604	0.0604
Max. rate of fatty acid synthesis	R174M	mol C/h	1.550	1.550
Acetate and ketone bodies in mammary tissue	C29	mol C	0.1485	0.1485*)
Affinity constant for acetate and ketone body oxidation	K175	mol C	0.0886	0.0886
Max. rate of acetate and ketone body oxidation	R175M	mol C/h	3.704	3.704
Affinity constant for milk lactose synthesis	K177	mol C	0.3074	0.308
Max. rate of milk lactose synthesis	R177M	mol C/h	5.736	5.732
Glucose in mammary tissue	C30	mol C	0.1782	0.1782*)
Affinity constant for glucose oxidation	K178	mol C	0.0953	0.0953

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 8 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Max. rate of glucose oxidation	R178M	mol C/h	1.040	1.040
Affinity constant for milk fat synthesis	K179	mol C	0.2284	0.2273
Glycerol esterification of fatty acids	L179	mol C/mol C	0.06863	0.06863
Max. rate of milk fat synthesis	R179M	mol C/h	8.382	8.407
Free fatty acids in mammary tissue	C31	mol C	0.123	0.123*)
Affinity constant for fatty acid oxidation	K180	mol C	4.065	4.385
Max. rate of fatty acid oxidation	R180M	mol C/h	6.843	6.843
Rate constant for milk lactose secretion	K182	h^{-1}	2.084	2.084
Milk lactose in mammary tissue	C33	mol C	1.01	1.01*)
Rate constant for milk fat secretion	K183	h^{-1}	0.056	0.056
Milk fat in mammary tissue	C34	mol C	55.866	55.866*)
Affinity constant for milk protein synthesis	K59	mol N	0.578	0.578
Max. rate of milk protein synthesis	R59M	mol N/h	0.917	0.917

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 8 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Amino acids in mammary tissue	A18	mol N	0.578	0.578*)
Rate constant for milk protein secretion	K60	h^{-1}	1.976	1.976
Milk protein in mammary tissue	A19	mol N	0.232	0.232*)
Muscle tissue				
Volume of muscle tissue fluid	V6	l	155.0	155.0
Affinity constant for amino acid deamination	K184	mol C	1.984	1.984
Max. rate of amino acid deamination	R184M	mol C/h	0.1594	0.1594
Carbon:nitrogen ratio in protein	KCA	mol C/mol N	3.8	3.8
Affinity constant for acetate and ketone body oxidation	K185	mol C	4.089	4.089
Max. rate of acetate and ketone body oxidation	R185M	mol C/h	2.616	2.616
Acetate and ketone bodies in muscle tissue	C35	mol C	1.55	1.55*)
Affinity constant for lactate production from glucose	K186	mol C	5.582	5.582

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 8 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Max. rate of lactate production from glucose	R186M	mol C/h	1.639	1.639
Glucose in muscle tissue	C36	mol C	1.860	1.860*)
Affinity constant for glucose oxidation	K187	mol C	0.2232	0.2232
Max. rate of glucose oxidation	R187M	mol C/h	0.028	0.028
Affinity constant for fatty acid oxidation	K188	mol C	14.259	14.259
Max. rate of fatty acid oxidation	R188M	mol C/h	20.928	20.928
Free fatty acids in muscle tissue	C37	mol C	0.349	0.349*)
Rate constant for lactate outflow	K189	h^{-1}	0.1252	0.1252
Lactate in muscle tissue	C38	mol C	3.270	3.270*)
Affinity constant for muscle protein synthesis	K62	mol N	0.4723	0.4723
Independent part of max. rate of muscle protein synthesis	L62	mol N/h	0.0	0.0
Dependent part of max. rate of muscle protein synthesis	M62	mol N*l/(h*ug)	0.399	0.399
Amino acids in muscle tissue	A20	mol N	4.251	4.251*)

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 8 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Rate constant for muscle protein breakdown	K63	h^{-1}	$4.1*10^{-4}$	$4.1*10^{-4}$
Protein in muscle tissue	A21	mol N	498.0	498.0*)
Adipose tissue				
Volume of adipose tissue fluid	V7	l	4.42	4.42
Affinity constant for fatty acid synthesis	K190	mol C	0.0376	0.0376
Independent part of max. rate of fatty acid synthesis	L190	mol C/h	0.0	0.0
Dependent part of max. rate of fatty acid synthesis	M190	mol C*l/(h*ug)	1.500	1.500
Acetate and ketone bodies in adipose tissue	C39	mol C	0.221	0.221*)
Affinity constant for acetate and ketone body oxidation	K191	mol C	0.2256	0.2256
Max. rate of acetate and ketone body oxidation	R191M	mol C/h	1.435	1.435
Affinity constant for glucose oxidation	K193	mol C	0.1775	0.1775
Max. rate of glucose oxidation	R193M	mol C/h	0.235	0.235

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 8 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Glucose in adipose tissue	C40	mol C	0.265	0.265*)
Rate constant for free fatty acid outflow	K194	h^{-1}	0.5296	0.5296
Free fatty acids in adipose tissue	C41	mol C	3.04	3.04*)
Affinity constant for body fat synthesis	K195	mol C	3.6442	3.659
Independent part of max. rate of body fat synthesis	L195	mol C/h	0.0	0.0
Dependent part of max. rate of body fat synthesis	M195	mol C*l/(h*ug)	3.383	3.383
Glycerol esterification of fatty acids	K196, K198	mol C/mol C	0.0625	0.0625
Affinity constant for body fat breakdown	K197	mol C	4349.6	4292.0
Independent part of max. rate of body fat breakdown	L197	mol C/h	9.454	9.454
Dependent part of max. rate of body fat breakdown	M197	mol C*l/(h*ug)	11.375	11.375
Depot fat in adipose tissue	C43	mol C	3030.0	3030.0*)
Rate constant for glycerol outflow	K199	h^{-1}	2.370	2.37

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 8 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Glycerol in adipose tissue	C44	mol C	0.046	0.046*)
Other tissues				
Volume of other tissue fluid	V8	l	20.0	20.0
Affinity constant for acetate and ketone body oxidation	K200	mol C	0.1332	0.1332
Max. rate of acetate and ketone body oxidation	R200M	mol C/h	1.699	1.699
Acetate and ketone bodies in other tissues	C45	mol C	0.200	0.200*)
Affinity constant for glucose oxidation	K201	mol C	0.0449	0.0449
Max. rate of glucose oxidation	R201M	mol C/h	0.101	0.101
Glucose in other tissues	C46	mol C	0.240	0.240*)
Affinity constant for fatty acid oxidation	K202	mol C	1.839	1.839
Max. rate of fatty acid oxidation	R202M	mol C/h	6.978	6.978
Free fatty acids in other tissues	C47	mol C	0.045	0.045*)
Affinity constant for protein synthesis	K65	mol N	0.313	0.313

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

(to be continued)

Appendix 8 (continued)

Parameter or state variable	Symbol	Unit	Numerical value Original[1]	Final[2]
Max. rate of protein synthesis	R65M	mol N/h	0.214	0.214
Amino acids in other tissues	A22	mol N	2.817	2.817*)
Rate constant for protein breakdown	K66	h^{-1}	$6.2*10^{-4}$	$6.2*10^{-4}$
Protein in other tissues	A23	mol N	330.0	330.0*)

1) Assumed or estimated from the literature
2) Finally adjusted after repeated simulations
*) Initial value at the beginning of the run

APPENDIX 9: List of all nutrient fluxes obtained with the static and the dynamic model

Nutrient or metabolite flux	Symbol	Unit	Static model	Dynamic model
Rumen compartment				
Intake of sugar	FSU100	mol C/d	140.35	141.04
Intake of starch	FST100	-	20.741	20.849
Intake of cell wall carbohydrates	FCE100	-	282.96	284.29
Intake of glycerol	FGL100	-	2.769	2.753
Intake of fatty acids	FLI100	-	44.617	44.892
Intake of carbohydrates and lipids	F100	-	491.44	493.83
Flow of unfermentable sugar	FSU101	-	0.0	0.0
Flow of unfermentable starch	FST101	-	0.0	0.0
Flow of unfermentable cell wall carbohydrates	FCE101	-	113.19	113.72
Flow of unfermentable glycerol	FGL101	-	0.0	0.0
Flow of unfermentable fatty acids	FLI101	-	40.155	40.403
Flow of unfermentable carbohydrates and lipids	F101	-	153.34	154.12
Flow of fermentable sugar and glycerol	FSU102	-	143.12	143.79
Flow of fermentable starch	FST102	-	20.741	20.849
Flow of fermentable cell wall carbohydrates	FCE102	-	169.78	170.58

(to be continued)

Appendix 9 (continued)

Nutrient or metabolite flux	Symbol	Unit	Static model	Dynamic model
Rumen compartment				
Flow of fermentable fatty acids	FLI102	mol C/d	4.462	4.489
Flow of fermentable carbohydrates and lipids	F102	-	338.10	339.71
Outflow of unfermentable sugar	FSU103	-	0.0	0.0
Outflow of unfermentable starch	FST103	-	0.0	0.0
Outflow of unfermentable cell wall carbohydrates	FCE103	-	113.19	113.72
Outflow of unfermentable glycerol	FGL103	-	0.0	0.0
Outflow of unfermentable fatty acids	FLI103	-	40.155	40.400
Outflow of unfermentable carbohydrates and lipids	F103	-	153.34	154.12
Microbial uptake of sugar	FSU105	-	4.932	4.862
Microbial uptake of starch	FST105	-	0.825	0.681
Microbial uptake of cell wall carbohydrates	FCE105	-	56.656	56.572
Microbial uptake of fatty acids	FLI105	-	4.462	4.489
Microbial uptake of carbohydrates and lipids	F105	-	66.875	66.604

(to be continued)

Appendix 9 (continued)

Nutrient or metabolite flux	Symbol	Unit	Static model	Dynamic model
Rumen compartment				
Fermentation of sugar	FSU106	mol C/d	135.32	136.06
Fermentation of starch	FST106	-	19.501	19.774
Fermentation of cell wall carbohydrates	FCE106	-	79.968	80.679
Fermentation of carbohydrates and lipids	F106	-	234.79	236.51
Outflow of fermentable sugar	FSU107	-	2.862	2.864
Outflow of fermentable starch	FST107	-	0.415	0.401
Outflow of fermentable cell wall carbohydrates	FCE107	-	33.154	33.323
Outflow of fermentable carbohydrates	F107	-	36.431	36.588
Formation of ATP from carbohydrates	F108	mol ATP/d	175.07	176.34
Use of microbial carbohydrates and lipids for amino acid-C	F109	mol C/d	40.864	39.022
Outflow of microbial starch	FST110	-	2.796	3.304
Outflow of microbial cell wall carbohydrates	FCE110	-	15.380	15.965
Outflow of microbial lipids	FLI110	-	16.779	17.416
Outflow of microbial carbohydrates and lipids	F110	-	34.955	36.284

(to be continued)

Appendix 9 (continued)

Nutrient or metabolite flux	Symbol	Unit	Static model	Dynamic model
Rumen compartment				
Outflow of acetate	FAC111	mol C/d	101.45	101.60
Outflow of propionate	FPR111	-	59.974	60.182
Outflow of butyrate	FBU111	-	41.108	41.191
Outflow of CH_4	FCH111	-	22.007	21.940
Outflow of CO_2	FCO111	-	55.588	55.589
Outflow of VFA, CH_4 and CO_2	F111	-	280.13	280.51
Fermentation of protein	F112	-	54.282	52.667
Formation of BCFA from protein	F113	-	8.944	8.678
Formation of VFA, CH_4 and CO_2 from protein	F114	-	45.338	43.989
Formation of ATP from protein	F115	mol ATP/d	0.0	0.0
Intake of crude protein in concentrates	FCO	mol N/d	20.448	20.543
Intake of crude protein in roughages	FRO	-	16.112	16.189
Intake of crude protein	FO	-	36.560	36.732
Flow of unfermentable protein	F1	-	7.312	7.347
Flow of fermentable protein	F2	-	29.248	29.385
Flow of dietary ammonium	F3	-	0.0	0.0
Flow of dietary urea	F4	-	0.0	0.0

(to be continued)

Appendix 9 (continued)

Nutrient or metabolite flux	Symbol	Unit	Static model	Dynamic model
Rumen compartment				
Outflow of unfermentable protein	F5	mol N/d	7.312	7.346
Microbial uptake of amino acids and peptides	F6	-	26.404	26.333
Outflow of fermentable protein	F7	-	5.484	5.504
Microbial excretion of amino acids	F8	-	2.640	2.452
Microbial protein synthesis	F9	-	24.933	25.055
Outflow of microbial amino acids and peptides	F10	-	0.278	0.246
Degradation of microbial amino acids	F11	-	24.065	24.218
Degradation of microbial protein	F12	-	4.987	5.011
Outflow of microbial protein	F13	-	19.946	20.044
Outflow of NH_3/NH_4^+	F14	-	2.450	2.438
Microbial uptake of NH_3/NH_4^+	F15	-	11.790	11.864
Absorption of NH_3/NH_4^+	F16	-	5.464	5.505
Microbial amino acid synthesis	F17	-	20.525	20.628
Outflow of microbial NH_3/NH_4^+	F18	-	0.052	0.100
Outflow of microbial total N	F19	-	20.276	20.391

(to be continued)

Appendix 9 (continued)

Nutrient or metabolite flux	Symbol	Unit	Static model	Dynamic model
Rumen compartment				
Microbial excretion of NH_3/NH_4^+	F20	mol N/d	15.278	15.390
Hydrolysis of urea	F21	-	4.426	4.419
Intestinal lumen compartment				
Entrance of indigestible cell wall carbohydrates and fatty acids	F116	mol C/d	165.89	167.73
Entrance of digestible sugar, starch and glycerol	F117	-	7.060	7.593
Entrance of digestible fatty acids	F118	-	51.779	52.061
Flow of indigestible cell wall carbohydrates and fatty acids	F119	-	165.89	167.74
Hind gut fermentation of cell wall carbohydrates and fatty acids	F119F	-	36.495	36.902
Flow of digestible sugar, starch and glycerol	F120	-	0.706	0.723
Hind gut fermentation of sugar, starch and glycerol	F120F	-	0.706	0.723
Glucose uptake from the lumen	F121	-	6.354	6.469
Flow of digestible fatty acids	F122	-	5.178	5.203
Fatty acid uptake from the lumen	F123	-	46.601	46.859

(to be continued)

Appendix 9 (continued)

Nutrient or metabolite flux	Symbol	Unit	Static model	Dynamic model
Intestinal lumen compartment				
Outflow of acetate	FAC124	mol C/d	14.329	14.489
Outflow of propionate	FPR124	-	13.803	13.958
Outflow of butyrate	FBU124	-	2.574	2.602
Outflow of CH_4	FCH124	-	2.215	2.239
Outflow of CO_2	FCO124	-	6.586	6.659
Outflow of VFA, CH_4 and CO_2	F124	-	39.507	39.946
Formation of ATP from starch and cell wall carbohydrates	F125	mol ATP/d	26.208	26.506
Excretion of undigested carbohydrates and lipids	F126	mol C/d	152.55	154.02
Net protein degradation in the hind gut	F127	-	20.284	20.302
Fermentation of protein-C in the hind gut	F127A	-	2.761	2.780
Entrance of indigestible dietary and microbial protein	F22	mol N/d	8.626	8.657
Entrance of digestible dietary and microbial protein	F23	-	24.394	24.483
Entrance of NH_3/NH_4^+ from rumen liquor and from rumen microbes	F24	-	2.502	2.539
Flow of indigestible dietary and microbial protein	F25	-	8.626	8.657

(to be continued)

Appendix 9 (continued)

Nutrient or metabolite flux	Symbol	Unit	Static model	Dynamic model
Intestinal lumen compartment				
Flow of digestible dietary and microbial protein	F26	mol N/d	4.973	4.992
Dietary and microbial amino acid uptake from the lumen	F27	-	19.421	19.491
Protein degradation in the hind gut	F28	-	8.744	8.767
Excretion of undigested protein	F29	-	10.352	10.403
Entrance of indigestible endogenous protein	F30	-	0.438	0.440
Entrance of digestible endogenous protein	F31	-	8.653	8.667
Flow of indigestible endogenous protein	F32	-	0.438	0.440
Flow of digestible endogenous protein	F33	-	1.653	1.655
Endogenous amino acid uptake from the lumen	F34	-	7.000	7.012
NH_3/NH_4^+ absorption from the small intestine	F35	-	2.502	2.539
Microbial amino acid synthesis in the hind gut	F36	-	3.406	3.424
NH_3/NH_4^+ absorption from the hind gut	F37	-	9.434	9.611

(to be continued)

Appendix 9 (continued)

Nutrient or metabolite flux	Symbol	Unit	Static model	Dynamic model
Intestinal lumen compartment				
Hydrolysis of urea in the hind gut	F38	mol N/d	4.096	4.268
Intestinal wall compartment				
Oxidation of acetate and ketone bodies	F128	mol C/d	15.396	15.430
Oxidation of glucose	F129	-	0.172	0.178
Absorption of glucose	F130	-	3.269	3.363
Synthesis of glycerol	F131	-	2.913	2.929
Absorption of triglycerides	F132	-	49.514	49.788
Intestinal protein synthesis	F39	mol N/d	12.192	12.157
Absorption of amino acids	F40	-	26.421	26.517
Secretion of endogenous protein	F41	-	9.091	9.107
Degradation of intestinal protein	F42	-	3.101	3.051

(to be continued)

Appendix 9 (continued)

Nutrient or metabolite flux	Symbol	Unit	Static model	Dynamic model
Liver compartment				
Absorption of propionate	F133	mol C/d	73.777	74.141
Absorption of butyrate	F134	-	4.368	4.379
Absorption of acetate and 3-OH-butyrate	F135	-	155.10	155.51
Gluconeogenesis from propionate	F136	-	54.081	54.046
Oxidation of propionate	F137	-	19.696	20.094
Oxidation of butyrate	F138	-	4.368	4.379
Outflow of glucose	F139	-	82.351	82.312
Keto acids produced by amino acid deamination	F140	-	31.293	31.710
Keto acids used in amino acid synthesis	F141	-	4.693	4.763
Gluconeogenesis from keto acids	F142	-	16.270	16.245
Oxidation of keto acids	F143	-	10.330	10.702
Gluconeogenesis from glycerol and lactate	F144	-	12.000	12.022
Esterification of liver fat	F145	-	0.043	0.044
Esterification of lipoproteins	F146	-	1.300	1.300
Liver fat synthesis	F147	-	0.694	0.696

(to be continued)

Appendix 9 (continued)

Nutrient or metabolite flux	Symbol	Unit	Static model	Dynamic model
Liver compartment				
Lipoprotein synthesis	F148	mol C/d	20.800	20.803
Acetate and ketone body synthesis	F149	-	13.800	13.830
Fatty acid oxidation	F150	-	1.775	1.765
Liver fat breakdown into glycerol	F151	-	0.174	0.173
Liver fat breakdown into fatty acids	F152	-	2.776	2.774
Outflow of lipoproteins	F153	-	22.100	22.105
Outflow of acetate and ketone bodies	F154	-	13.800	13.830
Liver protein synthesis	F43	mol N/d	3.929	3.998
Outflow of amino acids	F44	-	29.200	29.208
Deamination of amino acids	F45	-	8.235	8.345
Liver protein breakdown	F46	-	3.929	3.995
Amino acid synthesis	F47	-	1.235	1.253
Urea synthesis	F48	-	24.400	24.745
Outflow of urea	F49	-	24.400	24.746

(to be continued)

Appendix 9 (continued)

Nutrient or metabolite flux	Symbol	Unit	Static model	Dynamic model
Extracellular fluid compartment				
Uptake of acetate and ketone bodies in the intestinal wall	F155	mol C/d	15.396	15.430
Uptake of acetate and ketone bodies in the mammary gland	F156	-	82.124	82.342
Uptake of acetate and ketone bodies in muscle tissue	F157	-	13.858	13.896
Uptake of acetate and ketone bodies in adipose tissue	F158	-	33.046	33.130
Uptake of acetate and ketone bodies in other tissues	F159	-	24.472	24.537
Uptake of glucose in the mammary gland	F160	-	68.568	68.593
Uptake of glucose in muscle tissue	F161	-	10.432	10.449
Uptake of glucose in adipose tissue	F162	-	4.578	4.587
Uptake of glucose in other tissues	F163	-	2.042	2.043
Uptake of glycerol and lactate in the liver	F164	-	12.441	12.461
Uptake of free fatty acids in the liver	F165	-	22.643	22.618
Uptake of free fatty acids in muscle tissue	F166	-	12.000	12.026

(to be continued)

Appendix 9 (continued)

Nutrient or metabolite flux	Symbol	Unit	Static model	Dynamic model
Extracellular fluid compartment				
Uptake of free fatty acids in other tissues	F167	mol C/d	4.000	4.008
Uptake in the liver of glycerol from chylomicrons	F168	-	0.728	0.731
Uptake in the liver of fatty acids from chylomicrons	F169	-	11.650	11.703
Uptake in the mammary gland of fatty acids and glycerol from chylomicrons	F170A	-	32.494	32.707
Uptake in adipose tissue of fatty acids and glycerol from chylomicrons	F170B	-	4.642	4.647
Uptake in the mammary gland of fatty acids and glycerol from lipoproteins	F171A	-	19.337	19.360
Uptake in adipose tissue of fatty acids and glycerol from lipoproteins	F171B	-	2.763	2.745
Uptake of fatty acids and glycerol in the mammary gland	F172	-	51.831	52.067
Uptake of fatty acids in the mammary gland	F172A	-	48.782	49.004
Uptake of glycerol in the mammary gland	F172B	-	3.049	3.063
Uptake of fatty acids and glycerol in adipose tissue	F173	-	7.405	7.393

(to be continued)

Appendix 9 (continued)

Nutrient or metabolite flux	Symbol	Unit	Static model	Dynamic model
Extracellular fluid compartment				
Uptake of fatty acids in adipose tissue	F173A	mol C/d	6.969	6.958
Uptake of glycerol in adipose tissue	F173B	-	0.436	0.435
Uptake of amino acids in the intestinal wall	F50	mol N/d	9.091	9.120
Uptake of amino acids in the mammary gland	F51	-	11.000	10.995
Uptake of amino acids in muscle tissue	F52	-	4.482	4.480
Uptake of amino acids in other tissues	F53	-	4.618	4.615
Uptake of amino acids in the liver	F54	-	9.800	9.786
Uptake of urea in the rumen	F55	-	4.426	4.419
Uptake of urea in the hind gut	F56	-	4.096	4.268
Excretion of urea in the urine	F57	-	15.878	16.059
Mammary gland compartment				
Fatty acid synthesis from acetate and ketone bodies	F174	mol C/d	26.440	26.473
Oxidation of acetate and ketone bodies	F175	-	55.684	55.868

(to be continued)

Appendix 9 (continued)

Nutrient or metabolite flux	Symbol	Unit	Static model	Dynamic model
Mammary gland compartment				
Glycerol synthesis	F176	mol C/d	1.783	1.785
Milk lactose synthesis	F177	-	50.520	50.541
Oxidation of glucose	F178	-	16.265	16.267
Milk fat synthesis	F179	-	70.405	70.640
Oxidation of fatty acids	F180	-	4.817	4.837
Esterification of milk fat	F181	-	4.832	4.848
Milk lactose secretion	F182	-	50.520	50.541
Milk fat secretion	F183	-	75.237	75.493
Outflow of amino acids	F58	mol N/d	0.0	0.0
Milk protein synthesis	F59	-	11.000	10.995
Milk protein secretion	F60	-	11.000	10.995
Muscle tissue compartment				
Ketones produced by amino acid deamination	F184	mol C/d	3.408	3.401
Oxidation of acetate and ketone bodies	F185	-	17.266	17.297
Glycolysis into lactate	F186	-	9.825	9.848
Oxidation of glucose	F187	-	0.600	0.600
Oxidation of fatty acids	F188	-	12.000	12.026
Outflow of lactate	F189	-	9.825	9.847

(to be continued)

Appendix 9 (continued)

Nutrient or metabolite flux	Symbol	Unit	Static model	Dynamic model
Muscle tissue compartment				
Outflow of amino acids	F61	mol N/d	4.903	4.889
Muscle protein synthesis	F62	-	4.482	4.490
Muscle protein breakdown	F63	-	4.903	4.898
Adipose tissue compartment				
Fatty acid synthesis from acetate and ketone bodies	F190	mol C/d	16.000	16.025
Oxidation of acetate and ketone bodies	F191	-	17.046	17.106
Glycerol synthesis	F192	-	1.200	1.200
Oxidation of glucose	F193	-	3.378	3.386
Outflow of fatty acids	F194	-	38.643	38.650
Body fat synthesis	F195	-	19.200	19.207
Esterification of body fat	F196	-	1.200	1.200
Body fat breakdown into fatty acids	F197	-	34.874	34.875
Body fat breakdown into glycerol	F198	-	2.180	2.180
Outflow of glycerol	F199	-	2.616	2.615

(to be continued)

Appendix 9 (continued)

Nutrient or metabolite flux	Symbol	Unit	Static model	Dynamic model
Other tissue compartment				
Oxidation of acetate and ketone bodies	F200	mol C/d	24.472	24.538
Oxidation of glucose	F201	-	2.042	2.043
Oxidation of fatty acids	F202	-	4.000	4.008
Outflow of amino acids	F64	mol N/d	4.897	4.897
Protein synthesis	F65	-	4.618	4.626
Protein breakdown	F66	-	4.897	4.908

APPENDIX 10: List of Tables

(to be continued)

Appendix 10 (continued)

(to be continued)

Appendix 10 (continued)

APPENDIX 11: List of Figures

(to be continued)

Appendix 11 (continued)

(to be continued)

Appendix 11 (continued)

(to be continued)

Appendix 11 (continued)

The reader my expectant mind projected
was, gentle reader, not a bit like you.
So if this book was less than you expected,
believe me, I've been disillusioned too.

(Piet Hein)