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Dynamic models: their use in understanding and predicting nutrient response

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A mathematical model is a means whereby the behaviour of a system may be represented by one or more equations. The development of such a model and its use in understanding or predicting the operation of a system is termed simulation. Modelling techniques have been applied in many scientific disciplines and thus the mathematical principles which are essential to model development are well established (Shannon, 1975; France & Thornley, 1984). These principles include the classification of models in a number of ways, but only dynamic models, i.e. ones which explicitly represent the time-variable, will be discussed here.

In considering the use of models to examine responses to nutrients, two types of application must be distinguished. First, the fitting of equations to data sets within experiments to aid between-treatment comparisons. Second, the prediction of responses using values and hypotheses obtained in more than one experiment. Both types of model can also aid in improving our understanding of responses although the within-experiment application tends to concentrate on one aspect of a system (e.g. the rate of passage model of Blaxter *et al.* 1956), while the predictive model generally attempts to resynthesize different parts of a system into the whole.

The objectives of the present paper are to examine the possible role of models in assessing responses to nutrients, to describe the principles of modelling and finally to discuss the contribution which dynamic models can make to improving our understanding of ruminant nutrition.

The potential of models

The use of models to help interpret data through improving between-treatment comparisons is relatively well-developed in ruminant nutrition. Blaxter *et al.* (1956) developed an equation to estimate the retention of digesta in the gut, based on the excretion of stained particles in the faeces, while Ørskov & McDonald (1979) suggested the use of the Mitscherlich equation to describe the disappearance of material from a dacron bag in terms of a rate-constant and a potential digestibility. These equations enable values collected over a period of time to be expressed in terms of specific variables which can then be compared statistically between treatments. The type of curve which best fits the data may also give information about the mechanisms involved, for example, the number of compartments which exert a significant effect on rate of passage through the gut (Blaxter *et al.* 1956).

In contrast, the use of more complex models to understand and predict responses to nutrients in ruminants is less-well developed than in other disciplines of agricultural science, e.g. plant and crop physiology (de Wit, 1970; Thornley, 1980) and it is the development and use of this type of model which will be concentrated on in the present paper. Thornley & France (1984) suggested that the relatively slow acceptance of models as a tool in nutritional research may be due, among other reasons, to a lack of awareness among some nutritionists of the fundamental principles of science outside their own particular discipline together with a fear of mathematics and computers, which has led to a poor appreciation of the need for a sound mathematical basis to modelling. This can be overcome by collaboration between biologists and applied mathematicians. A further caution cited by Thornley & France (1984) is the falsely high expectations of the predictve capability of mechanistic models. If the ultimate model capable of predicting responses in all dietary situations were already available, then there would be no need for a continuing research programme in this area. However, our understanding of digestion and metabolism is not yet complete and mechanistic modelling merely provides another tool in improving our understanding.

The contribution of modelling to increasing our understanding lies in the power of computers to cope simultaneously with the complex interactions involved in processes such as digestion and metabolism. Illustrations of such interactions will be given in the following two subsections and the progress achieved by models in one of these areas will be referred to in the final section. It should be remembered that modelling is simply an extension of the logical thought processes on which all experimentation should be based.

Interactions between nutrients. The way in which growing and lactating animals respond to different nutrients is the result of complex interactions which occur during digestion and metabolism, following the non-continuous ingestion of dietary nutrients. For example, the synthesis of protein in muscle or milk requires energy in addition to amino acids, while the conversion of excess amino acids to glucose may decrease the animal's requirement for glucose from other sources. Thus the response to protein is likely to be influenced by factors such as the total energy supply and the availability of glucose. Hence apparent contradictions in the literature in terms of response to one particular nutrient, may be explained in terms of differences in the basal supply of other nutrients. This was clearly demonstrated by Tyrrell *et al.* (1979) who showed that acetate was more efficiently utilized by cattle consuming a diet of hay plus concentrates compared with those consuming hay alone. The addition of concentrates may have altered not only protein supply, but also the supply of propionate or glucose, or both, and thus it is difficult from feeding experiments to attribute the interaction to a specific nutrient(s). The technique of intragastric infusion developed by Ørskov *et al.* (1979*b*) provides a physical model for examining interactions between nutrients. Energetic efficiencies of various mixtures of volatile fatty acids have been derived with this system in young sheep (Ørskov *et al.* 1979*a*; Table 1). Only infusion A was found to be used with a significantly higher efficiency than the other infusions

Table 1. *The efficiency of utilization of energy* (k_f) *in young sheep maintained by intragastric infusion* (*from Ørskov* et al. 1979)

Infusion	Molar ratios of VFA infused Acetic	Propionic	Butyric	k_f
A	35	55	10	0·78
B	45	45	10	0·64
C	55	35	10	0·57
D	85	5	10	0·59

and the authors concluded that this general lack of difference suggests that the effect of diet on the efficiency of utilization of energy for growth (k_f) cannot be specifically attributed to differences in utilization of the volatile fatty acids. However, as pointed out by MacRae & Lobley (1982), the experiment was conducted with animals receiving a high level of protein (23% of the energy) and they implied that a different result might have been obtained if less casein had been infused. These results will be considered further in the final section of the present paper in relation to the results of a simulation exercise where the interactions of varying protein, glucose and total energy input to growing sheep could be readily assessed.

Animal effects. A further dimension of complexity which affects the interactions between nutrients is the physiological state of the animal. For example, some workers have reported an increase in the energetic efficiency of growth with age as the proportion of energy deposited as protein increases (Geay *et al.* 1976; Graham, 1980). Both endogenous (bulls *v.* steers) and exogenous (implants) hormones may also influence the ratio, protein:fat deposited and hence efficiency (Webster, 1985). Thus to increase our understanding of responses and our ability to predict them, we need to consider the effect of manipulating the animal's ability to deposit protein relative to fat on the metabolic interactions between nutrients. While it is possible to embark on such a general programme of research, the increasing economic constraints would suggest that such exhaustive experimentation is not feasible or efficient and the use of models to predict the responses and to help evaluate hypotheses becomes increasingly attractive. However, to ensure credibility in the behaviour of simulation models as stressed earlier, mathematical principles must be adhered to and these will be described in the following section.

Principles of modelling

The basis of a good model is a clear definition of the objective of the exercise since this will determine the level of representation (i.e. the choice of components) and the degree of aggregation. These decisions will then influence the structure of the equations and the way in which parameters are defined. These four aspects will be discussed separately in relation to specific examples.

Level of representation. While objectives may be broadly classified as to whether the aim is to predict or to increase understanding, the distinction is not clear-cut, since prediction models may also improve our understanding, while mechanistic models improve our understanding, but with the ultimate aim of improving prediction. Using the hierarchical system discussed by France & Thornley (1984), a mechanistic model of the whole animal implies representation of parts of the animal, i.e. metabolites or tissues, while consideration of the animal as one unit is empiricism. Similarly, at the level of the liver, representation of hepatocytes or metabolites is mechanistic, while a decision not to consider how the liver functions is again empiricism. In practice, few whole-animal models are truly mechanistic since, for example, maintenance is not yet sufficiently understood to be described mechanistically. Thus, models may be considered as being on a spectrum with some components being represented mechanistically and some empirically.

Aggregation. Once the choice of components is made, the method of representing their metabolism has to be considered, since to represent each individual step of every reaction would introduce an unnecessary degree of complexity. Both the methods and the degree of aggregation suitable to any model are again dependent on the objective, and the following four methods of aggregation, as suggested by Gill (1984), will be discussed in relation to specific models.

First, models may be simplified by assuming common pathways for different nutrients. To illustrate this with reference to models of energy utilization, in the predictive model of Graham *et al.* (1976) the energy input was described wholly in terms of metabolizable energy (ME), while in the more-detailed model of Gill *et al.* (1984), where the objective was to examine the possible reasons for different efficiencies of utilization of ME, the metabolism of acetate, propionate, fatty acids, glucose and protein were represented separately. However, the metabolism of butyrate was assumed to be the same as that of acetate.

Aggregation may also be achieved by incorporating individual steps of a reaction into one overall pathway. Thus, in models which incorporate fat synthesis, Baldwin *et al.* (1976) quoted four intermediary fluxes in the synthesis of triglyceride from acetate, while in the model of Koong *et al.* (1982) fat appeared to be synthesized directly from carbohydrate input. The main aim of the theoretical model discussed by Baldwin *et al.* (1976) was to understand adipose metabolism, while that of Koong *et al.* (1982) was to predict, and hence a higher degree of aggregation was associated with the more predictive model.

A third means of increasing aggregation, which is used to some extent in all models, is that of ignoring minor aspects of metabolism. Thus, France *et al.* (1982) in their model of rumen fermentation did not consider the fermentation of lipid or the presence of lignin, since neither were important relative to their objective of predicting the supply of protein and volatile fatty acids to the tissues. On the other hand, Baldwin *et al.* (1977) considered the input of both these substrates, since they were interested in the total content of material in the rumen in addition to the prediction of nutrient supply.

Finally, no model can consider the availability of all metabolites and thus, for example, most metabolism models may assume that co-enzyme A is never a limiting substrate. In the rumen, most models developed in the UK and the USA do not allow for sulphur deficiency (Baldwin *et al.* 1977; France *et al.* 1982) while models developed in Australia are more likely to take account of this possibility (Black *et al.* 1980–1981).

These methods of aggregation are likely to be incorporated to some extent in all models, but as has been demonstrated, their use is closely related to the specific objectives.

Structure of equations. The flux of metabolites between pools (state variables) in the metabolism models of Baldwin (Waghorn & Baldwin, 1984; Baldwin *et al.* 1986) is generally described in terms of Michaelis-Menten or mass-action kinetics. Other representations of metabolism are also possible (e.g logistic functions to describe growth) and examples are given in France & Thornley (1984). The inputs to and the outputs from each pool are then summed algebraically by a process in which separate differential equations are integrated by the computer at set iteration intervals to calculate the concentrations to be used during the next iteration. Methods of integration and the choice of iteration interval are also discussed in France and Thornley (1984).

Definition of parameters. The previously-stated decisions on how to represent the system to be modelled depend partly on the objectives and partly on knowledge as to whether the data required to define the parameters exist. The main criterion in choosing data with which to define parameters is that the data used for each pool are compatible. Thus, while it is possible to use the data obtained from both in vivo and in vitro experiments, different limitations may apply in each system and use of both types of data within one model may bias the results. In this regard Baldwin and his group at Davis have developed the ability to determine the parameters required for their models in their own laboratory. Thus, their models have progressed from the whole-cow model of Smith (1970) which did not function adequately, to more detailed models of the mammary gland (Waghorn & Baldwin, 1984) and adipose tissue (Baldwin *et al.* 1976) to improve the representation of these specific tissues, returning again to the whole-animal level with the metabolism model of Baldwin *et al.* (1986).

This illustrates how modelling progresses by defining areas of poor representation and inadequate knowledge to the design of experiments to rectify the limitations and provide data and hypotheses for a new model.

The contribution of dynamic models to ruminant nutrition

This section will consider how a modelling approach can improve the value of data collected and their interpretation and also help in the structuring of a research programme.

Better quantification of data. The ability of models such as those of Blaxter *et al.* (1956) and Ørskov & McDonald (1979) to estimate relative rates of passage and digestion and compare the effects of treatments has already been demonstrated. However, the relevance of such numbers to the overall nutritional status of the animal requires their incorporation into a composite model. Such models in relation to fibre have been developed by Mertens (1973), and Mertens & Ely (1979), and have demonstrated the importance of considering the competitive effects of digestion and passage in relation both to physical limitation of voluntary intake and to the efficiency of utilization of fibre. With regard to voluntary intake, the effects within a 24 h period may be more important than those from day-to-day (Forbes, 1978) and thus E. Aitchison, M. Gill, J. France and M. S. Dhanoa (unpublished results) developed a model to estimate rates of passage and digestion using values for the weight of digestible and indigestible fibre present in the rumen from 5 to 24 h after feeding. The rates of passage thus obtained were markedly lower than those estimated using chromium-mordanted hay, and suggested that the first order kinetics used to describe passage obtained from between-day studies may not be appropriate to the period immediately after feeding once daily. Unfortunately, the data available were not of sufficient resolution to define an alternative mathematical approach, but the knowledge gained can be used in designing further experiments.

Clarification of experimental objectives. Such quantitative assessment of data highlights the gaps in current knowledge in relation to specific objectives and thus enables priorities to be assigned to different areas of research. For example, in evaluating the model of Gill *et al.* (1984) it became apparent that very few complete profiles of absorbed nutrients were available in the literature. The results of simulations using the model also drew attention to both the limitations imposed by our empirical representation of maintenance and to the need for better quantitative determination of the conversion of propionate to glucose with the effect of this on the supply of NADPH. While it could be argued that a similar conclusion might be reached by reviewing the literature, the advantage of the model is that it provides a quantitative framework within which to assess the dietary regimens under which glucose is likely to be either limiting or in excess.

Development and evaluation of hypotheses. Another advantage of the modelling approach may also be at least partly achieved by construction of a flow diagram without actually parameterizing and running a model. This is the development of research hypotheses which are useful in the interpretation of experimental results in situations where sufficient data for parameterization are not available. For example, Thomas *et al.* (1980) observed a decrease in intake of silage alone in response to addition of lactic acid, but this decrease was not apparent when the silage was supplemented with fish meal. While it is possible to suggest reasons for this interaction from straightforward consideration of the data, construction of flow diagrams which link energy and protein utilization both in the rumen and at the tissue level may stimulate recognition of other mechanisms of interaction.

Where a model can be parameterized, research hypotheses may be evaluated as illustrated by the model of Gill *et al.* (1984). This model was developed with the objective of examining how different efficiencies of utilization of ME are related to nutrient supply, with the emphasis on requirement for NADPH in the synthesis of triglycerides as discussed by MacRae & Lobley (1982). However, the results of simulations (J. L. Black, M. Gill, J. H. M. Thornley, D. E. Beever and J. D. Oldham, unpublished results) illustrate that the effect of an energy increment of a high-protein diet (e.g. the infusions of Ørskov *et al.* 1979*a*) would be to increase protein synthesis and associated ATP requirement to a greater extent than the same increment of a lower-protein diet if, on the lower-protein diet, amino acid supply restricted potential protein synthesis. In this case, the requirement for glucose for fat synthesis and its effect on the efficiency of acetate utilization would be less with the high-protein diet. Thus, in the simulations the effect of increasing protein input on acetate utilization was initially through a change in the ATP requirements of the tissues and only at very high protein levels was there an increased gluconeogenesis (and hence NADPH production) from excess amino acids. Both the biological value of absorbed protein and the animal's potential for protein synthesis will also affect these responses and can be examined using the model. This demonstrates the power of computer models to evaluate the relative importance of inter-related hypotheses in a wide variety of situations.

Encouraging collaboration. As was stated earlier, progress in modelling is achieved by identifying areas requiring further elucidation. Baldwin's group at Davis have the biochemical expertise available to integrate their experimental and modelling programme. This is not true within many groups and therefore progress requires collaboration, not just between biologists and mathematicians but also between nutritionists, microbiologists, biochemists and physiologists. This must be a beneficial effect since the clarity of thought invoked by modelling eases communication between disciplines.

Improving prediction. Current empirical methods of prediction of, for example, voluntary intake, are of limited accuracy (Neal *et al.* 1984) and increasing further the degree of complexity by taking account of more factors does not necessarily decrease the error involved. With more mechanistic models, the inclusion of more elements of the system should decrease the error of prediction, and increase our understanding of it, such that a simpler representation may then be developed without decreasing the accuracy of prediction (Bywater, 1984). Further, the application of empirical models is restricted to a data-set similar to that from which they were developed while a truly mechanistic model should be able to predict response in a wide range of situations.

Conclusions

The development of a model through formulation of a flow diagram, mathematical representation of the fluxes, parameterization and subsequent evaluation can improve our understanding of a system and take us closer to the ultimate goal of predicting responses. To achieve the end-point of a realistic model requires adequate mathematical input and the availability of appropriate data. However, some progress can be achieved in terms of both clarifying experimental objectives and developing research hypotheses through the first step of constructing a flow diagram. Considerable benefits in understanding the functioning of the whole animal may be gained by adopting a multi-disciplinary approach at this stage, since, for example, biochemists and nutritionists tend to view metabolism from different angles, and a combination of their skills will lead to a better representation. Thus the modelling approach provides a useful framework within which to structure a research programme.

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