Use of Mechanistic Nutrition Models to Identify Sustainable Food Animal Production

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Abstract

To feed people in the coming decades, an increase in sustainable animal food production is required. The efficiency of the global food production system is dependent on the knowledge and improvement of its submodels, such as food animal production. Scientists use statistical models to interpret their data, but models are also used to understand systems and to integrate their components. However, empirical models cannot explain systems. Mechanistic models yield insight into the mechanism and provide guidance regarding the exploration of the system. This review offers an overview of models, from simple empirical to more mechanistic models. We demonstrate their applications to amino acid transport, mass balance, whole-tissue metabolism, digestion and absorption, growth curves, lactation, and nutrient excretion. These mechanistic models need to be integrated into a full model using big data from sensors, which represents a new challenge. Soon, training in quantitative and computer science skills will be required to develop, test, and maintain advanced food system models.
INTRODUCTION

Food animal production has been a component of agricultural output for more than 11,000 years (1). This is at least partially driven by the desire to consume animal products, which likely arises from consumption of meat during the preagricultural period (2). That desire continues today, as evidenced by increases in animal product consumption as expendable income increases (3).

The animal production system contributes to human-edible nutrients through provision of meat, dairy products, and eggs. Animal-based food products also contribute to human health, mainly in children. Global human health is being negatively affected by unbalanced diets and obesity in all countries (4). However, undernutrition is still a big problem in low-income countries (5), where billions of people consume diets that are deficient in energy or micronutrients (3). Animal proteins rank highest in protein quality, considering composition and bioavailability of essential amino acids (6). Animal products are an important source of many nutrients in the human diet. These positive factors must be weighed against the impact of animal production on the overall food supply and its environmental impact (7).

The world’s land mass is composed of 0.84 billion hectares that are permanently frozen or with growing seasons too short to produce significant vegetation (8), 6.1 billion hectares of arid land (9) with minimal vegetative output, 1.6 billion hectares suitable for grain crop cultivation and production, 4 billion hectares that are forested, and 1.8 billion hectares that are suitable for grazing (8). Considering output per hectare, the potential production of fibrous crops is approximately 31.2 million tonnes (mmt)/y and of grain crops is 2,980 mmt/y (8).

In comparison, there are an estimated 28.8 billion food animals in the world today, of which 3.9 billion are ruminants (cattle, buffaloes, sheep, and goats) or have significant hind-gut fermentation that can make extensive use of dietary fiber and 24.9 billion nonruminants that can make minimal use of dietary fiber (8). Accounting for animal size in each category yields 1,292 mmt of fiber-fermenting animals and 212 mmt of non-fiber-fermenting animals. If people (average mass of 62 kg; 10) are added to the latter category, the mass becomes 680 mmt today, and assuming no change in animal numbers, the non-fiber-fermenting world mass will grow to 814 mmt by 2050. These animals result in annual production of 248.1 mmt of meat (chickens, turkeys, ducks, geese, other birds, pigs, rabbits, asses, horses, mules, guinea fowl, other rodents, and terrestrial snails) and 87 mmt of eggs from non-fiber fermenters and 86.1 mmt of meat (cattle, buffalo, sheep, goats, camels, and other camels) and 827.9 mmt of milk from fiber fermenters per year. This approximates to 28.5 kg of protein and 561 Mcal of energy per hectare of arable land (~1.42 billion hectares) for fiber fermenters and 36.4 kg of protein and 584 Mcal of energy per hectare of arable land for non-fiber fermenters.

For both classes of food animals, improving efficiency of human-edible food production from a given land mass is a priority. In addition to expanding the food supply, this also reduces environmental impact. From mass balance, greater animal product nutrient capture per unit of nutrient consumed results in reduced nutrient excretion (11). Gains in animal efficiency have been very large where feed availability has been high owing to dilution of a fixed maintenance cost with greater rates of production (11).

Additional efficiency gains may have also occurred through improved nutrition. Imbalance of nutrients relative to requirements contributes to inefficiency, as excess nutrients, other than energy, are generally excreted. If vitamins, minerals, or amino acids are provided in inadequate quantities relative to the genetic potential for production, production will be reduced, or the animal will become sick and nonproductive. In such a case, other nutrients cannot be used at maximum levels, and the animal excretes them. Thus, although the efficiency of the limiting nutrient will be high, the efficiency of the other nutrients will be reduced. Balancing all the nutrients to achieve
equanimity relative to potential production avoids the problem, resulting in gains in efficiency. Such gains have been realized in all animal production species through the application of greater nutritional knowledge to feeding programs, but greater advances have been realized for non-fiber fermenters. For example, growing pigs can be fed to achieve 80% nitrogen (N) efficiency (12), whereas growing cattle typically achieve less than 40% N efficiency (13). Although a portion of the difference is due to inherent differences in dietary N digestibility, the absorbed efficiencies are also lower in beef animals. Additional focus not only on maximizing production to dilute out maintenance costs but also in achieving greater efficiency at a given level of production is required. This latter goal requires better knowledge of the mechanisms underlying requirements.

For complex systems such as the food system, models must be used to integrate the individual components to provide quantitative relationships between inputs and outputs. With adequate models, one can explore resource allocation subject to system constraints to identify optimum solutions under varying conditions. Models also aid in understanding the system and available knowledge, thus providing direction for further research (14, 15). Thus, the important driving mechanisms of a system must be captured in the models so that they are able to provide predictions of the full range of possible outcomes.

Because consumption of animal-source foods—and consequently livestock production—will continue to increase to supply humans with adequate protein and nutrients in both developed and developing countries (16), in this review, we discuss the development and applications of mechanistic nutrition models as a strategy to improve animal agriculture and its sustainability.

We include discussion covering all aspects of modeling from empirical to more mechanistic models; advantages and limitations; and current examples of models of nutrient digestion, growth, lactation, and nutrient excretion. In particular, we include a broad discussion of topics of interest, such as precision livestock farming, and integration of models, while highlighting the importance of mechanistic modeling for sustainable food production and challenges, as well as future directions.

NUTRITIONAL MODELING FOR SUSTAINABLE AGRICULTURE

Because the food system is complicated (Figure 1), unintended consequences can occur when changes are adopted based solely on an empirical assessment of an isolated piece of the system (17). For the most part, the system self-optimizes based on economics. An oversupply of output from one part of the system is taken advantage of by another part of the system, with output price driving rational use. However, if one desires to constrain the system to achieve goals that are not reflected in the current economic framework (an environmental goal) or to project outcomes for the future (a 50% increase in the required food supply), it is impossible to envision the resulting shifts in the system (18). It is also impossible to empirically test the impact of some changes, e.g., global climate change. Thus, systemic responses must be explored using models of the system.

The accuracy of such projections will depend on the adequacy of the model and the complexity of the question (19). If one is simply interested in the total food supply, submodels representing the parts of the food system likely could be fairly simple (20). However, if one is interested in the supply and use of individual key nutrients, such as energy, amino acids, vitamins, or minerals, the required complexity becomes much greater, and if one also desires to represent the impact of environmental stress and potential genetic adaption to such stress on the biological components of the system, the problem becomes very large. Finally, consideration of even a limited number of system modifiers, such as fertilizers, herbicides, insecticides, nutrient supply, probiotics, antibiotics, or management practices, requires even greater complexity in the underlying biological models.
Model Characterization

As France & Thornley (21) described, models can be used for data description or for predicting outcomes based on novel inputs. Biologists have used models for several centuries for both purposes (22), but the vast majority of use is for the former as part of the normal statistical analyses commonly performed to assign probabilities to treatment effects. All models consist of three elements: (a) the inputs or driving variables, (b) the parameters and model structure, and (c) the predicted outcome or output. Inputs are generally denoted using $X$ with a subscript to denote different inputs. Model parameters are generally denoted using Greek letters such as $\alpha$, $\beta$, and $\lambda$, and outputs as $\hat{Y}$, with a subscript to denote different predictions if there are multiple. Thus, a simple model can be denoted as

$$\hat{Y}_i = \alpha X_i + \beta.$$  \hspace{1cm} (1)

Models of both types can be further subdivided based on three criteria, again laid out by France & Thornley (21). Models that contain a time element—that is, they predict through time—are denoted as dynamic versus static models that do not contain time and thus predict a single outcome based on the inputs. Growth models provide an example of the former (23). These models will predict body weight at any point in the life span of an animal given inputs of age and any other driving factors required by the model. By comparison, one might also predict body weight from animal circumference. Provided the circumference-to-weight ratio is not a function of age, this
would be a static model. In this latter case, time, age, is not a driving element of the model, whereas animal circumference is a driving variable.

The second model descriptor denotes the treatment of variance. Equation 1 is a deterministic model in that it provides a single prediction for a given value of \( X \). Thus, sources of variation in the system are ignored. In contrast, a stochastic model explicitly represents variation sources. For example, if Equation 1 represents a biological function in an animal, then \( \alpha \) and \( \beta \) will be subject to genetic variance. Additionally, \( X \) will have measurement error, as will \( Y \). All four sources of variance can be explicitly represented in the model

\[
\hat{Y}_i \sim N(\mu_Y, \sigma_Y^2) = \alpha \sim N(\mu_\alpha, \sigma_\alpha^2)X_i \sim N(\mu_X, \sigma_X^2) + \beta \sim N(\mu_\beta, \sigma_\beta^2).
\]

In this case, they are modeled as normal distributions with a mean of \( \mu \) and a variance of \( \sigma^2 \) for each, but other variance distributions can be used. Alternatively, the variance can be aggregated into a single generic error term (\( \epsilon \)), as is typically done for statistical models:

\[
\hat{Y}_i = \alpha X_i + \beta + \epsilon_i \sim N(0, \sigma^2_\epsilon).
\]

Thus, there is a population of predicted outcomes (\( \hat{Y} \)) for each value of \( X \).

The third category defines models as either empirical or mechanistic. The former describes the class of models defined by Equation 1 if they describe animal performance, for example, as a function of energy intake. The key point is that predictions of output are made using inputs from the same level of aggregation or function, i.e., animal intake and animal output. However, a myriad of underlying mechanisms result in the positive relationship between energy intake and product synthesis, and these are not encoded in the equation.

Conversely, equations that draw on elements of underlying function to describe higher-level function are mechanistic. As an example, one can represent energy supply to the animal as a function of digested nutrients and animal performance as a function of nutrient partitioning to maintenance and production. This captures elements of function one level below the animal level and uses that information to predict performance. The lower-level process descriptions are empirical relationships (digestion, partitioning, and the yield of product per unit of nutrient supply), but the inclusion of lower-level function makes the model mechanistic. Essentially all mechanistic models are empirical at their lowest level. One can always descend another layer below the current, unless one has descended to a description of subatomic particles that truly represent the bottom level of aggregation. Thus, a food system model would by definition be a mechanistic model if it draws on submodels, e.g., crop and animal output.

### From Empirical to Mechanistic Elements

Early models of metabolic responses to nutrient inputs were empirical owing to the lack of underlying information and subsequently the lack of computational power. Knowledge of digestion and energy metabolism allowed Atwater & Bryant (24) to describe energy retention, heat production, and gas exchange as a function of nutrient intakes, heats of combustion, nutrient digestibilities, and nutrient use yielding physiological fuel values that are still in use today for some species. Over the last 120 years, efforts have focused on improving representations of nutrient and energy supply and the efficiency of energy and nutrient use by the animal, leading to ever more complicated models that have become more mechanistic (25–27). Nutrient supply subsystems consider ruminal degradation, microbial growth and action, intestinal digestion, and partitioning of nutrients to maintenance and multiple productive functions (25, 27). By aggregating the underlying subsystems, one can use knowledge gained from multiple experiments to describe animal function.
Such assembly and testing against additional animal performance measures provide another level of evaluation. Inadequate representations of an underlying process quickly become apparent when testing across a broad range of animal and diet types. Thus, model integration not only allows us to build from lower levels of function but also tests the completeness of the knowledge captured.

Smith (28) used these concepts to develop a model of the dairy cow by integrating cellular metabolism in 10 different body tissues. They identified several knowledge deficiencies that are still being addressed today. In general, there was an inadequate understanding of the quantitative aspects of metabolite metabolism for most tissues, including microbial metabolism in the rumen. Efforts were undertaken by the group at the University of California, Davis, over the subsequent 20 years, resulting in the development of several tissue models (29–39) that described tissue metabolism from cellular and subcellular processes. Key concepts from that work were used to reformulate the earlier animal model into a refined, more aggregated version (40–42) that remains in use for research purposes today. This latter model was used to identify another round of knowledge deficiencies that stimulated yet further experimental and modeling work (43–59). These efforts exemplify the potential value of using mechanistic models in concert with experimental work to evaluate knowledge sufficiency and identify areas of deficiency.

Use for Data Interpretation and Extension

Another use of models is in the interpretation and extension of experimental data. Every scientist uses statistical models to interpret their data. These are generally simple models that, in the case of analysis of variance (ANOVA), reduce to estimation of deviations from the study mean. However, the inclusion of covariate adjustments and linear or quadratic responses that reflect continuous variables results in models that begin to resemble Equation 3. Obviously, animals do not respond to varying nutrient supply in a discrete fashion, jumping from one ANOVA determined mean to the next. Thus, the use of continuous functions to represent the system begins to capture the true underlying mechanisms.

This approach has the added advantage of describing the system in mechanistic terms. Assessing empirical observations of transport activity for a tissue or cells by ANOVA may demonstrate that mean transport increases as substrate increases and that the process is saturable; however, it does not inherently provide biological parameters that can be used to understand the activity relative to substrate supply. Fitting a continuous function of the proper form yields estimates of affinity and maximal capacity of the system. These parameters can be observed to determine whether there was a change in affinity or maximal capacity in response to treatment. For example, one would expect amino acid transport rates to increase for muscle cells when treated with insulin. Assessing those rates at varying amino acid supply with high and low insulin and determining the maximal rate and affinity provides an indication of whether the response was mediated by increased active transporters (increased maximal rate) or by an alteration in the transporter protein conformation (increased affinity). This mechanistic model yields insight into the biological mechanisms and provides guidance regarding further exploration of the system.

Mass balance and knowledge of stoichiometry can be used to derive flux estimates for pathways that cannot be directly observed. Such mass balance models are generally designed to estimate additional fluxes within the system given constraints of available precursors, observed inputs and outputs, and known stoichiometric relationships (60, 61). These models may or may not include kinetic representations of the conversion among metabolites. van Milgen (62) developed a generic framework to construct mass balance systems that can be applied to a variety of problems. When applied to cellular or tissue metabolic networks, some aggregation of minor fluxes is generally undertaken, but because the major fluxes must be represented between each branch or pivot point,
they tend to be fairly detailed descriptions of the major pathways. Changes in the flux estimates associated with treatments can be compared with gene and protein expression data for proteins catalyzing that flux to identify potential driving mechanisms.

In many cases, mass balance solutions result in a range of possible solutions rather than a single unique solution. Although a range of possible solutions is not as satisfying as a single value, it still represents scientific progress. Consideration of nitrogen, carbon, and energy balance in addition to metabolite balance further constrains the problem and may result in unique solutions. The presence of bidirectional exchange fluxes is also problematic if information on the individual fluxes is desired. Mass balance approaches are able to derive only the net flux. Both identity problems can generally be resolved using appropriate isotopic tracers in combination with mass balance (49, 63–68).

When this work is conducted using steady-state observations, it can often be solved algebraically, but non–steady state data necessitate the use of dynamic models, and these models typically cannot be solved analytically. In such cases, numerical integration is used to solve the model with respect to time, and an optimizer is used to estimate fluxes based on minimizing residual errors using least-squares or maximum likelihood methods (49, 68). In such systems, the labeled fluxes are represented as a product of the unlabeled flux and the precursor pool enrichment. This ensures that isotopic movement in the system is linked to unlabeled flux. A critical assumption for all the tracer-based work is that tracer fractionation does not occur, which is not always the case (69).

Models of whole-tissue metabolism with isotope representations have been constructed (34, 70, 71), and studies have been conducted to collect data adequate for parameterization of the models (46, 72, 73). However, efforts to solve those problems proved intractable at the time. The major limitation was computation time, although experience with such large problems certainly contributed. The models required approximately 30 s to run to steady state. The latter data sets contained 200 or more observations for each tissue when the various isotopic tracers and substrate concentrations were considered. At 200 observations, 100 min were required to simulate all the data a single time. Optimizing 20 or 30 parameters using simplex or slope-based algorithms typically requires 2,000 or more interactions for convergence when the data have normal biological variance, and the initial parameter guesses are reasonably close to the final estimates, i.e., ±50%.

A single parameter estimate solution thus often required two weeks of computing time, and there was no information available for use in deriving reasonable initial parameter estimates for most of the substrate cycles; thus, the initial solutions were not meaningful. After a year of effort with little to show in return, other problems became more attractive to work on, and therefore these models remain unsolved in terms of parameter estimates.

Even if the problem had been solved for a reasonable parameter set, one should undertake solutions from multiple starting points to help avoid local solutions. This typically entails starting from initial parameter values that are set to values greater and less than the final estimate. Assessing all combinations of high and low for 20 parameters requires 1 million solves (220), which would have required 39,000 years of computing time on a single processor at that time. One would not likely need to assess all combinations, but even 10% of the combinations still approaches the half-life of the 14C isotope used in the experiments and greatly exceeds the life span of even the youngest and most naïve research scientist.

On current computers, each simulation would require 1 s or less, and the individual runs and the subsequent effort to ensure a global solution could be parsed to different processors within a large computing cluster, allowing a single solve in 30 min on 200 cores and the global solution in a few months on 10,000 cores if 10% of the possible combinations of starting points were explored. Thus, these models could be solved today. The key point is that mechanistic models are
generally much larger and thus computationally more expensive than small empirical models, and this should be considered when constructing the model and collecting the data. Making use of parallel processing on very large computing clusters is an absolute must when working with these types of models.

**ANIMAL PRODUCTION MODELS: THE MIGRATION FROM EMPIRICAL TOWARD MECHANISTIC REPRESENTATIONS**

Models of nutrient supply and requirements have been developed for all of the major animal agriculture species (25–27, 74, 75), plus species commonly used as models for human nutrition (76, 77). These models are generally composed of relationships at the animal level, with a few relationships representing some aspects of underlying function.

**Nutrient Digestion and Absorption**

Digestion models for monogastric species have generally been based on empirical representations of the process. Atwater & Bryant (24) described energy supply to the animal using static digestion coefficients for nonfibrous carbohydrate, protein, and lipids. Most current animal models of intestinal digestion continue to use such a representation, which implicitly assumes that digestion and absorptive processes can be reduced to a single fractional transfer coefficient that describes the entire process. This fails to capture any of the variation intrinsic to the feed or animal regulation of digestion and absorption. Feed variation has been addressed by defining a coefficient for each feed and summation of digested nutrients across feeds. This is an expedient solution that addresses the problem, but it does little to improve our knowledge of the feed factors that underpin the variance. The scientific effort that has been expended describing nutrient digestibilities for all the typical dietary ingredients for all the major animal species is substantial, and the work continues to allow ever-greater refinement of nutrient supply predictions. However, one must wonder whether, if even half of that effort could have been applied to gaining an understanding of the interaction of digestive elements with the ingredient matrix, we would now have a universal mechanistic solution that would negate the need of further ingredient description work.

Taghipoor et al. (78, 79) used a mechanistic approach including representations of the flow of digesta through the intestine, the effects of viscosity on mixing and diffusion of nutrients to the lumen wall, the reduction in digesta nutrient concentrations over time in the tract, and nutrient absorption. However, evaluations of the model were perfunctory owing to an absence of data, and thus it is unclear if the concepts encoded are truly consistent with the biological system. There has been much additional work on the representation of flow from the stomach and through the small intestine, where residence time and diffusion have been shown to be important elements. Despite the lack of data, the model provides an opportunity to begin to compare empirical observations of components of the system to evaluate the validity of the concepts used and the equation forms chosen.

The empirical models of digestion generally are fitted to total tract data and thus represent all elements of the tract, including the large intestine. The swine digestion model of Bastianelli et al. (80) is one of the few that specifically represented digestion within each compartment of the intestinal tract, including digestion and fermentation in the large intestine. Although measured data were inadequate to fit model parameters, the model did represent some of the phenomena described for different diets when compared with a moderately sized set of observations. This study highlights a major limitation of the mechanistic modeling, that of parameter identification. Each mechanism described in the model must be parameterized, and thus additional data are

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needed for such models that are not commonly available, requiring assumptions. Each assumption should be explored for its impact on the overall model and its conclusions. If the impact is small, efforts to collect the data required to derive the parameter are likely not worthwhile, but large effects generally should be explored experimentally.

Digestion and absorption in ruminants are further complicated by ruminal fermentation. Empirical models of ruminal fermentation have generally proven to be unsatisfactory owing to the complexity of the system. The large contribution of fermentation end products to the nutrient supply of the animal necessitated the creation of better models, which contributed to the development of mechanistic modeling in the ruminant nutrition field. Several models have been developed either as independent models or within larger animal model frameworks, with varying degrees of complexity (32, 81–85). Extensive testing of the Dijkstra and later Baldwin models has been undertaken (54, 86, 87), and these efforts have identified at least two mechanisms that remain problematic. Degradation rates of the insoluble protein and carbohydrate vary significantly across ingredients and even within sources. In situ incubations have generally been adopted to allow variation inherent to the ingredients to be used empirically as a driving variable, with moderate success. Errors of prediction of ruminal outflows are about 30%, but the error of measurement is high. Thus, it is not completely clear how much additional variation could be explained by a better characterization of the feed or of the degradation process.

The second area of deficiency encompasses microbial fermentation. The microbial population represents another diverse biological entity. The empirical representations used across these models predict microbial outflow from the rumen with 30% error, and predictions of volatile fatty acid production, the primary end products of fermentation, exhibit more than 20% errors with significant slope bias. The latter indicates that the model is inappropriately conceived relative to the true driving elements. Attempting to address the problem by incorporating thermodynamic mechanisms to control partitioning of carbon among the fatty acids provided no additional benefit (54), indicating that potential mechanism may not be a major factor within the range of diets commonly fed to lactating cows.

The problem appears to derive partially from inappropriate responses in microbial growth with respect to ruminal ammonia availability, which is also predicted with bias (88), and thus updates to the representation of nitrogen cycling across the rumen wall have been initiated. However, given the empirical nature of microbial metabolism in these models, it seems unlikely that significant additional progress will be made in prediction accuracy and precision in the absence of some type of representation of the underlying microbial metabolism.

**Growth**

Growth is the accumulation of the biomass over time and thus is a dynamic (time-dependent) process. The growth curve often is sigmoidal in shape (89), which reflects a low mass of rapidly multiplying cells early in life and a declining rate of cell division as maturity is approached. Models describing growth include linear, logarithmic, logistic, and Gompertz representations (Table 1), and these models have been used to determine that growth rate varies by species, genetic composition, age, physiologic state, nutrition, feed additives, management, and environmental factors. Of these, the Gompertz and logistic equations are the most used (90) (Figure 2), but others seem to be favored for some species (90–94).

In general, the models use animal age as a driving input. This likely derives from Brody's (100) observation that there was an exponential relationship between weight and cumulative feed intake, the latter providing the time element. Fitzhugh (101) pointed out that feed intake was not always available, and animal age could be substituted for this input.
Table 1  Growth models used in animal production

| Growth models         | Equation                                      | Descriptions                                                                 |
|-----------------------|-----------------------------------------------|-------------------------------------------------------------------------------|
| Linear (95)           | $W_t = Y_0 + \beta t$                         | Where $Y_0$ = the initial weight, $\beta$ = slope, $t$ = time, $\beta > 0$ if the animal is gaining, $\beta < 0$ if the animal is losing live body weight |
| Logarithmic (95)      | $W_t = e^{e - \beta / t}$                    | Where $t \neq 0$, $\alpha$ and $\beta$ are parameters, $t$ = time, $e = 2.71828$ |
| Logistic (95, 96)     | $W_t = \frac{Y_\infty}{1 + e^{-\alpha t}}$  | Where $t \geq 0$, $Y_\infty$ = limit to growth parameter, $\alpha$ and $\beta$ are parameters, $t$ = time, $e = 2.71828$, $Y_\infty$ are all positive |
| Gompertz (95, 97)     | $W_t = Y_\infty e^{-\alpha e^{-\beta t}}$   | Where $t \geq 0$, $Y_\infty$ = limit to growth parameter, $\alpha$ and $\beta$ are parameters, $t$ = time, $e = 2.71828$, $Y_\infty$ are all positive |
| Brody (95, 100)       | $W_t = \alpha e^{kt}$                         | Phase I: exponentially increasing                                             |
|                       | $W_t = Y_\infty(1 - \beta e^{-kt})$          | Phase II: exponentially decreasing after the point where the exponential growth ends |
|                       | Where $\alpha$ = parameter, $e = 2.71828$, $k$ = growth rate, $t$ = time |
|                       | $W_t = Y_\infty(1 - \beta e^{-kt})$          | Where $\beta$ = parameter, $e = 2.71828$, $k$ = growth rate, $t$ = time |
|                       | Von Bertalanffy (98)                          | Where $Y_\infty$ = the limit to growth parameter, $\beta = a/\eta$, $a$ = constant of integration, $\eta$ = constant, $\lambda$ = growth rate parameter, $1 - k$ = shape parameter, $e = 2.71828$, $t$ = time |
|                       | Schnute & Richards (99)                      | $W_t = \frac{W_f}{(1+\alpha e^{-kt})^{1/n}}$ Where $W_f$ = the asymptotic weight, $t$ = time, $k$ = growth rate, $h$, $p$, $n$ = constants, $e = 2.71828$ |
| Negative exponential (95) | $W_t = Y_\infty(1 - e^{-\beta t})$          | Where $t \geq 0$, $Y_\infty$ = the limit to growth parameter, $\beta$ = rate of growth parameter, $e = 2.71828$, $t$ = time, $Y_\infty$ and $\beta$ are positive |
| Morgan–Mercer–Flodin (91, 95) | $W_t = AB + kt^d/(B + t^d)$                  | Where $t$ = time, $A$ = mature weight, $B$ = initial weight, $k$ = the growth rate, $d$ = the shape parameter for an inflection point |

Figure 2

The number of publications that used different growth models, as summarized by Narinc et al. (90).
These empirical models have been used to identify slaughter age, management and health challenges, age of sexual maturity, and genetic potential in animals. They have also been used to explore differences among animals owing to genetics, management, and nutrition. Berry et al. (94) found that different strains of Holstein-Friesian females had differing maturing rates. In beef cattle, the growth curve shape has changed in response to genetic selection (101) and environmental conditions (92). Capturing growth curves changes in the nutrient requirement models can potentially reduce dietary costs by allowing more precise feeding programs.

Di Marco et al. (102) provided a more mechanistic representation using DNA growth and nutrient supply to drive growth of body components. The accumulation rate of DNA ($dQ_{DNA}/dt$) was represented as a function of protein mass ($Q_{Prt}$), mature DNA mass, and nutritional state:

$$\frac{dQ_{DNA}}{dt} = K_{DNA} \times Q_{Prt}^{X1} \times \left( \frac{Q_{DNAmx} - Q_{DNA}}{Q_{DNAmx}} \right) \times Nut. \quad 4.$$

The variable $Nut$ assumed a value of 1 in the reference state and exceeded 1 when energy and protein supply were greater than the reference state. $X1$, $K_{DNA}$, and $Q_{DNAmx}$ are parameters that must be derived from representative data. The quantity of DNA at any point in time was determined by numerical integration of Equation 4 from a starting DNA mass, i.e., at birth or conception.

Body protein mass ($Q_{Prt}$) was derived by numerical integration of the difference between rates of synthesis and degradation. Synthesis ($F_{AAPrt}$) was driven by the supply of amino acids (AA), the predicted DNA mass, and the ratio of protein to DNA relative to the ratio at maximal protein and DNA:

$$F_{AAPrt} = V_{AAPrt} \times Q_{Prt}^{X2} \times \left( \frac{Q_{Prtx} Q_{DNAmx} - Q_{Prt} Q_{DNA}}{1.0 + K_{AAPrt} / C_{AA}} \right). \quad 5.$$

Protein degradation was represented as a mass action function of protein mass and hormonal state:

$$F_{PrtAa} = K_{PrtAa} \times Q_{Prt}^{X3} \times Hor. \quad 6.$$

This model captures the concepts of hyperplastic growth of DNA catalyzed by the amount of protein present and proceeding at a declining rate until reaching 0 at a mature DNA mass, as well as protein synthesis driven by the mass of DNA modulated by the targeted ratio of protein to DNA. In this case, the maximal rate of protein synthesis should reflect ribosomal capacity and the quantity of mRNA coding for the aggregated growth components. Di Marco et al. (102) used the model to describe body and visceral protein mass for growing cattle, but the system could be applied to any level of aggregation, including individual cells.

When fat deposition was represented as a function of energy supply in excess of that required for maintenance and lean tissue growth, the model predicted empty body growth reasonably well (103) but had larger errors for predictions of body composition (104), indicating the model fails to capture the full range of mechanisms controlling body composition, which is not surprising given the level of aggregation.

In theory, representing maximal protein synthesis as a function of ribosomal activity rather than as a constant and including a representation of the expression of the specific mRNA coding for growth proteins would add explanatory power. If both weight gain and body composition can be predicted well, these models have value in managing individual animals to achieve optimum slaughter time, thus increasing meat output and minimizing costly fat production.
Lactation

Lactational yield has also been well characterized, with Wood’s (105) equation representing the hallmark early work from an empirical standpoint:

$$\hat{Y} = a(DIM)^b e^{-cn},$$

where $a$, $b$, and $c$ were parameters and $DIM$ represented days after parturition. He subsequently derived an alternative equation that was more mechanistic, representing energy supply and body reserves (106).

Dijkstra et al. (107) described the underlying mammary tissue growth and senescence from a mechanistic standpoint. They fitted the model to DNA or tissue mass for several species and adapted it for use with milk production curves. Hanigan et al. (58) modified the equation to represent continuous cell death, whereas the prior model assumed no cell death prior to parturition:

$$Q_{\text{Cells}}(t) = Q_{\text{Cells}}(T_0) \times e\left\{ \text{Sign} \times \mu_{\text{Division}}(T_0) \times \left[ 1 - e^{-K_{\text{Decay}} \times |t|} \right] - (K_{\text{Apoptosis}} \times |t|) \right\},$$

where $Q_{\text{Cells}}$ represented the mass of mammary cells (tissue) or mammary DNA, $\mu$ represented the growth rate at conception, $K_{\text{Decay}}$ the rate of loss of synthetic activity, and $K_{\text{Apoptosis}}$ the rate of cell death. Conceptually, the model assumes that a population of seed cells $[Q_{\text{Cells}}(T_0)]$ undergo binary cell division, yielding daughter cells that undergo clonal expansion at an initial rate of $\mu_{\text{Division}}(T_0)$, which declines ($K_{\text{Decay}}$) as parturition approaches, until completely ceasing proliferation at some point after parturition. Cell death was assumed to be by mass action based on the total cell population.

Cessation of proliferation after parturition is inconsistent with experimental evidence, and thus the model will not match in vivo cell turnover if such data are collected. However, in the absence of quantitative observations of cell turnover, one cannot address this limitation. Given accurate predictions of mammary cell mass, one can focus on a description of enzymatic activity per cell, which is more easily measured, and the two can be independently represented in the model (58).

One can use Equation 8 to infer response mechanisms by examining the temporal responses to factors of interest. As Hanigan et al. (108) noted, responses to varying nutrient inputs, somatotropin, and insulin appear to be due to changes in activity per cell, as there are no carryover effects from those treatments. If rates of cell division were stimulated or cell loss were inhibited by any of those factors, one would anticipate a difference in cell numbers and thus tissue activity between the control and treatments that grow with treatment length and persist upon treatment cessation. The lack of an apparent shift in cell numbers in response to somatotropin contrasts with the results of Capuco et al. (109), who found that indicators of the rate of proliferation and apoptosis suggested increased cell growth. Although the models are not sufficiently developed to eliminate a proliferative response to somatotropin, they point out the inconsistency of results across studies that evaluated short-term markers of cell turnover and the longer-term milk component responses. Thus, the mechanistic modeling work and the experimental work remain in disagreement, and this problem requires a scientific resolution.

The concepts of cell numbers and cell activity have been used as a basis for mechanistic representations of lactation (58, 110). Replacement of a more aggregated representation of overall cell activity (cell number times activity per cell) in Baldwin’s (85) model addressed several problems with predictions of milk production and composition and provided a more mechanistic framework for representing the effects of additional nutrients, hormones, photoperiod, and milking frequency, some of which have been modeled at the cellular level (61, 70, 111–113).
Nutrient Excretion

Several empirical models have been developed to predict nutrient excretion, including methane and ammonia. In the absence of knowledge of nutrition, these equations can be used, but where nutrient inputs are known, the excretion products can likely be more accurately predicted based on mass balance. If the nutrient is not absorbed and deposited in product, then it must be excreted. Thus, the validity and performance of these equations reflect the validity and performance of the underlying representations of nutrient digestion, absorption, and use, as discussed above. This offers another opportunity to evaluate model performance. If predictions of nutrient digestibility and use are made without bias and with acceptable precision, mass balance dictates that nutrient excretion should be predicted without bias.

Appuhamy et al. (114) developed a four-pool (reticulorumen, postreticulorumen, extracellular, and intracellular), mechanistic model to predict urinary and fecal water outputs of dairy cows. The model predicted fresh manure output for dairy cows with good accuracy and precision (root mean squared prediction error = 14.6%). Another model used mass balance to predict the ammonia emission from manure belts in poultry layer houses (115). Nutrient excretion by sows was predicted based on energy and nutrient partitioning (116). In that effort, urinary N was predicted with less precision than fecal and milk N, indicating additional driving factors should be considered. These efforts need to be expanded to more species and animal states, as the resulting models are essential tools for management of manure and nutrient excretion by agricultural animals to reduce environmental impact and maximize capture of nutrients in crops.

INTEGRATION OF MODELS FOR PROMOTING SUSTAINABLE FOOD PRODUCTION

Although integration of data and models remains a challenge even for computer science (117), it is an essential component of a sustainable food production system. Food production system models that utilize a range of subsystems (represented empirically or mechanistically; Figure 1) allow simulations of the full range of potential inputs and outputs, and are more likely to lead to significant, novel solutions to the problem of food sufficiency and security. The model integration process also helps ensure that trade-offs within the larger food system are properly weighted by capturing all the significant interactions in an entire model. For example, the gross efficiency of N use by ruminants is low, ranging between 10% and 40% (118), and ruminants produce large amounts of methane. However, they can make use of ingredients that are not human edible, resulting in positive additions to the human food supply. Identifying strategies to improve nitrogen efficiency and reduce methane production while maintaining positive human-edible food outputs will create value in the system, but these outputs must be accurately predicted and responsive to important inputs. Use of simpler empirical models fails to capture some of the potential input options, resulting in a priori discrimination against any inputs that act via the excluded mechanisms.

Information integration using mechanistic models also identifies knowledge gaps in animal nutrition and food production systems and provides information on the relative importance of that knowledge. On the negative side, mechanistic models are generally more complicated, often requiring more inputs and using more parameters that must be estimated. Therefore, there is also more potential for model problems that can lead to biased predictions. Integration of more mechanist models into a larger food system model (Figure 1) would allow simulations of the full range of potential inputs and is more likely to lead to significant, novel solutions. Capturing those mechanisms in food system models will allow the environmental costs to be weighed against making use of land not suitable for grain production to add to the food supply.
Amino acid feeding provides an example of the interaction of animal nutrition with other system elements. The deficiency of a single AA in the diet will reduce animal performance and cause greater urinary nitrogen excretion. The animal will therefore require more days to reach a target slaughter weight, resulting in more days of maintenance, reduced efficiency of gain, more urinary and fecal excretion, and fewer animals marketed from the facility over its lifetime. More land will be required to support feed requirements, and more energy will be consumed per unit of food to heat the building and manufacture the materials required to build the facility. More manure per unit of product owing to added days on feed, and more N in the manure owing to reduced N efficiency, will result in greater methane and ammonia emissions from the storage facility. However, slower-growing animals will have lower heat production, and thus their performance should be affected less by heat stress associated with climate change. Therefore, the loss in efficiency owing to heat stress will be less than for an animal that is growing at its full potential. Finally, the animal may be more susceptible to disease owing to undernutrition, which will increase production costs and further reduce the efficiency of production. If many farms experience similar deficiencies, food production from available land mass will decline, making it more difficult to maintain food sufficiency. This scenario underscores the complexity of the system. The balance of these forcing factors can be assessed with a food system model only if the underlying animal models contain mechanisms to represent the effects of amino acids, disease, heat stress, and energy partitioning responses and excretion is predicted mechanistically from mass balance.

The impacts of genetic selection in animals and plants should also be represented in the animal system if predictions are to be made very far into the future. Additionally, use of genetic information as an input to the models can improve model precision. Currently, mechanistic nutrition models do not generally consider the effects of genetics.

Regardless of the complexity chosen, the animal models would typically become subsystems of a whole-farm model (Figure 3). This allows aggregation of the different physiological states in an animal life cycle to yield total animal unit inputs and outputs from the enterprise. It also allows
representation of multiple different farm types to capture the range in farm diversity and provides estimates of outputs and economics at that level, which are useful for assessing business viability and risk. Farms may be organized, e.g., by watershed to determine water pollution or watersheds organized into regions.

The integration of models can help to identify limitations of the current system as a whole. We need further efforts in modeling research and computer science technology to effectively integrate submodels into a high-level model.

Movement toward greater integration of more mechanistic submodels will capture some important driving factors in the system; however, one must not forget that the models, despite their perceived complexity, remain simplified abstractions of reality. As such, there is always risk associated with their use. Limited knowledge of interactions among inputs variables (or among submodels) or missing input information in the model may result in unexpected outcomes. This is demonstrated by the use of dairy genetic selection models that included a representation of the genetic gain for milk production but did not represent reproductive performance for more than 40 years, leading to a continuous decline in reproductive efficiency until that criterium was added to the model (119). This is a perhaps not a perfect example, as the geneticists predicted this could happen, but it demonstrates the potential for the negative impact of model use on variables outside of the system and reinforces the importance of recognizing model scope not only when constructing the model but also in its application. More detailed submodels may capture all the major factors within each subsystem, but that does not ensure that all interactions among subsystems are captured, nor does it ensure that all interactions with external inputs and outputs are captured. Many of the current environmental problems are at least partial unintended consequences of human activity because the cost of environmental impact has not been represented in the economic system (120). Consideration of environmental impacts as discussed quantifies the impact of such activity so that informed decisions can be made. Less obvious external interactions will undoubtedly require consideration as they are identified. Model use may increase the importance of those interactions by moving the system to activity that is more sensitive to those inputs or outputs; however, model use does not create the interactions. They already exist, and they could exert negative influence on the system even if no models are used to force the system.

FUTURE DIRECTIONS OF PRECISION AGRICULTURE

Inclusion of increasing detail in models is the natural course of development of system models. This requires the collection of more inputs but results in a broader array of predicted outputs. Such a course of development meshes well with the reductionist nature of science and provides a method to integrate the knowledge generated from such activity. The challenge is ensuring that the underlying models accurately and precisely reproduce reality. Large, complex models require great care during development, as they are more difficult to parameterize and ensure proper function.

Parameter estimation in mechanistic models generally requires more robust data than those generated in typical factorial experiments using only two levels of each test factor. Such an approach may be adequate to identify the presence of a mechanism, but it does not provide the detail required to construct a full output response surface (the number of dimensions ranges from 2 to infinity depending on model complexity). Because investigators conducting modeling are often not part of the experimental team, the limitation of the factorial data is often not recognized and thus not addressed. Integration of experimental and modeling work within projects helps avoid this problem and improves scientific progress and efficiency. Short of that goal, the simple recognition
by experimentalists that mechanism identification should be followed by full response characterization would result in the generation of more complete data relative to model development needs.

The prevalence of sensors monitoring animal and equipment performance in agricultural systems has grown tremendously over the past decade and provides high-resolution data that can be used as model inputs and for model development. They can also be used for model calibration in the field. Models cannot be expected to represent each animal or plant within a farm with perfect accuracy owing to biological diversity and unrepresented forcing factors. Thus, the model will not perfectly represent each field or pen of animals. However, if measures of system performance are collected in real time, the model could be set up to self-calibrate to the data being collected from the specific field or pen. Such calibration will help ensure that the decision support system tied to the model generates unbiased and more precise predictions of outcomes. Thus, models and software must be designed to take advantage of those opportunities. Model sensitivity results should also be used to identify additional measurements that would aid model application so that efforts can be focused on developing methods of making those measurements.

As the range of data collection increases, the need for automation tools for model development intensifies. Mechanistic models are generally built based on a survey of the existing knowledge and decisions on the level of complexity required to achieve the stated objectives. Both are subject to potential bias. In the absence of a methodical, hypothesis-based approach to construction and testing, it is expedient to over-specify the model, which can result in poor model performance owing to inappropriate parameterization.

Machine learning uses artificial intelligence with algorithms to automatically create models for science, business, and government. This method uses advanced computer science to explore raw data and identify patterns and causalities necessary for detection or classification. This technique is based on inputs, outputs, and detection of patterns in the input variables (121); thus, the resulting models do not necessarily recreate the underlying biology. They simply identify a structure that results in high statistical association and correlation. This does not necessarily equate to knowledge of the system and can result in spurious results (122).

Mechanistic models are constructed to try to understand how the system works and to reproduce behavior based on the discovered mechanisms. Knowledge of the primary inputs and outputs, the potential pathways that are used, and the rate-limiting steps is used to construct the framework. Several of the pathways can be specified a priori based on the release of products unique to that pathway. However, other pathways may not be required owing to limited flux existing in that pathway, or they may be aggregated with other pathways to simplify the model. Ideally, these decisions would be checked for necessity by comparing model performance with and without the aggregation or omission. If there are only 1 or 2 of these decisions, this is quite easy to check, but if there are 20 such decisions, each with 2 potential outcomes, then all combinations should be checked, resulting in $2^{20}$ tests—obviously not something that should be attempted by hand.

Conceptually, an automation tool for model development should be possible, as the process of development follows a pattern that can be encoded, and it seems it could represent an extension of the current machine-learning algorithms. Much of the needed information is already present in the protein and metabolism databases. Potential model structures could be generated from a list of pathways and branching points, the molecular structure of pathway input and output molecules, and a list of possible equation forms that can be used to represent the kinetics. The stoichiometric code would have to consider positional information so that data from isotopic labeling experiments can also be used. This should include tracking of molecular pairing (isotopomers) to take advantage of that information. Such an approach would be extremely useful, as model construction and testing could be fully automated so that all possible levels of aggregation could be statistically tested. The potential models would each be fitted to available data and
ranked for consistency and quality of predictions. This latter step would require some logic to allow assumptions and to identify over-parameterization, as the data are rarely adequate to identify all parameters in more complicated models. Identification of over-parameterization could be used to exclude model structures suffering from such problems. Such a tool would allow for complete testing of potential model structures using a quantitative approach to ensure the resulting model is no more complicated than necessary (123).

The effective use of large volumes of disparate data and development and use of machine learning applied to mechanistic modeling represents a new challenge for food system scientists. Historically, food scientists have been trained primarily in experimental methods and classical statistical analyses, with the occasional individual taking up modeling. In the future, more scientists with training in quantitative and computer science skills will be required to develop, test, and help maintain advanced food system models.

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Errata

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