

# Brief history and future of animal simulation models for science and application

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**Abstract.** Mathematical equations have been used to add quantitative rigour to the description of animal systems for the last 100 years. Initially, simple equations were used to describe the growth of animals or their parts and to predict nutrient requirements for different livestock species. The advent of computers led to development of complex multi-equation, dynamic models of animal metabolism and of the interaction between animals and their environment. An understanding was developed about how animal systems could be integrated in models to obtain the most realistic prediction of observations and allow accurate predictions of as yet unobserved events. Animal models have been used to illustrate how well animal systems are understood and to identify areas requiring further research. Many animal models have been developed with the aim of evaluating alternative management strategies within animal enterprises. Several important gaps in current animal models requiring further development are identified: including a more mechanistic representation of the control of feed intake; inclusion of methyl-donor requirements and simulation of the methionine cycle; plus a more mechanistic representation of disease and the impact of microbial loads under production environments. Reasons are identified why few animal models have been used for day-to-day decision making on farm. In the future, animal simulation models are envisaged to function as real-time control of systems within animal enterprises to optimise animal productivity, carcass quality, health, welfare and to maximise profit. Further development will be required for the integration of models that run real time in enterprise management systems adopting precision livestock farming technologies.

**Additional keywords:** adoption, decision making, farming systems, feed intake, immune response, metabolism, methyl-donor metabolism, monogastrics, ruminants, simulation modelling.

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## Introduction

The use of mathematical equations to describe components of animal systems has a long history extending over 100 years (Dumas *et al.* 2008). In 1914, Wood and Yule reflected on predicting the amount of fat, work or milk that could be produced from an animal supplied with a diet containing a known amount of starch equivalents (Wood and Yule 1914). The purpose for developing equations to describe such processes is to add quantitative rigour to the assessment of the likely outcomes from an event based on evaluation of existing knowledge. The process, frequently called ‘simulation modelling’, can involve one equation or the integration of many equations.

The first equations used to predict components of animal systems from the 1920s to the 1960s were ‘static’ models that represented the state of the system for only one instance in time (Brody and Ragsdale 1921; Huxley 1924; Blaxter 1962). These first models were used to describe the growth of animals or animal parts (Huxley and Teissier 1936) and to predict the energy and nutrient requirements for many domestic livestock species at specific liveweights (FAO/WHO 1957, 1965; ARC 1965). However, with the advent and increasing use of computers during the late 1960s and 1970s, the number of equations included in models grew substantially. The models became ‘dynamic’, where time was described explicitly and

outcomes were predicted over varying periods of time using varying iteration intervals (Whittemore and Fawcett 1974; Graham *et al.* 1976). Many of the earlier animal simulation models were based largely on regression equations that described associations between two or more variables and which implied little about the underlying mechanisms controlling operation of the system. Predictions from these models were frequently poor when applied to situations outside the range from which the original data were collected (Black 1995).

The realisation that regression equations were unsuitable for most models, stimulated development of ‘mechanistic’ models based on either the laws of physics and chemistry or on equations with known characteristics derived specifically to represent the perceived mechanisms of a system (Black 1995). The latter equations are known as ‘conceptual’ or ‘deductive’ equations and examples are given by Baldwin and Black (1979) and Thornley (2008) to predict sigmoidal growth curves for animal organs or whole animals. Mechanistic models have been used to describe a range of animal systems, including: nutrient metabolism and energy transactions in individual organs or whole animals using biochemical pathways based on Michaelis–Menten kinetics (Garfinkel 1966; Baldwin and Smith 1971); assessing the effects of skin blood flow rate, wool follicle numbers, absorption of sulfur containing amino

acids and pregnancy on the rate of wool growth, wool protein composition, wool follicle cell turnover rate and uptake of sulfur-containing amino acids by other tissues (Black and Reis 1979); wool follicle initiation and development based on the reaction–diffusion theory (Nagorcka and Mooney 1989); and the impact of the climate on animals through the physics of heat exchange between the animal and its environment (Bruce and Clark 1979).

The most important characteristic of effective mechanistic models is that they can predict the outcome of an event before it has been observed. This principle is well demonstrated by the reaction diffusion model of Nagorcka and Mooney (1989) for wool follicle initiation (Black 1995). The model predicted that the number of wool follicles initiated at a specific phase of fetal development would be a function of skin surface area. Adelson (1991) tested the hypothesis by placing either a 2 cm teflon hemisphere or a 2 cm flat disc on opposite sides of a 71 day old fetus after the primary follicles had been initiated but before the secondary follicles were formed. The hemisphere : disc surface area was 2 : 1 and the model predicted that the ratio of secondary : primary follicles would be twice as great for the skin over the hemisphere than over the disc. The experiment showed the secondary : primary follicle ratio to be 2.76 for the hemisphere and 1.33 for the disc, confirming the prediction.

There has been continuing development of animal models over the last 30 years (Dumas *et al.* 2008), with most being a combination of physical-chemical theory representations and conceptual equations. Nevertheless, a question remains about the value of animal models to science and to practical agriculture. This paper considers reasons for developing animal simulation models, highlights several areas where further development of concepts would be valuable for their application and suggests ways that could improve their use in practical agriculture.

### Reasons for developing animal models

The philosophy behind development of computer models to simulate animal systems has been described previously by many authors including Baldwin and Koong (1980) and France and Dijkstra (2000). The two primary reasons for developing mathematical models are (1) to demonstrate, quantitatively, how well a system is understood and then direct future research towards improving that understanding; and (2) to integrate disparate pieces of current knowledge to assist decision making either for prioritising research activities or for direct application by enterprise managers. The former represents a formalisation of the process used by all research scientists whereby ideas and concepts about the operation and control of a system are developed using data obtained from experiments. This procedure leads to the development of hypotheses, the conduct of new experiments and acquisition of more knowledge that allows a deeper understanding of the system. Modelling simply adds rigour by forcing each step in the process to be described quantitatively in terms of mathematical equations and not subjectively. Hypotheses about the operation of a system can be more readily evaluated using mathematical models than with traditional subjective approaches. Inputs or components of the modelled system representing concepts of the mechanisms

can be readily changed to test hypotheses and examine the closeness of predictions to experimental observations. Thus, hypotheses can be more thoroughly refined before costly experiments are conducted to improve understanding of the system.

The other major advantage of modelling is that many small systems can be integrated into larger systems. Frequently, the complexity of the interactions in these larger systems is so great that it is impossible for the human mind to follow the consequences of changes to the system over time. For example, the effects of a period of cold weather and differences in stocking density on the growth rate and final body composition of pigs can be predicted by simulation models, but cannot be reasonably deduced because of the interaction between the many factors over time (Black *et al.* 1993).

In the 1970s and 1980s, the capacity to integrate numerous systems into one model led to the concept that fundamental biological knowledge, when incorporated into simulation models, could be used to assist decision making on farms. Models could integrate numerous parts of an animal system and, combined with a representation of an enterprise structure, they could predict outcomes of productivity over long periods of time. These predictions could be used to help managers make decisions about the most profitable strategies to adopt. Numerous models with this intention were developed, including those for pigs (Whittemore 1983; Black *et al.* 1986; Moughan *et al.* 1987; de Lange *et al.* 2001; van Milgen *et al.* 2008), for sheep (Graham *et al.* 1976), for beef and dairy cattle (Oltjen *et al.* 1986; Baldwin *et al.* 1987a, 1987b, 1987c; Nagorcka and Zurcher 2002) and for poultry (Emmans 1981; Emmans and Fisher 1986; Emmans 1989; Johnston and Gous 2006).

Most models designed for practical application have a similar structure (Oltjen *et al.* 1986; Emmans and Oldham 1988; Baldwin 1995; Black and de Lange 1995; Ferguson 2006; van Milgen *et al.* 2008). The animal component of the models commences with a description of the animal, including: an estimate of its genetic potential to deposit protein and energy (or fat); a description of the diet; of the social and climatic environment; and of health status. Feed intake is predicted either from simple algorithms or a complex set of equations (Poppi 2008; Black 2009). Ingested feed is then digested, again using either simple algorithms (Graham *et al.* 1976) or complex models of digestion, particularly for ruminants (Black *et al.* 1981; Dijkstra *et al.* 1992; Baldwin 1995; Nagorcka *et al.* 2000) and also for pigs (Bastianelli and Sauvant 1998; Rivest *et al.* 2000). Individual nutrients available for metabolism are predicted. Most models estimate the energy and individual amino acids needed for maintaining the integrity of the animal in relation to its current physiological state and the impact of the social, climatic and disease environment. Several models simulate the requirements for macrominerals (Kebreab *et al.* 2008). Various procedures, including Michaelis–Menten kinetics and simpler algorithms, are then used to partition available nutrients between competing body functions. The net outcomes from considering these metabolic processes are predictions of accumulation rates of protein, fat, specific minerals, total animal weight, carcass weight, wool growth rates, milk yield, excretion of nitrogen, methane and minerals, efficiency of feed use and other variables. Some models predict the order of limiting amino acids and

the amount required to overcome any deficiency. Similarly, deficiencies in macromineral supply and effects on bone strength are also predicted by some models (Black 2009). The majority of current animal models are deterministic and predict the outcome for one animal that represents the mean of a group of similar animals, rather than being stochastic where a range of possible outcomes representing natural variability is predicted. Nevertheless, stochastic elements have been added to several deterministic models by (1) undertaking multiple simulations within one 'run' of the model where input variables under either genetic control, such as capacity to deposit fat and protein, or environmental control are varied for each simulation to accommodate all animals within a group (Knap 1995; Baudracco *et al.* 2013), and (2) using normal curve and statistical variance assumptions for economically important variables such as carcass weight and back fat thickness in pigs to predict their likely frequency and range for determining prices paid for all animals in a group (Black *et al.* 1993). Stochastic modelling of individual animals has been used in broiler models as a means for determining optimum economic amino acid concentrations in diets (Gous and Berhe 2006), for assessing animal movement within areas (Preisler *et al.* 2004; Smouse *et al.* 2010) and for predicting the spread of diseases through animal populations (Rorres *et al.* 2011; Stevenson *et al.* 2013). Models have been used to predict the spread of contagious diseases such as spongiform encephalopathy (Thornley and France 2008) and foot-and-mouth disease (Thornley and France 2009).

Most models cited above could generally be described as 'robust' and predict animal performance under a range of circumstances with reasonable accuracy. Components of several models continue to be upgraded and improved. New components are being added including representations of disease (Sandberg *et al.* 2006; Black 2009), macromineral balances and greenhouse gas emissions (Rigolot *et al.* 2010). Several models include components that allow the exploration of strategies to ameliorate environmental pollution from cattle including methane emissions (Ellis *et al.* 2008), nitrogen (Ellis *et al.* 2011) and phosphorus (Kebreab *et al.* 2008).

Some models predict enterprise profitability and cash flow, while others identify management strategies that optimise the use of enterprise resources for maximum profit (Black *et al.* 1993; Gous and Berhe 2006). Others contain 'expert systems' to aid the interpretation of model outputs by people other than those involved in construction of the model (Menzies *et al.* 1990; Oltjen *et al.* 1990). Several animal models are also linked directly to least-cost diet formulation software where nutrient requirements predicted by the simulation model are transferred to a diet formulation predictor (Black *et al.* 1993; de Lange *et al.* 2001; Ferguson 2014; Gous 2014).

Although many models have been of substantial value for analysing specific farm enterprise options (de Lange *et al.* 2001; Nagorcka and Zurcher 2002; Black and Banhazi 2013; Ferguson 2014; Gous 2014), their uptake by industry has been less than anticipated. The models have been valuable for assessing the impacts of alternative management strategies in isolated applications and for setting research priorities, but they have not been used for day-to-day decision making as had been envisaged by many of the model developers. The remainder of

this paper examines several areas where models could be improved to better predict reality of animal performance and what may be needed to encourage their use for everyday decision making on farm.

### Gaps in animal nutrition models

Several important areas of animal models must be improved to more effectively simulate the performance of commercially raised livestock. The following three are considered: prediction of feed intake and incorporation of maximum energy intake into diet formulation software; inclusion of methyl-donor metabolism and requirements; and mechanistic representation of the immune response and diseases.

#### *Prediction of voluntary feed intake*

An accurate prediction of feed intake is the most critical step in all animal models for realistic determination of the efficiency of nutrient utilisation and of animal performance. Many different concepts and approaches have been used to model feed intake of animals (Black 2009). These include (1) simple algorithms fitted to experimental data and based largely on animal weight and the available energy content and/or composition of the diet (Poppi 2008; Black 2009); (2) maximum efficiency of oxygen utilisation with animals ceasing to eat when the intake of net energy per litre of oxygen consumed is maximised (Tolkamp and Ketelaars 1992); (3) minimal discomfort theory where feed intake corresponds with the minimal total physical and metabolic discomfort experienced by an animal (Forbes 2007, 2009); (4) continual minute by minute prediction of the energy and protein status from metabolite concentrations in blood and of rumen fill in cattle relative to pre-determined limits using a binary system to initiate and terminate feeding bouts (Nagorcka *et al.* 2004); (5) the potential-constraint theory where an animal will eat to satisfy its total energy needs determined by its genetics and physiological state unless constrained by various dietary, environmental, health or social factors (Black *et al.* 1986; Nyachoti *et al.* 2004; Poppi *et al.* 1994); and (6) first limiting nutrient theory where animals eat to meet their requirements for the first limiting nutrients in the feed (Emmans 1981; Kyriazakis and Emmans 1998).

Although there are limitations to each of these approaches for predicting voluntary feed intake, the potential-constraint and first limiting nutrient concepts appear to be the most effective over a wide range of situations (Black 2009; Ferguson 2014). However, these have limitations. First, Forbes (2009) criticised the approach of a single, but changeable feedback mechanism limiting feed intake, because it does not fit with physiology concepts of how an animal functions. Second, whenever the model iteration interval is greater than a few minutes, being 1 day in many of the models mentioned, the commencement and cessation of feeding bouts cannot be predicted nor can the impact be predicted from variations within a day as occurs with changes in pasture availability or with changes in climatic conditions. These criticisms have been overcome by an approach similar to that used by Nagorcka *et al.* (2004) where the concentration of crucial metabolites controlling hunger and satiety within the blood is predicted on a minute by minute basis. Similarly, several models using the first limiting nutrient

approach have used hourly rather than daily integration intervals (Ferguson 2014; Gous 2014). However, no current animal model truly represents the biological control of feed intake. There is an opportunity to develop a more comprehensive mechanistic model of voluntary feed intake in animals on the basis of current understanding of the metabolic and physical regulation of intake. This could be achieved by describing essential metabolic pathways, changes in metabolite pool sizes and physical, neural and endocrine interactions in a model with short iteration intervals.

Voluntary feed intake is controlled by the following two main processes: (i) rate of removal of digesta from the gastrointestinal tract (GIT) through changes in transit time and in the rate of digestion and absorption of dietary constituents; and (ii) brain-controlled hunger and satiety responses resulting from the physical consumption of feed, absorption of products of digestion and metabolites produced from subsequent biochemical reactions. Although the broad mechanisms for feed-intake control are similar for ruminants and monogastric animals (Roche *et al.* 2008; Black *et al.* 2009), understanding of these mechanisms is more advanced for the latter group of animals. The processes that could be modelled for monogastric animals, particularly the pig, are summarised below and described in detail by Black *et al.* (2009).

Feed intake is stimulated in monogastric animals as the rate of passage of digesta increases, particularly through the stomach and small intestine. Physical characteristics of the diet that cause mild distension stimulate the rate of stomach emptying and propagative peristaltic contractions in the GIT and increase feed intake. However, excessive distension inhibits these responses, slows rate of passage and induces satiety via the vagus nerve–hindbrain–forebrain reflex. Increasing the amount of indigestible fibre, or other undigested particles, in a diet for pigs can increase or decrease rate of passage and feed intake depending on the amount of fibre and size of particles. Small indigestible fibre particles are less effective for stimulating rate of passage than are medium-sized particles, which in turn, are more effective than very large particles. Excessive distension of the GIT and reduced rate of passage can also be caused by diets with high soluble fibre content that increases digesta viscosity. Although precise details of the interactions between particle size, viscosity and gut anatomy are not fully understood, development of components of the model based on the principles of rheology would allow these relationships to be explored and to identify whether more experiments are required to clarify the interactions.

Nutrients and their metabolites, present in the GIT and absorbed, control feed intake over the short and long term through the direct or indirect release of endocrines and their interaction with local and central neural processes. Consumed carbohydrates, fats and proteins that are partially digested by mammalian and microbial enzymes directly affect the release of hormones from the (GIT) and pancreas (peptide tyrosine tyrosine (PYY), glucagon-like peptide-1 (GLP-1), oxyntomodulin and apolipoprotein A-IV). The quantitative and temporal release of these hormones depends on the composition of nutrients consumed, their site and extent of digestion and products released within the GIT. They appear not to be released if the ingredients are indigestible, as these indigestible particles appear

to simply stimulate the rate of digesta passage. The nutrient-released hormones act to slow the rate of stomach emptying, reduce the frequency, pressure and progressive distance of peristaltic contractions in the small intestine and reduce feed intake. The action of these hormones has been defined as the ileal brake (Spiller *et al.* 1984). Hence, rate of passage can be stimulated by mild distension, but inhibited by excessive distension and the presence of undigested nutrients near the terminal ileum and colon. The nutrient-stimulated hormones also act through the vagal nervous system or directly on specific regions of the brain to have longer-term effects on reducing feed intake.

In animal nutrition models, it has not been traditional to model the release of endocrines, interactions between physical distension and neural control of functions. However, some aspects of these mechanisms have been undertaken in models of human metabolic control and should now be attempted in animal systems (Dalla Man *et al.* 2007; Farhy 2010; Chambers *et al.* 2013). Furthermore, recent research shows that the rate of digestion of grains and pulses in the small intestine of pigs is closely related to the diffusion rates of amylolytic and protease enzymes into the feed particles (Al-Rabadi *et al.* 2009, 2011a, 2011b; Mahasukhonthachat *et al.* 2010a, 2010b; Dhital *et al.* 2010; Tinus *et al.* 2012). The rate of enzyme diffusion appears to be influenced by several factors including particle size, physical and chemical characteristics of the grain such as degree of compaction, hardness, endosperm cell-wall integrity, gelatinisation, retrogradation of starch and surface hardening of pellets. Amylase diffusion rates were found to be eight times slower than diffusion rates of water for barley grain and 13 times slower for sorghum (Al-Rabadi *et al.* 2009). Enzyme diffusion rate and digestion rate has been shown to decrease with the square of grain particle size, with a doubling of particle size reducing starch digestion rate four-fold (Al-Rabadi *et al.* 2009). These concepts relating enzyme diffusion rates to digestion rate of feed ingredient components, in combination with estimates of the rate of gastric emptying and peristaltic activity within the small intestine determining rate of digesta passage, could readily form the basis for mechanistic simulation of the effects of digestive processes on feed intake.

Such a modelling approach would enable quantitative prediction of nutrients digested in both the small and large intestines. Having the capacity to distinguish between small and large intestine digestion is important in monogastric animals to estimate the composition of the nutrients absorbed and to predict the loss of energy from the animal as heat of fermentation or in methane and voided gut microbes.

Long-term control of feed intake, energy metabolism, body composition and bodyweight is under the influence of two opposing energy monitoring systems within the body. These are adenosine monophosphate-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR), which act both peripherally and centrally within the hypothalamus. AMPK is activated by metabolic or environmental conditions that deplete cells of ATP by monitoring the adenosine monophosphate (AMP):ATP ratio. AMPK inhibits ATP-consuming pathways and stimulates ATP-producing catabolic pathways through the regulation of key metabolic enzymes involved in lipid, carbohydrate and protein metabolism.

Within the hypothalamus, AMPK regulates the concentration of a key intake controlling metabolite, malonyl-CoA. Low energy status and high AMPK activation also lead to inactivation of mTOR which, contrary to AMPK, reflects high energy status of an animal. Activation of mTOR within the hypothalamus is also controlled by insulin and leptin. Basal insulin and leptin concentrations are directly proportional to the amount of fat, or adiposity status, of an animal. Malonyl-CoA and mTOR have a central role in controlling expression of the hypothalamic melanocortin system, which has a major role in regulating feed intake and energy expenditure. Low energy, or adiposity status, results in low concentrations of malonyl-CoA and low activation of mTOR, which stimulates the expression of melanocortin system orexigenic peptides, neuropeptide tyrosine and agouti-related peptide, and reduces the expression of anorexigenic peptides, proopiomelanocortin,  $\alpha$ -melanocyte-stimulating hormone and cocaine and amphetaminelated transcript, thereby increasing intake and reducing energy expenditure. Conversely, high energy status with high concentrations of malonyl-CoA and high activation of mTOR, reduce the expression of the orexigenic peptides, increase the expression of anorexigenic peptides and reduce feed intake, while increasing energy expenditure.

These perceived mechanisms of interactions between current and long-term energy status and eating bouts of animals could be readily simulated. The modelling could be either at a metabolic level similar to that described above or at a simpler level based on a prediction of current energy status of the animal through, for example, blood metabolite concentrations as used by Nagorcka *et al.* (2004), in combination with an ongoing estimate of current adiposity relative to a genetic potential.

#### Feed intake potential in diet formulation

Diet-formulation software used to combine available ingredients to meet nutrient requirements of animals at least cost does not consider the effects of the ingredients on feed intake. The value of a diet as an energy source to an animal depends on the total amount of energy made available for metabolism in megajoules per day. Total energy available to an animal is determined by the amount digested along the whole digestive tract, when accounting for energy losses from the animal associated with microbial digestion through heat of fermentation and methane, (energy content, MJ/kg) and the total amount of the diet consumed (kg/day). Animal performance and productivity is driven by the intake of metabolisable energy.

The digestible, metabolisable or net energy content of each ingredient is used in current feed-formulation software to predict the combination of ingredients that will meet a specified energy content of the formulated diet. Results from a large research program in Australia investigating the energy value of cereal grains for different livestock types (Black 2014), show there is little relationship between the available energy content of grains and voluntary feed intake when the grains are incorporated into diets. The correlation coefficients relating diet intake to digestible energy (DE) content of grains were 0.07,  $-0.34$ , 0.39 and  $-0.24$  for cattle, pigs, broiler chickens and layers respectively. The lack of a clear relationship between DE content of grains and intake is further illustrated by the

results from Cadogan *et al.* (1999), where the DE content of five different cultivars of wheat fed to young pigs ranged only from 14.39 to 14.96 MJ/kg dry matter (4%), but feed intake ranged from 389 to 691 g/day (78%, Table 1). These low and negative correlations illustrate that formulating diets with high or low DE content does not guarantee high or low total energy intakes. The poor relationship between DE content and intake reinforces the information outlined in the previous section of this paper, which suggests different characteristics of diets determine digestibility and intake.

Thus, the effect of an ingredient added to a diet on feed intake needs to be incorporated into least-cost feed-formulation software. There are two possible ways this could be achieved. First, an intake value could be applied to each ingredient and ingredients combined to maximise this value at least cost. For example, an apparent metabolisable energy (AME) intake index has been applied to ~300 cereal grains, including wheat, barley, triticale, sorghum, maize and rice fed to broiler chickens (Black *et al.* 2014). The index was derived by measuring the AME content (MJ/kg) and feed intake (kg/day) in 22-day-old broiler chickens to calculate AME intake (MJ/day). The AME intake for each grain was then divided by the highest AME intake value to provide an AME intake index with theoretical values from 0 to 100. The index value was used rather than the MJ/day intake value because the latter is not constant and changes each day as a chicken grows. The index provides a constant estimate of the relativity between grain samples in the amount eaten when incorporated into a diet. Near-infrared spectroscopy calibrations have been developed to predict the AME intake index value for any cereal grain (Black *et al.* 2014). Similar calibrations have been developed for predicting the DE intake index for growing pigs.

As cereal grains represent from 60% to 70% of diets used in commercial pig and poultry enterprises, application in feed formulation software of an intake index value to cereal grains alone would be a valuable method for taking some account of the effect of grain combinations on likely feed intake of animals. However, as illustrated in the previous section, the addition of other ingredients that alter the rate of passage of digesta, such as indigestible fibre or components that change digesta viscosity, can have marked effects on feed intake. Hence, a second approach would be to imbed a mechanistic model of feed intake within the feed-formulation software to calculate the impact of all ingredient combinations on feed intake. Algorithms that would maximise intake while supplying other specified nutrients at least cost would need to be incorporated into the feed

**Table 1. Digestible energy (DE) content of wheat grain cultivars and intake by young pigs of diets containing the same wheat samples**

From Cadogan *et al.* (1999). Values within columns followed by the same letter are not significantly different (at  $P = 0.05$ )

Wheat cultivar	DE (MJ/kg)	Diet intake (g/day)
Currawong	14.96a	389a
Dollarbird	14.51b	537b
Rosella	14.49b	551b
Thriller	14.39b	691c
Lawson	14.87ab	691c

formulation software. This would not be a trivial task, but is a logical extension from development of mechanistic models of feed intake and putting them into day-to-day use.

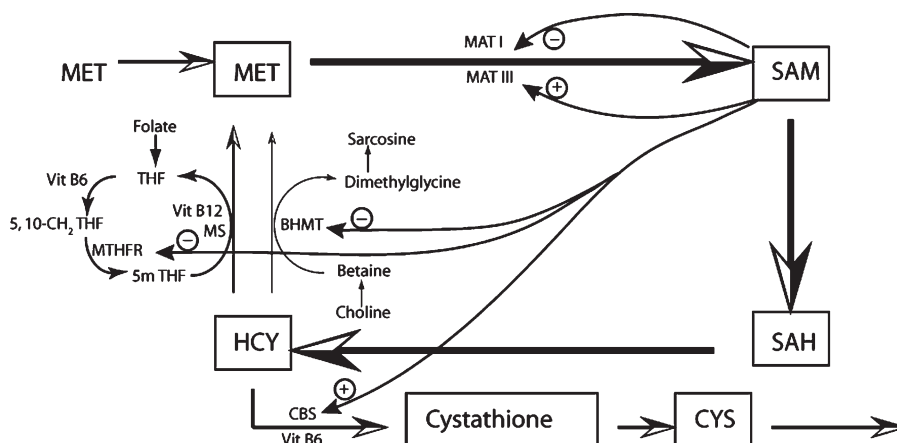
### Methyl-donor requirements

The addition of a methyl group to metabolites and other compounds within the body is essential for maintenance of life within animals. Over 300 methylation reactions have been identified (Brosnan and Brosnan 2006). Methylation is necessary for many functions, including the following: biosynthesis of creatine, phosphatidylcholine and adrenalin; metabolite transport across cell membranes; DNA function and gene expression; hormonal signalling of insulin, growth hormone and corticosteroids; neurotransmission; immune function; muscle contraction; cell growth; protein synthesis; cell membrane integrity; removal of toxins and oxygen free radicals; and others (Brosnan *et al.* 2007; Obeid 2013). Methylation of DNA has an important role in epigenetics and the translation of gene expression across generations (Niculescu 2012). Abnormal methylation, either hypo- or hypermethylation, is associated with numerous disorders, including embryonic death, neural-tube dysfunction, low cognitive ability, diabetes, cardiovascular disorders, Alzheimer's disease, fatty liver syndrome, osteoporosis, low immunity, cancer, osmotic stress and others (Cronjé 2008; Obeid 2013).

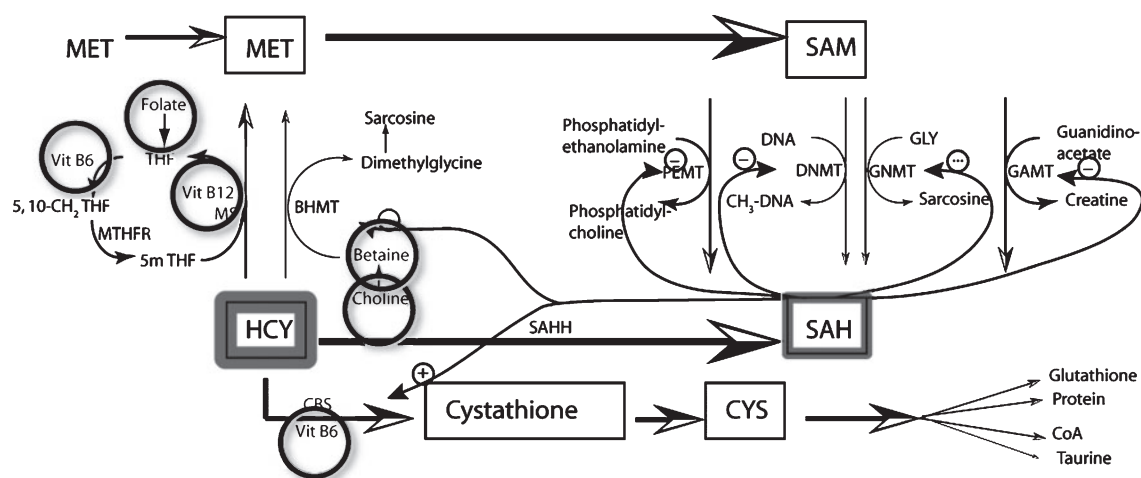
Although the methyl group is a simple carbon-hydrogen molecule,  $\text{CH}_3$ , it has long been recognised that all methyl groups are initially derived from the diet (Anon 1947). Many compounds contain methyl groups, but methyl donors are unique in that the methyl group is attached either to a sulfur or nitrogen molecule. Despite the essential role of methyl groups in animal metabolism and their need to be supplied from the diet, animal nutrition specialists have not included methyl groups in diet formulation software, nor their metabolism within simulation models.

Maintenance of methyl groups within an animal is controlled through the methionine cycle. The control of the methionine cycle has been widely studied and is now well understood (Mudd *et al.* 2007; Williams and Schalinske 2007; Cronjé 2008). The process is summarised in Figs 1 and 2. Methionine is converted to S-adenosylmethionine (SAM) via two isomers of the enzyme methionine adenosyl transferase (MAT I, MAT III). These interacting enzymes maintain the concentration of methionine, and therefore SAM, within close limits despite wide fluctuations in methionine supply. SAM is responsible for the transfer of methyl groups to other compounds within the body, which results in the formation of S-adenosylhomocysteine (SAH). SAH is converted to homocysteine (HCY) via SAH hydrolase in a reversible reaction, which favours the synthesis of HCY unless there are perturbations to the cycle. HCY concentrations are kept low by the irreversible transsulfuration of HCY to cystathione and then to cysteine, which is used for the synthesis of several essential compounds including glutathione, taurine, coenzyme A and proteins. The conversion of HCY to cystathione requires vitamin B6. HCY is also converted back to methionine to complete the methionine cycle with methyl groups coming either from 5-methyl tetrahydrofolate or from betaine. Vitamin B6 and B12 are required as cofactors in the folate cycle which provides the methyl group for one reaction converting HCY back to methionine. The folate cycle depends on a supply of dietary folate. Similarly, when betaine is used for transmethylation of HCY to methionine, betaine is required in the diet or can be synthesised from dietary choline.

The methionine cycle is normally under precise regulation to maintain constant supply of methyl groups to perform the many reactions for which they are needed. However, there must be an optimum supply from the diet of methionine, folate, betaine, choline and vitamin B6 and B12 to maintain this equilibrium. A deficiency of any one of methionine, folate, betaine and choline can be partially compensated for by the others, but the cycle is readily perturbed if dietary provision of these compounds and the



**Fig. 1.** Normal allosteric regulation of enzymes of the methionine cycle by S-adenosyl methionine (SAM). A plus symbol indicates stimulation of enzyme activity and a minus symbol indicates inhibition of enzyme activity. The thickness of arrow lines is scaled according to the magnitude of the flow along the indicated paths. BHMT, betaine-homocysteine methyltransferase; CBS, cystathionine β-synthase; CYS, cysteine; HCY, homocysteine; MAT, methionine adenosyl transferase; MET, methionine; MS, methionine synthase; MTHFR, 5,10-methylenetetrahydrofolate reductase; SAH, S-adenosylhomocysteine; and THF, tetrahydrofolate). From Cronjé (2008).



**Fig. 2.** Perturbed allosteric regulation of enzymes of the methionine cycle by S-adenosylhomocysteine (SAH). Accumulation of HCY reverses the direction of the SAH–HCY reaction and increases the level of SAH. Deficiencies of compounds that may result in accumulation of HCY are encircled. A plus symbol indicates stimulation of enzyme activity and a minus symbol indicates inhibition of enzyme activity. The thickness of arrow lines is scaled according to the magnitude of the flow along the indicated paths. BHMT, betaine-homocysteine methyltransferase; CBS, cystathionine β-synthase; CYS, cysteine; DNMT, DNA methyltransferase; GAMT, guanidinoacetate methyltransferase; GNMT, glycine N-methyltransferase; HCY, homocysteine; MET, methionine; MS, methionine synthase; MTHFR, 5,10-methylenetetrahydrofolate reductase; PEMT, phosphatidylethanolamine methyltransferase; SAM, S-adenosyl methionine; and THF, tetrahydrofolate. From Cronjé (2008).

cofactors vitamin B6 and B12 are not optimal. Perturbation of the cycle results in excess concentrations of HCY (Obeid 2013), with many negative effects on metabolic processes in an animal and a resultant lowering of production and health status.

Several mathematical models of the methionine cycle have already been developed and used to explore circumstances in human nutrition and health (Reed *et al.* 2004, 2006, 2008; Prudova *et al.* 2005; Nijhout *et al.* 2006). There is an opportunity for animal scientists to further develop models of the methionine cycle and to quantify the need for transmethylation reactions under a range of genetic and environmental situations. The ultimate objective from developing such models would be prediction of the optimal amount of each of the dietary components (methionine, cysteine, folate, betaine, choline, vitamin B6 and vitamin B12) needed for predetermined rates of animal production for animals varying in genetic background and in different environments. The circumstances that lead to either hypo or hypermethylation of DNA and the consequences for epigenetic effects may be a predicted outcome from such mechanistic models. Furthermore, since these models could predict precise dietary requirements for all components needed for full functionality of the methionine cycle, these requirements could then be incorporated into diet formulation software. This long-neglected area of animal nutrition, where the dietary need for methyl donors has not been considered, would be addressed.

#### Mechanistic representation of disease

Stimulation of the immune response associated with high microbial load and pathogens has a major impact on the performance of intensively reared animals. Commonly, the performance of commercially raised pigs is ~20% less than for

pigs grown in ideal environments (Black *et al.* 2001). Although group penning contributes to this decrease in performance, a major effect is through stimulation of the immune system. Similarly, chickens reared in a germ-free environment were shown to grow 18% faster and have 11% greater feed conversion efficiency than those raised in a commercial environment (Muramatsu *et al.* 1988).

Diseases and immune stimulation affect several physiological functions of animals, including feed intake, oxygen exchange rate, efficiency of energy utilisation, body protein synthesis and catabolism, body temperature control and tolerance to heat stress. Klasing (2007) estimated that total lysine requirements of chickens increased by 7–10% in association with upregulation of the immune system. The major contributors to the increase in lysine requirements were hypertrophy of the liver and production of acute-phase proteins. The acute-phase proteins also contain higher proportions of cysteine than do muscle proteins and cysteine requirements have been estimated to increase by 7% during immune stimulation. Several measurements of oxygen consumption in humans with sickle cell disease (Borel *et al.* 1998) or other forms of trauma (Roe and Kinney 1965) suggest that fever increases metabolic rate by ~10–15%, with most of the increase in energy expenditure being due to increases in the rate of protein turnover associated with infection.

The effects of disease have not been incorporated into many models developed for predicting animal growth, except in a simple form. For example, in pig models, Moughan (1995) incorporated the overall effect of the environment, including disease, by reducing potential protein deposition to an ‘operational maximum’ rather than using the ‘genetic maximum’. Similarly, for the model of Black *et al.* (1986), it is recommended that the potential rate of protein deposition and

feed intake are depressed, while maintenance requirement is increased when simulating the effects of disease (Mullan *et al.* 1994). However, recognition of the importance of diseases in commercial pig production has resulted in several concerted efforts to develop approaches for simulating the effects of diseases on feed intake and performance within pig models (Sandberg *et al.* 2006; Black 2009; Kyriazakis and Doeschl-Wilson 2009).

These more detailed approaches for modelling disease assume that there is usually a lag between the time of infection and discernable physiological responses; the magnitude of the responses depends on the severity of the disease as determined by the pathogen load and virulence; there may or may not be a recovery phase, depending on the disease and its severity; recovery in the physiological function may or may not reach pre-infection levels; time to recovery depends on nutritional status of the animal; the magnitude of the response is influenced by pig genotype; and animals previously infected with a specific disease may be immune to further infection or have a diminished response. Many of these concepts are well developed by Sandberg *et al.* (2006) in relation to predicting the effects of disease on feed intake. However, more effort is required to develop parameters for the algorithms for each of the major diseases affecting pigs or other animals before they can be used effectively in practical models.

### Future application of models

#### *Value and limitations of models for practical decision making*

Despite the enormous potential benefits that should come to practical agriculture through the integration of fundamental scientific knowledge, simulation models have had limited success in helping everyday farm management (Newman *et al.* 2000; Becu *et al.* 2008; Ferguson 2014; Rivera-Torres 2014). The most successful models have been those around which business decisions depend, as illustrated by the almost universal use of diet formulation software by the intensive animal industries. Furthermore, some of the more complex models, although not used directly by farm managers, have had a major impact on understanding and have significantly influenced farm practice. Keating and McCown (2001) provided an example of a complex pest-control model that was used to set simple rules on when to spray or not spray and these rules are now generally applied by farmers. Similarly, the pig model described by Black *et al.* (1986) showed that, provided humidity was less than 90%, maintenance of wet skin for evaporation would prevent heat stress and this prediction led to the introduction of spray cooling systems within Australian piggeries from the late 1980s.

There are several important reasons for failure of most of simulation models to have a significant impact on decision making at the enterprise level and to influence farm profitability. Many systems have been developed by scientists without close knowledge of the decisions that are made on farms or businesses. Their primary purpose was frequently to better understand the biological and physical interactions of a system. The earlier detailed mechanistic models often addressed many biological interactions in great detail, but did not include

specific components that relate to the economic decisions that need to be made at the business level. There is clear evidence that the most successful models for field application have involved a close association during development between the model builders and end users (Ferguson 2014). Successful adoption is improved greatly when the emphasis of model development is on its application as well as on science. However, even those animal models that were constructed in consultation with end users and include integrated diet formulation software, profit optimisation, cash flow predictions and expert systems to interpret results (Black *et al.* 1993), are generally not used consistently to make day-to-day enterprise decisions.

Many animal models are complex and require a great deal of time to understand how they operate and the details of their underlying concepts. Most models require a large number of inputs to run the simulations. This information, such as temperature and humidity changes, air flow rates, genotype description, initial weights, health status, and others, is often not readily obtained at the enterprise level. Finally, most enterprises do not take measurements of farm productivity in sufficient detail to allow the accuracy of the model outputs to be evaluated. A survey of the Australian dairy industry found that farmers and their consultants believe they can rarely afford the time for these activities and are often unconvinced there will be an increased return in profit from the effort involved (Black 2005). There is a perception among these groups that many biological relationships in agricultural systems have what is known as 'flat' response curves and payoff functions (Pannell 2004). The consequence of these flat functions is that there is a wide range over which inputs can vary, without major effects on profitability. Thus, there can be a wide margin for error in the actual inputs used with little consequence on performance, profitability or risk. Farmers, therefore, frequently do not see any major difference in profitability when inputs are optimised compared with decisions that are 'more-or-less' correct. An important application of simulation models is to identify which response surfaces are not flat and where small changes in inputs can have marked effects on productivity and profitability.

#### *Decision-making process*

Most models are known as 'hard' systems and deal only with the biophysical aspects of animal enterprises. However, decision making includes 'soft' systems components relating to personal and social factors that are rarely taken into account during model development (Newman *et al.* 2000). The following five steps in decision making have been recognised: (1) appraising the challenge and identifying the problem; (2) surveying the alternative solutions; (3) weighing the advantages and disadvantages of the alternatives; (4) deliberating about commitment to the decision; and (5) taking action (Robinson 2004). All five phases regularly present difficulties to decision makers, yet most animal models assist with only phases (2) and (3). For many enterprise managers, the challenge or problem is not recognised. When the problem is recognised, managers frequently would like someone else to use the simulation model to provide the quantitative information relating to phases (2) and (3) and then allow them to make the final decisions in relation to their own specific goals and aspirations.



Ferguson (2014) listed the following five factors that he believes are essential for the adoption of animal models by enterprises: (1) all significant stakeholders are part of the model design and development process; (2) foster a modelling culture in the enterprise; (3) ensure robust scientific theory and biology within the model with flexibility to add new components as required; (4) include a capacity for the model to optimise management strategies that enhance profit; and (5) spend time to ensure that customers gain confidence in the model for decision making. Although each of these points is important, ongoing commitment from the model 'champions' is required to ensure its continuing application within the enterprise. An additional component is required if animal models are to be adopted and continuously used for day-to-day decision making in commercial enterprises – the models must fit seamlessly into and become an essential part of the enterprise management system.

#### *Integration of models into farming systems for real-time decision making*

Electronic measurement, interpretation and control of industrial manufacturing are common practice and are being incorporated into animal enterprises through precision livestock-farming systems (Wathes *et al.* 2008; Banhazi *et al.* 2012; Pomar *et al.* 2014). Detailed animal simulation models should become an integral part of such systems, particularly for intensive livestock industries where variation among individual animals contributes to major inefficiencies in resource use and limit enterprise profitability. Methods for integrating pig models into precision farming systems have been described in recent years (Banhazi and Black 2009, 2011; Banhazi *et al.* 2012; Hauschild *et al.* 2012; van Milgen *et al.* 2012; Pomar *et al.* 2014). Although concepts vary, the principles involve the use of existing or developing electronic technologies to identify individual animals, measure important environmental variables, monitor individual animal weight and body condition, monitor individual or herd health status, as well as control feed composition and feed intake for each animal. Models will run in real time with a separate simulation for each pig in the group. The model will become integral to day-to-day management by: (1) automatically combining available diets to optimise amino acid content for individual pigs depending on relative prices of ingredients and price penalties for fat pigs; (2) determining whether ambient temperature is above or below thermoneutral and the relative costs and benefits from altering environmental temperature and wind speed leading to automatic environment control; (3) identifying whether pigs are under- or over-stocked and the economic benefit from adjusting stocking rate; (4) manipulating feed supply to each pig to ensure optimum growth rate and body composition for meeting specific buyer pricing regimes to maximise profit; and (5) selling individual pigs at a time that maximises enterprise returns.

Animal simulation models that integrate current relevant knowledge are envisaged to become an indispensable and virtually invisible part of the management of future intensive animal enterprises. Electronically measured data will be incorporated into model simulations, the data interpreted through the model and used to control feeding, the environment and sale of animals in real time to maximise profit.

## Conclusions

Animal simulation models have progressed greatly since the first use of mathematical equations to describe animal functions 100 years ago. Most of the current animal-nutrition models represent animal systems well and several have been used to successfully predict outcomes that had not previously been observed. Nevertheless, there are opportunities for further development of specific aspects of animal models. These include a more mechanistic representation of the control of feed intake, prediction of methyl-donor requirements and representation of the methionine cycle and methylation processes, and more mechanistic representation of individual animal diseases and the effects of microbial loads within commercial animal environments. Few models have been used for day-to-day decision making on farm, partly because of the: complexity of the models; difficulty in obtaining accurate information needed as model inputs; and flat pay-off response curves for many agricultural systems. However, a strong future for animal models is envisaged when they will be incorporated into precision livestock-farming systems, run real time for individual animals and will be used to electronically control operations within an enterprise.

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