Metabolic Constraints on Voluntary Intake in Ruminants

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ABSTRACT: The weak point in all current methods or models of diet formulation is the prediction of intake. The major uncertainty is not in the cases in which physical constraints apply, but in those in which voluntary intake is limited by feedback from metabolic factors. Voluntary intake is, ultimately, a psychological phenomenon, involving the integration of many signals, and reflects the flexibility of biological systems evolved to cope with variability in food supply, composition and animal state. Conditions giving rise to regulatory signals may provide a framework for modeling metabolic constraints on intake. The empirical evidence for metabolic feedback shows that the animal's productive potential, which affects its ability to utilize nutrients, interacts with the balance of absorbed nutrients to regulate intake. The relative importance of the sites where nutrient imbalance occurs (microbial or host animal metabolism) is unclear, as is the relevant time scale (minutes or days) of response. A model of the effects of asynchrony of nutrient supply to ruminal microbes suggests that ammonia and microbial recycling and the contribution of hind-gut fermentation reduce the asynchrony in the balance of nutrients absorbed into the bloodstream. Hitherto, rather little progress has been made in mathematical modeling of the metabolic processes controlling intake. Models that describe the phenomenon in terms of global variables, such as total energy intake, protein supply, and protein synthetic capacity, can simulate the way constraints may operate without requiring or providing a deeper understanding of the metabolic processes involved. Models describing the flux of energy and materials down established metabolic pathways have the potential to explore constraints on intake, but until the problem of parameterizing such models can be overcome, that potential will remain untapped.

Key Words: Ruminants, Voluntary Intake, Metabolism

Introduction

Food intake is the most important factor determining animal performance, and yet the prediction of intake is the weak point in all current methods or models of diet formulation. Forages of low digestibility are thought to place constraints on intake, which arise from their slow clearance from the rumen and passage through the gastrointestinal tract, and prediction of intake by modeling these processes has shown good agreement with observed intake in cattle and sheep fed a range of forages (Illius and Gordon 1991, 1992). More highly digestible feeds can potentially be eaten in greater quantities before the presumed physical constraints of gut clearance apply, and voluntary intake is then more likely to be determined by metabolic constraints related to the animal's ability to utilize absorbed nutrients. The role of metabolic constraints in controlling intake of low quality forages has been demonstrated (Egan, 1977), resulting in serious reappraisal of whether physical constraints are the major determinant of intake of such forages (Tolkamp and Ketelaars, 1992; Mathison et al., 1995). The proposed metabolic constraint of Tolkamp and Ketelaars (1992), however, is contentious (Emmans and Kyriazakis, 1995). At present, the major uncertainty in the prediction of intake lies not in the cases in which physical constraints apply, but in those cases in which voluntary intake is limited by feedback from metabolic factors. We review some of the evidence for metabolic control of intake and examine progress in the mathematical modeling of metabolic constraints. Before proceeding, it is worth noting that the probable reason that voluntary intake is so difficult to predict from first principles is that it is, ultimately, a psychological phenomenon. That is to say, it involves the neural integration of many signals and is subject to psychological phenomena such as perceptual constraints and learning (Illius and Gordon, 1993; Provenza, 1995). It reflects the flexibility of
biological systems evolved to cope with variability in food supply and composition and animal state. Although we now have some understanding of what some of these signals might be (e.g., Baile and McLaughlin, 1987), the elucidation of how their integration is affected by the animal’s physiological and mental state remains an important challenge.

In this article, we present a conceptual framework for considering metabolic constraints on intake and discuss the role of modeling in investigating the control of intake. We caution that simplistic models may produce the wrong answers, and we illustrate this with an example of how nutrient ratios may affect intake via microbial and host metabolism. Lastly, we address the problems and potential of more detailed mechanistic models.

A Conceptual Framework for Considering Metabolic Constraints

Assume that an animal has, at any point in time, some maximal productive capacity. Such a capacity will depend on its genetic potential for, e.g., growth or lactation, and will vary over the animal’s lifetime, according to its stage of growth, reproductive status, physical and climatic environment, ability to store any surpluses, and so on. It follows that the animal has some maximum rate at which it can utilize or dispose of nutrients and energy-yielding substrates (which, for present purposes, we will include in the term nutrients). The ratio of those nutrients will depend on the mix of purposes to which they are put, such as protein or fat deposition, lactation, thermoregulation, or locomotion. In other words, the inputs required will depend on the outputs to be achieved, such that an exact balance between inputs and outputs exists that leaves unchanged the state of body stores. The mixture of foods that can provide these quantities of nutrients could be defined as the optimal diet. The economically optimal diet will depend on the cost of ingredients and the value of the products. Some deviation from this can be accepted, provided that body stores can be added to or depleted to balance intake with requirements at maximal production. Surplus amino acids can also be deaminated, subject to some limit (see Kyriazakis, 1994), and surplus minerals may be excreted (e.g., Ca, Manston, 1967; P, Clark et al., 1973). Such a diet matches requirements less exactly, but is still nonlimiting (Emmans, 1991; Kyriazakis, 1994). Further deviations from the optimal diet, such as would cause a deficit of an essential amino acid relative to the other nutrients absorbed, may cause the animal to compensate by eating more, provided it can dispose of the surplus nutrient in surplus. Such a response is commonly found in simple-stomached animals such as chickens and pigs (Free- man, 1979; Kyriazakis et al., 1990) but may be absent from ruminants offered diets varying in protein content (Ranhotra and Jordan, 1966; Orskov et al., 1971, Kyriazakis and Oldham, 1993). If the animal cannot compensate for dietary imbalances by eating more, perhaps because it is constrained by the ability to dispose of the surplus nutrients, then production must decline, because the ability to call on reserves is exceeded. Yet further deviation from the optimal diet will cause the animal to reduce its intake (e.g., in lambs; Rogers and Egan, 1975).

This conceptual model of metabolic constraints on intake is presented in Figure 1a, showing the response of an animal (a sheep at half of its potential mature size) aiming to achieve its nutrient requirements for target protein and lipid deposition from diets with various ratios of metabolizable protein to metabolizable energy. Protein and energy requirements for maintenance and potential protein growth were calculated according to the method of Illius and Jessop.
Figure 2. Pathways of acetate clearance (a) and glucose requirement for lipogenesis (b).

(1995) and lipid deposition allometrically related to lean deposition. Food intake is assumed to be constrained by the maximum possible rates of heat loss and protein catabolism, and the heavy line in Figure 1a gives the maximum feasible intake, subject to these constraints, and that minimizes excess nutrient intake. The optimal diet lies at the intersection of the two lines, giving protein and energy intakes requirements. The position of the protein requirement line, and hence the optimal protein:energy ratio, will be markedly influenced by the biological value of the absorbed amino acids. This will be affected by microbial activity, composition of bypass protein, and the aggregate pattern of amino acids required by the animal’s tissues. At present, the rates of turnover of individual essential amino acids in an animal’s body have received little attention, and it is not possible to predict quantitatively the short-term effects on amino acid patterns available to cells. The model is modified in Figure 1b to reflect the animals’ intolerance of large nutrient imbalances (leading to reduced intake; see above). Below the optimal protein:energy ratio, compensating increases in food intake will result in increased lipid synthesis due to the excess energy intake. Lipogenic capacity may itself be limited, for example in early-lactation rats in which the elevated levels of growth hormone inhibit lipogenesis (Marenchenko et al., 1992), resulting in an inability to increase fat mass (Pine et al., 1994). At protein: energy ratios greater than optimal, the increased deamination provides energy, abating the additional requirement for energy to match protein intake. Increased N losses may be economically and environmentally undesirable.

Nutrient imbalances are presumed to constrain intake because of the build-up of the excess metabolite. For example, acetate clearance in adipose tissue is dependent on a supply of glucose to balance the NADPH and ATP requirements for triglyceride formation with the supply of these from acetate catabolism (Figure 2). Without adequate glucose, blood acetate rises and the resulting metabolic feedback would presumably cause intake to be reduced. It can be seen (Figure 1) that this will only occur at low protein: energy ratios, where there is a deficit of gluconeogenic precursors. The modeling of the regulation of metabolic pathways themselves is a complex theoretical field (Crabtree, 1993).

The sensory element of animals’ responses to nutrient imbalances is regarded as involving sensations of discomfort or malaise, which cause reduced intake or avoidance (Provenza, 1995). Animals seem to use these sensations and other aspects of “post-ingestional feedback” to avoid nutrient imbalances and toxins and to modify nutrient intake if they are given the opportunity to select from an adequate range of dietary ingredients (Burritt and Provenza, 1992; Provenza et al., 1994). Neural mediation of the response to aversive stimuli, and the involvement of the emetic system, particularly the area postrema, is currently the subject of active research (Provenza, 1995).

The foregoing introduces the main elements of a theory of metabolic constraints on intake: animal state and productive capacity, the animal’s allocation of nutrients to maintenance and productive activities, the corresponding optimal diet, and its tolerance of deviations from the nutrient ratio supplied by the optimal diet. We must also introduce the dynamic element, by addressing the time scales over which the animal responds to fluctuations in nutrient supply and makes allocation decisions. Because the animal’s physiological and behavioral responses to nutrient intake depend on its state, and because its state is in turn affected by nutrient intake, we observe a sequence of states and responses that depends on time. This is not merely a consequence of the time lags between eating and absorption, but raises questions about how animals prepare for future states, such as
by building up body reserves to offset the risk of future food shortages. The problem of dynamic optimization of state-dependent behavior has received much attention recently in the burgeoning literature on optimality approaches to diet selection (Stephens and Krebs, 1986; Newman et al., 1995). Optimality theory assumes that natural selection tends to maximize fitness (i.e., survival and reproduction, or lifetime reproductive success), and it follows that animals have evolved to make decisions that, in their natural environment, would give the best achievable balance between benefits and costs. To generalize, we can say that the value to an animal of performing an action, such as eating a certain quantity of food A, depends not only on current factors such as its state of hunger, body reserves, the use to which the food could be put, and the opportunity cost of that action, but also on the consequences for the animal’s future states. An example of a state-dependent decision with long-term consequences is the dependence of ovulation rate on degree of maturity in body mass and on body condition (Robinson, 1990). This represents a trade-off between increased offspring output and reduced offspring and maternal survival. Thus, “decisions” animals make about food intake, diet selection, and allocation of nutrients to growth and reproduction can be seen against the background of the optimal life history strategy, whereby decisions and the underlying physiological mechanisms leading to increased lifetime reproductive success are under natural selection. This argument may seem esoteric to those who work with the physiology and nutrition of farm animals, but two points should be remembered. First, the duration of artificial selection is extremely short, compared with the preceding period of natural selection, and farm livestock therefore retain many characteristics adapted to survival in the wild. Second, it is not true that animals in managed systems cannot make decisions of the type reviewed above: voluntary intake and the relationship of growth, body condition, and reproduction are good examples of responses that managers cannot truly control but with which they must work.

Accepting that the decisions animals make have consequences for their fitness, it follows that the ability to limit voluntary feed intake, according to the costs and benefits, will be likely to have evolved under natural selection. This point was well made by Tolkamp and Ketelaars (1992), although it should be added that natural selection will tend to solve the actuarial problem of the future schedule of costs and benefits. This reinforces the need to think of the control of food intake in dynamic terms, with explicit reference to time scale.

Relationship Between Animal State and Metabolic Feedback

One recent line of evidence that rates of nutrient utilization are involved in the regulation of intake comes from the effect of animal state on diet selection under choice feeding. Starting from classical approaches to self-selection of diets (e.g., in pigs: Evvard, 1915; in rats: Richter et al., 1938), Emmans, Kyriazakis, and co-workers at Edinburgh have shown that, given an appropriate choice of feeds, chickens, pigs, and sheep select nutrient ratios that match their requirements. The form of these trials typically involves offering a choice of two feeds differing in one constituent, such as protein, for a number of days or weeks. An initial period of learning greatly improves the performance of the animal throughout the choice period, suggesting that they are capable of learning the metabolic consequences of consuming a particular food. Growing pigs offered isocaloric feeds differing in protein content selected a combination with a protein concentration that matched their declining requirements for protein deposition as they increased in size (Kyriazakis et al., 1990). Where neither of the two feeds was capable of providing a sufficiently high protein concentration (i.e., both feeds were limiting in protein), the pigs preferred the highest protein feed, with less than 30% of the diet comprising the more limiting feed. Moreover, when both feeds offered had a higher protein content than that required, the pigs avoided excessive protein intake by choosing predominantly (i.e., more than 90% of the diet) the feed with the lower protein content. This showed clearly that pigs could select a diet that matched their changing requirements and could avoid nutrient imbalances. Even more strikingly, Kyriazakis and Emmans (1991) showed that young pigs selected diets that compensated for a preliminary period of feeding that made them either relatively thin or relatively fat for their size and therefore for their assumed “desired” fatness at a given protein weight. When both groups were offered the same two feeds, they selected distinctly different diets that allowed them to grow both fat and protein at different rates, such that the body composition of the two groups had converged by the end of the experiment.

It might be thought that ruminant animals face a more complex problem in selecting a diet, because digestion and metabolism in the rumen is interposed between the nutrient ratio of foods eaten and the nutrient ratio absorbed. Cropper (1987) and Hou (1991) confounded the skeptics by showing that sheep selected a diet with a protein content that varied consistently with degree of maturity and with time, and, using operant conditioning, that sheep were prepared to perform work to maintain the composition of their diet (Hou et al., 1991). Further evidence of the association between nutrient requirements and diet selection in sheep was provided by Kyriazakis and Oldham (1993), who offered lambs growing between 23.5 and 45 kg one of six isocaloric diets (11 MJ)/kg, based on molassed sugar-beet pulp and sweet potato) and with metabolizable protein:energy ratios ranging from 4 to 14 g/MJ, either alone or as a choice with the
highest protein feed. Food intakes were not significantly different between treatments, as might be expected from Figure 1. Comparison of protein deposition in the sheep offered single diets with that in sheep selecting between two feeds showed that sheep selected diets that maximized their growth rates by avoiding diets too high or low in protein relative to energy (Figure 3). It was notable that the intakes of sheep offered single feeds low in protein showed no evidence of compensation to achieve higher protein intake. Without knowledge of the ability of the patterns of absorbed amino acids to meet the animals' requirements, the optimal protein:energy ratio cannot be defined. Kyriazakis et al. (1994, 1996) subsequently provided more definitive evidence of the link between requirements and intake in growing sheep, by two routes. First, they observed diet selection over a sufficiently large growth interval (20 to 80 kg live weight) to demonstrate the decline in the selected protein concentration as requirements for protein deposition declined. Second, they manipulated protein requirement using subclinical infections of intestinal nematode larvae. Gastrointestinal parasitism is associated with endogenous protein loss from the mucosa and from invocation and maintenance of the immune response (Poppi et al., 1986; Kimambo et al., 1988). Lambs were offered a choice between a high and a low protein feed, with or without daily oral dosing with parasite larvae. After establishment of the infection and before the build-up of immunity, dosed lambs had reduced feed intake but increased selection of protein, compared with controls, with the result that daily protein intake was maintained.

Synchrony of Nutrient Ratios in Microbial and Animal Metabolism

The classic work of Egan (1977) showed that the intake of poor quality forages could be improved by increasing the supply of protein relative to energy in the absorbed nutrients. Additional protein was supplied post-ruminally, and no changes in the digestibility of the diet were observed. This work is widely taken as evidence of absorbed nutrient balance influencing the intake of even poor quality diets. Other studies (Leng, 1990) have demonstrated a similar increase in intake when poor quality forages were supplemented with ruminally available nitrogen. This has led to consideration of nutrient balance at two levels, that of the rumen and that of the nutrients absorbed by the animal, although these are inextricably linked, as will be discussed.

Asynchrony in Nutrients Supplied to Rumen. Most of the nutrients absorbed from the gastrointestinal tract are of microbial origin, unless diets contain significant quantities of digestible materials that escape ruminal fermentation. Consequently, the efficiency with which microbes utilize feed resources and the factors that impinge upon this have received much attention. There exists an optimal nutrient balance for rumen microorganisms, just as with more complex organisms, and failure to achieve this balance results in reductions in the efficiency with which nutrients are converted into compounds that can be used by the host animal. Asynchrony in the supply of nutrients to microbes has been reported to have a large impact on the efficiency with which substrates are fermented and on the rate of microbial growth (Beever, 1993). Restriction of the supply of ruminally available nitrogen relative to energy severely limits microbial growth and activity and can lead to a reduction in the rate of forage digestion (Leng, 1990). Restriction of the supply of fermentable carbohydrate relative to nitrogen similarly limits microbial growth and activity and results in an inefficient use of amino acids because greater amounts will be deaminated, increasing the loss of nitrogen from the animal in urine.

Recent energy and protein systems (Sniffen et al., 1992; AFRC, 1993) recognize the need to supply the correct balance of fermentable nitrogen and carbohydrate to ruminal microorganisms in order to maximize ruminal efficiency. Recently, there has been much attention given to the synchrony of supply of these two nutrients. Determination of the total nutrient supply at the level of the rumen is complicated by the fact that ruminally available nitrogen arises not solely from the feed but also from endogenous sources (Leng and Nolan, 1984). Failure to adequately represent this endogenous contribution can result in the wrong conclusion being reached.

Sinclair et al. (1993) examined the effect of asynchrony in the supply of fermentable nitrogen and carbohydrate on the production of fermentation end
products, namely microbial outflow from the rumen and VFA production. They formulated two contrasting diets that, from consideration of their degradability parameters (Ørskov and McDonald, 1979), were predicted to vary widely in the rate of provision of fermentable nitrogen and carbohydrate. From consideration of the rate of nutrient supply solely from the feed, it was predicted that ruminal microorganisms would be limited by the supply of ruminally available nitrogen for much of the day, but an empirical test failed to show significant effects. They did not, apparently, consider endogenous contributions to ruminally available nitrogen, which arise principally from urea entry to the rumen in saliva and by diffusion across the rumen wall, sloughing of cells from rumen epithelium, and recycling of microbial matter in the rumen. In addition, the dynamics of ammonia turnover in the rumen (i.e., ruminal outflow, rate of absorption of ammonia) influences the contribution that ammonia can make to the nitrogen requirements of microorganisms.

We examined the effects of these influences by simulation modeling (Jessop and Illius, unpublished results). The model uses the description of Sinclair et al. (1993) for feeds and their degradation characteristics, but is otherwise based on that of Illius and Gordon (1991, 1992) and Gordon and Illius (1996). The model described for predicting nutrient supply to ruminal microorganisms has also been used to predict nutrient absorption from the digestive tract (Gordon and Illius, 1996). Briefly, microbial growth and VFA production from supplied nutrients were described using relationships and stoichiometries of Reichl and Baldwin (1975). Two separate pools of ruminal microorganisms were represented: one associated with particulate matter, which was assumed to receive all slowly released nutrients and 25% of quickly released or soluble nutrients as well as all of the urea input from saliva, and one pool associated with free liquid, which received 75% of quickly released nutrients and urea input across the rumen wall (Czerkawski, 1986). Water flows in the rumen were from salivary (Bailey, 1961) and feed input and osmotic flux across the rumen wall (depending on the osmotic gradient between ruminal liquid and blood, ruminal surface area and water permeability of rumen epithelium [calculated from data of Argyle and Baldwin, 1988]). Free liquid outflow was varied to maintain ruminal volume within predefined limits (Illius and Gordon, 1991). The water-holding capacity of ingested feed was predicted from the NDF content (Ramanzin et al., 1994), and the small particle outflow rate was as given by Illius and Gordon (1991). The digestion of microbial matter and protein that passed out of the rumen was described following AFRC (1993): unfermented but potentially degradable fiber is further fermented in the hindgut assuming microbial activity similar to that in the rumen.

Predicted patterns of microbial protein requirement and dietary protein supply are compared in Figure 4 with and without endogenous recycling of microbial protein and NH₃, and including endogenous recycling of microbial protein (O) and NH₃ (◊) (b).

Figure 4. Predicted patterns of microbial protein requirement (∗) and dietary protein supply (O) (a) without endogenous recycling of microbial protein and NH₃, and including endogenous recycling of microbial protein (O) and NH₃ (◊) (b).
into question the wisdom of supplying ruminally available nitrogen in proportion to energy (AFRC, 1993) without any consideration of diet fermentability or feeding frequency. A significant reduction in dietary nitrogen supply could have been made without limiting ruminally available nitrogen supply.

With endogenous sources of nitrogen providing a background rate of ruminally available nitrogen, it is essentially the level and pattern of intake that will determine the extent of asynchrony. At low levels of intake, or under conditions in which the rate of intake is low and fairly constant (e.g., grazing), any asynchrony in dietary nutrients will be masked by endogenous inputs. It is only when intake is high enough to exceed this nitrogen input that significant asynchrony would be observed.

Asynchrony in Nutrients Absorbed from Gut. The rate of ruminal fermentation depends upon the fermentability and balance of nutrients available to ruminal microbes and can vary widely over the course of a day, particularly in meal-fed animals. Imbalance in the ratio of absorbed nutrients occurs when the two main end products of fermentation, microbial matter and VFA, are presented for absorption at different rates, which are influenced by the pattern of outflow of material from the rumen. Ruminal contents can be divided into a number of pools that each have different outflow rates with two pools (that of free liquid and that of small particles with their associated bound liquid) subject to varying relative outflow (Czerkawski, 1986). Volatile fatty acids are distributed equally between both pools, whereas microbial matter is substantially more concentrated in the bound pool. Volatile fatty acids are absorbed across the rumen wall at rates determined by the concentration difference of the undissociated acids between ruminal fluid and blood, the ruminal surface area, and the permeability of biological membranes to these acids. The effective concentration of the undissociated acids is relatively low in the rumen because ruminal fluid pH is usually significantly greater than the acids’ pKa. However, as VFA are washed out of the rumen with liquid outflow, the concentration of undissociated acids will be much greater as digesta enter the abomasum because the pH of abomasal contents is much lower than the pKa value. Variation in liquid outflow rate can therefore result in marked differences in the rate of VFA absorption. The microbial matter washed out of the rumen is associated principally with particulate outflow (Czerkawski, 1986). The pattern of outflow of pools varies, and it is likely that it is this variation that will cause the major change in balance of absorbed nutrients over time. Over a meal cycle there is marked variation in the liquid outflow rate from the rumen (Warner and Stacy, 1968). Depending on the characteristics of the feed, this can have quite different effects on the pattern of nutrient absorption. Water is held in the rumen as a consequence of the osmotic potential of ruminal contents relative to that of blood (Argyle and Baldwin, 1988) and as a consequence of rumen size. Consumption of feed, depending on its soluble ash content, alters the osmolarity of ruminal fluid and can result in considerable inflow of water from blood across the rumen wall. To maintain ruminal volume, outflow must increase. This results, initially, in an increase in the rate of delivery of VFA to the omasum and abomasum where, because of the low pH, absorption will be rapid and essentially complete. The microbial concentration in the free water pool is generally low (Czerkawski, 1986) and thus the protein to energy ratio of absorbed nutrients would fall immediately after eating because of the absolute amount of VFA being absorbed increasing. Depending on the soluble nutrient content of the feed and the degradability of those nutrients, the increase in microbial numbers in the free water pool can be rapid after feeding, causing an increase in microbial protein outflow with time. This would cause the protein to energy ratio of absorbed nutrients to increase. The predicted pattern of nutrient absorption is shown in Figure 5. It can be seen that the ratio of protein to energy varies to a greater extent in the “synchronous” diet of Sinclair et al. (1993) than it does in the “asynchronous” one, primarily because of the greater fermentability of this diet causing changes in the pattern of liquid outflow described above. At present, there is a paucity of data describing the patterns of liquid and particulate outflow from the rumen during a meal cycle, i.e., in non-steady state conditions. Nearly all experimental work has attempted to maintain steady-state by constant, low-level feeding over the 24-h period when large fluctuations in ruminal dynamics are unlikely.

Modeling Metabolic Constraints on Intake

Mathematical modeling is primarily a way of figuring out the consequences of one’s assumptions. It may thus lead to improved understanding of how complex systems work, and this or the model itself may eventually have some use as a predictive tool. Models of the metabolic and physiological constraints on intake can be viewed as falling into two categories: phenomenological models and process (or mechanistic) models. At the extreme, the former type of model aims to capture the main properties of the system’s behavior with the smallest number of parameters. Far from attempting a thorough description of the underlying processes, the aim of this type of modeling is to eliminate unnecessary detail. Verisimilitude in the depiction of the deeper causal relationships is neither sought nor obtained. Model behavior resembles the surface phenomena much as the terms in a polynomial represent the underlying complexities of response to the independent variable across its range without being explicit about the details. By limiting the number of parameters to the fewest possible, it is
Figure 5. Predicted patterns of the ratio of absorbed nutrients from “synchronous” (●) and “asynchronous” ( ○) diets.

possible to determine how the system responds to alteration of the conditions, as clearly defined by the parameter values. Process models, in contrast, aim to go much further in describing the underlying causal relationships and are, in principle, capable of representing the complexities of the system more faithfully, but often risk becoming bogged down in detail. As more and more factors are included, it becomes harder to see what is going on. In practice, there is considerable overlap between these two approaches to modeling. The former has to recognize the web of multiple causation, whereas for the latter, the attempt at a complete representation of every causal link is futile and has to be abandoned at some point. The short history of metabolic modeling, reviewed below, reflects this tension between reproducing the phenomena and understanding their causation. Models aimed primarily at intake prediction under physical constraints have recently been reviewed elsewhere (Illius and Allen, 1994).

Following the description of meal patterning in rats (Booth, 1978), Forbes (1980) developed a model to examine the interactions between metabolic control and physical limitation of eating behavior and feed intake in ruminants. The assumption was that animals would satisfy their energy requirements, subject to a physical constraint imposed by rumen capacity. Literature estimates of the relation between food digestion and passage rates were used to derive estimates of the rates of energy absorption and the quantity of food residues. Meal patterning was the outcome of a process whereby the rate of energy supplied by digestion was compared with the rate of energy utilization in maintenance, lactation, and growth and thresholds assigned to initiate and terminate eating, subject to physical constraints. The behavior of the model was not particularly sensitive to the values used for these thresholds. An alternative possible mechanism to that of dual thresholds is that of positive feedback, in which positive reinforcement of a decision is required in simulation models of decision making between behavior resulting from competing motivational states to prevent “chatter” or rapid switching between behaviors (Houston and Sumida, 1985). Because food intake in the Forbes models is, in effect, bounded approximately by the upper limit on energy utilization and the lower limit imposed by gut capacity and passage rate, all of which are inputs, the model obviously predicts intake well. The pattern of meals was also realistic, suggesting that the model gave a good representation of the surface phenomena, and the model clearly had heuristic value in showing that ruminant feeding behavior could be simulated numerically. On the other hand, the underlying mechanisms are probably somewhat different, and inevitably more complex, than those depicted. Throughout the animal kingdom, the satiation process seems to be under tight, preabsorptive sensory control (Smith and Gibbs, 1979). Most animals eat discrete meals that end before absorption of all the ingested nutrients can take place, suggesting that the origin of satiety signals is the gastrointestinal tract (Houpt, 1982; Le Magnen, 1985). Meals are terminated in expectation of the postabsorptive consequences rather than being solely the result of them, and thus satiety is a state partly specified by the stimulus conditions (Booth, 1985; Provenza, 1995). For example, the sense of taste plays a role in the termination of feeding (Swithers and Hall, 1994).

The study of the integration of chemostatic and physical constraints on ruminant feed intake was also the purpose of the model of Fisher et al. (1987). One of the objectives was to redress the omission of chemostatic feedback from the model of Mertens and Ely (1979). The method of incorporating feedback controls could be said to follow McClymont’s (1967) dictum that a balance is struck between all the negative and positive stimuli, rather than there being separate set-points or thresholds for each. They achieved this by a mathematical formulation expressing intake as a function of ruminal distension and nutrient flow. The function contains a double exponential term intended to capture the strength of each stimulus in relation to the other (i.e., chemostasis being generally weaker than distension signals, especially at high distension, but stronger at low distension). Investigation of the effect of varying the parameter values demonstrated how the relative strength of the stimuli could be altered, and values were found that gave good approximations between observed and predicted intakes. This is a clear example of the causation-free phenomenological approach, integrated with the more mechanistic Mertens-Ely description of digesta kinetics.

Neither Forbes (1980) nor Fisher et al. (1987) attempted to represent the mechanisms of intake
control in great detail, and therefore did not address mechanisms. An alternative approach, that of describing as far as possible the underlying metabolic processes, has been pursued by a number of authors, notably Baldwin et al. (1980, 1987) and Gill et al. (1984). These models described whole-animal metabolism in terms of the known biochemical pathways, with metabolites as state variables, and computed reaction velocities according to Michaelis-Menten kinetics, using parameter values estimated to yield sensible results at tissue level. The parameters are $V_{\text{max}}$ and $K_m$, the Michaelis-Menten constant, but may also include terms representing phenomena such as end-product inhibition and sigmoidal responses to substrate concentration. Baldwin et al. (1987) treated separately the metabolic transactions in the viscera (blood, liver, gastrointestinal tract, heart, udder, and lungs), adipose tissue and the remaining lean body, but allowed perfect communication between them. Gill et al. (1984) treated all transactions as occurring in a single pool, equal to blood volume. In both models, flux per unit mass of tissue was determined by the Michaelis-Menten parameters, and whole tissue flux was then calculated from the mass of tissue, with changes in tissue mass due to growth or catabolism being a dynamic component. One of the problems with these very detailed models is the difficulty of reaching satisfactory estimates of critical parameter values, especially when experimental work and modeling are not performed in harmony (Baldwin and Sainz, 1995). Even when they are, it is not clear that single, static values for parameters are a satisfactory representation of a system as dynamic and adaptive as intermediary metabolism. Baldwin et al. (1987) attempted to address this by varying values for $V_{\text{max}}$ and $K_m$ in the manner expected under hormonal influence. It may be doubted whether the “fully-detailed” pathway to modeling will ever have sufficient information to complete the task satisfactorily.

Popp et al. (1994) used the Gill model to examine the integration of intake regulation, the approach being to identify pathways that could limit intake and to calculate the first limiting pathway or factor. Both physical and metabolic pathways were examined, namely instantaneous intake rate, fecal output, ruminal fill, genetic potential for protein deposition, heat dissipation, and ATP degradation. The “ATP degrader” required by their model to avoid a build-up of ATP was used as an indicator of excessive energy intake or nutrient imbalance. This pathway was found to be limiting, sometimes simultaneously with other pathways, on diets ranging from poor-quality forages to cereals, and the authors concluded that this is indicative of the wide range of dietary conditions under which nutrient balance is implicated in intake regulation.

Illius and Jessop (1995) modified and extended the model of Gill et al. (1984) by generalizing the description of animal characteristics, distinguishing between protein synthesis and breakdown, and adding acid/base control. Metabolic activity was partitioned between two sites, liver and body, with simulation of blood flow and the diffusion of metabolites among blood, extra cellular fluid volume, and intracellular fluid volume. Together with some minor changes to the modeling of acetate metabolism, these changes removed the requirement for an ATP degrader, the excessive intake of energy or nutrient imbalance being indicated by a build-up of acetate instead of ATP. The purpose of the model was to examine the relation between nutrient intake and the intake of allelochemicals, the costs of detoxification, and the implications for diet selection by foraging ruminants. Many allelochemicals are excreted following conjugation, leaving a dissociated proton that perturbs acid/base status, requiring increased formation of bicarbonate. Conjugation and maintenance of acid/base status was shown to cause catabolism of amino acids and to result in loss of body protein and depletion of glucose. An interaction between the ability to maintain acid/base homeostasis and nutrient status was found, and the tolerance of the animal to absorbable allelochemical concentration in foods was defined by the ratio of allelochemical to nutrient absorption rate. The somewhat unexpected implication for diet selection was that animals with high nutrient status should be able, and thus perhaps willing, to eat higher amounts of allelochemical-containing foods than animals with lower nutrient intakes. It would normally be expected that the deterrent effect of allelochemicals would be overcome in hungry animals. However, the predictions are in line with observations that animals facing depletion of food resources during winter often discard or avoid current season’s growth of woody browse in preference for more mature growth (Bryant and Kuropat, 1980; Provenza and Malechek, 1984). Current season’s growth is less lignified than older twigs and thus is more digestible, but allelochemical concentration is also higher in current growths and acts as a strong deterrent to browsing (Bryant, 1981). We tested this prediction of the model by offering rats ad libitum quantities of an energy-rich but protein-deficient diet containing menthol or anisole together with one of four levels of a separate casein supplement (N. J Jessop, A. W. Illius, M. McDonald, and L. Wells, unpublished data). We previously found that these allelochemicals provoked the production and urinary excretion of significant quantities of glucuronic acid. The prediction that animals given larger amounts of protein supplement would eat larger amounts of the allelochemical diet, rather than less of it, was born out ($F_{3,32} = 13.63, P < .001$; see Figure 6). The hardest tests of a model being its ability to suggest an unexpected hypothesis, and for that to pass an experimental test, our results represent a vindication of the modeling exercise as an investigative tool.
Implications

Our conceptual model of metabolic controls on intake defines the optimal diet in terms of the animal’s ability to utilize nutrients, subject to constraints imposed by its ability to dispose of surplus. Optimality theory provides the background to such an approach, and applied studies would sometimes benefit from the wider perspective it offers. Nutrient balance experiments need to focus on the real issues: how far intake and nutrient utilization are actually constrained by ruminal and absorbed substrate ratios. Detailed metabolic modeling is most severely tested when it goes beyond explaining observed behavior to suggest unexpected hypotheses that can be experimentally tested. Although it seldom meets this challenge, we show that it can be done.

Literature Cited


Illius, A. W., and M. S. Allen. 1994. Assessing forage quality using integrated models of intake and digestion by ruminants. In:


