The role of mathematical models of host-pathogen interactions for livestock health and production - a review

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The role of mathematical models of host–pathogen interactions for livestock health and production – a review*

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Compared with the application of mathematical models to study human diseases, models that describe animal responses to pathogen challenges are relatively rare. The aim of this review is to explain and show the role of mathematical host–pathogen interaction models in providing underpinning knowledge for improving animal health and sustaining livestock production. Existing host–pathogen interaction models can be assigned to one of three categories: (i) models of the infection and immune system dynamics, (ii) models that describe the impact of pathogen challenge on health, survival and production and (iii) models that consider the co-evolution of host and pathogen. State-of-the-art approaches are presented and discussed for models belonging to the first two categories only, as they concentrate on the host–pathogen dynamics within individuals. Models of the third category fall more into the class of epidemiological models, which deserve a review by themselves. An extensive review of published models reveals a rich spectrum of methodologies and approaches adopted in different modelling studies, and a strong discrepancy between models concerning diseases in animals and models aimed at tackling diseases in humans (most of which belong to the first category), with the latter being generally more sophisticated. The importance of accounting for the impact of infection not only on health but also on production poses a considerable challenge to the study of host–pathogen interactions in livestock. This has led to relatively simplistic representations of host–pathogen interaction in existing models for livestock diseases. Although these have proven appropriate for investigating hypotheses concerning the relationships between health and production traits, they do not provide predictions of an animal's response to pathogen challenge of sufficient accuracy that would be required for the design of appropriate disease control strategies. A synthesis between the modelling methodologies adopted in categories 1 and 2 would therefore be desirable. The progress achieved in mathematical modelling to study immunological processes relevant to human diseases, together with the current advances in the generation and analysis of biological data related to animal diseases, offers a great opportunity to develop a new generation of host–pathogen interaction models that take on a fundamental role in the study and control of disease in livestock.

Keywords: host–pathogen interaction, mathematical model, animal, review, immune system dynamics

Implications

This review contributes to the ongoing efforts for enhancing animal health and sustaining livestock production. By providing an overview of the state-of-the-art in modelling host–pathogen interactions, this review aims to give relevant insight into the contributions and shortcomings of current mathematical models in enhancing our understanding of animal responses to pathogen challenge and for devising appropriate surveillance and control strategies to improve these responses. Combining existing and upcoming modelling approaches with current advances in the acquisition of biological data may serve as a road map for creating a new generation of models that play a fundamental role in combating disease in livestock.

Introduction

The increasing demand for more and healthier food and rising concerns about emerging livestock diseases brought on by climate and pathogen resistance to pharmaceuticals and infrastructure change have placed animal health high on the priority list of livestock production (Perry and Grace, 2009; Department of the Environment, Food and Rural Affairs (Defra), 2010; Simm, 2010). Research underpinning our understanding of how animals respond to pathogen challenge and how to improve this response has never been

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of greater importance. An animal's response to infectious pathogens is a complex interaction of properties of the host, pathogen and environment, and therefore requires contributions from research across a range of disciplines including different branches of biology, epidemiology and environmental science. Over the recent years, more and more mathematical modellers have been employed to study host–pathogen interactions, although the focus has been primarily on modelling immunological processes relevant to human diseases. In contrast, the application of mathematical models to address issues concerning animal health has been relatively sparse.

The aim of this review, written from the perspective of a mathematician working with animal scientists over several years, is to illustrate how mathematical host–pathogen interaction models can contribute to enhancing our understanding of animal responses to pathogens and ultimately help in improving animal health. This will be achieved by outlining the general role of mathematical models in a field dominated by experimental data and by providing some insight into various types of host–pathogen interaction models that differ in their objectives and approaches. Concrete examples will serve to illustrate how different assumptions, concepts and methodologies are implemented into quantitative models and how they can be applied to address important animal health issues. This review is targeted not only towards animal scientists who seek to better understand how mathematical models work and what they can achieve, but also towards modellers who are interested in finding out about modelling approaches that are outside their area of expertise. Ultimately, this review aims to shed light on a potential new approach to tackle animal diseases that uses modelling to integrate theory and experiments.

The need for mathematical host–pathogen interaction models

Complementing empirical studies

The wealth of data from large-scale field studies and small animal models (e.g. mouse or rat) collected in the past decades has substantially improved our understanding of a variety of factors influencing host response to pathogens. Recent advances in molecular and genomic tools have added another dimension to our knowledge base, by providing a detailed insight of the genes and pathways involved in the host immune response. However, results from empirical studies are often limited in scope and validity as they are constrained by physical boundaries. The stark contrast between the large body of research findings and the sparse translation of these findings into practical disease control strategies points to substantial knowledge gaps that need to be overcome. Successful disease control strategies not only require knowledge about individual components of the host or pathogen dynamics, but also some understanding of the system as it functions as a whole (Perelson, 2002).

Throughout history, the language of mathematics has proven well suited for integrating diverse empirical findings into a holistic quantitative framework (Morel, 1998; Nowak and May, 2000; Perelson, 2002). Mathematical models have the benefit over empirical studies that they are free from physical constraints, thus enabling to test a wide spectrum of scenarios that may be difficult to test experimentally. The possibility to calculate the state of all system components represented in the model for any desired duration of time and at any desired frequency may provide the information needed to explain the phenomena observed in empirical studies in which only limited amounts of measurements can be taken. The models thus not only help to test hypotheses emerging from experimental studies, but can also reveal and fill important knowledge gaps leading to the generation of new hypotheses that can be tested in future experiments. Table 1 lists diverse generic functions of mathematical models that have proven useful in existing host–pathogen interaction models, some of which will be described with concrete examples provided here.

Help in devising surveillance and control strategies

The importance of mathematical and computational models of immune system dynamics for the development and testing of pharmaceuticals is evident, and the majority of published models of human diseases have been developed for this very purpose. Less attention has been given to reflect how host–pathogen interaction models could prove useful for devising

Table 1 *Functions of mathematical/computational models of host–pathogen interactions*

Function	Description
Describe	1. Integrate findings of diverse empirical studies into a holistic quantitative framework.
	2. Clarify assumptions and conceptual understanding.
	3. Identify key system components.
	4. Identify knowledge gaps.
Simulate and analyse	5. Test alternative hypotheses by simulating different scenarios.
	6. Assess the role of individual components on the dynamics of the entire system.
	7. Provide estimates for quantities that are difficult to measure.
	8. Help interpreting experimental data.
	9. Explain (often conflicting) phenomena observed in empirical studies.
Predict	10. Generate new hypotheses that can be tested in future experiments.
	11. Provide predictions of outcomes of intervention strategies and suggest control strategies.
	12. Offer new ways to analyse and interpret data.

control strategies for diseases in animals. Decisions about which animals should be diagnosed, vaccinated, treated or selected for breeding are generally based on observable biomarkers (e.g. acute phase proteins or other plasma proteins, faecal egg counts (FECs) for parasite infections, somatic cell counts for mastitis, etc.). Although some biomarkers relate to a particular immune response process (e.g. specific antibodies related to the humoral response), others (e.g. FEC and weight gain) are the cumulative result of a variety of interacting processes related to pathogen, host and environment. No biomarker alone can predict or identify animals that are most susceptible or most severely infected with 100% accuracy. Mathematical host–pathogen interaction can describe the underlying biological processes related to specific biomarkers and elucidate how these processes change over time and relate to other key processes (and thus to other potential biomarkers). The modelled relationships could further lead to the proposition of new potential biomarkers related to other important processes. In addition, as models provide time trends of infection characteristics, they could be used to predict the optimal timing and frequency at which biomarkers should be applied to enhance the accuracy of disease diagnostics and predictions of genetic risk of infection and selection response or treatment efficacy.

Three categories of host–pathogen interaction models

As illustrated in Figure 1, most host–pathogen interaction models can be assigned to one of three categories depending on the questions addressed and the experimental evidence incorporated. The first category comprises the large group of mathematical models that describe the within-host infection and immune system dynamics. The model presented in Example 1 falls into this category. The aim of these models is to synthesise information obtained from diverse pathological and immunological studies into a holistic quantitative framework and use this to gain insights into how specific components of the pathogen and/or immune system function and interact. These types of models find their application mainly in the development and testing of pharmaceuticals.

The second category of models addresses the relationship between immune functions and other biological processes related to survival or production. One common assumption underlying these models is that all biological processes demand nutritional resources and that trade-offs occur between mounting an (or alternative types of) immune response(s) and maintaining fitness or production levels when resources become scarce (Sheldon and Verhulst, 1996; Lochmiller and Deerenberg, 2000). These types of models arise in evolutionary ecology or livestock production science, in which the focus is not only on the impact of infection on animal health but also on the undesirable side effects related to reproduction and production (e.g. growth rate and milk yield). The model presented in Example 2 falls into category 2.

The third category of host–pathogen interaction models deals with the question of how the interactions between hosts and pathogens affect their co-evolution. These models are important for anticipating the long-term impact of control strategies that alter host and pathogen genetics, such as, for example, the use of anthelmintics to control parasitism,

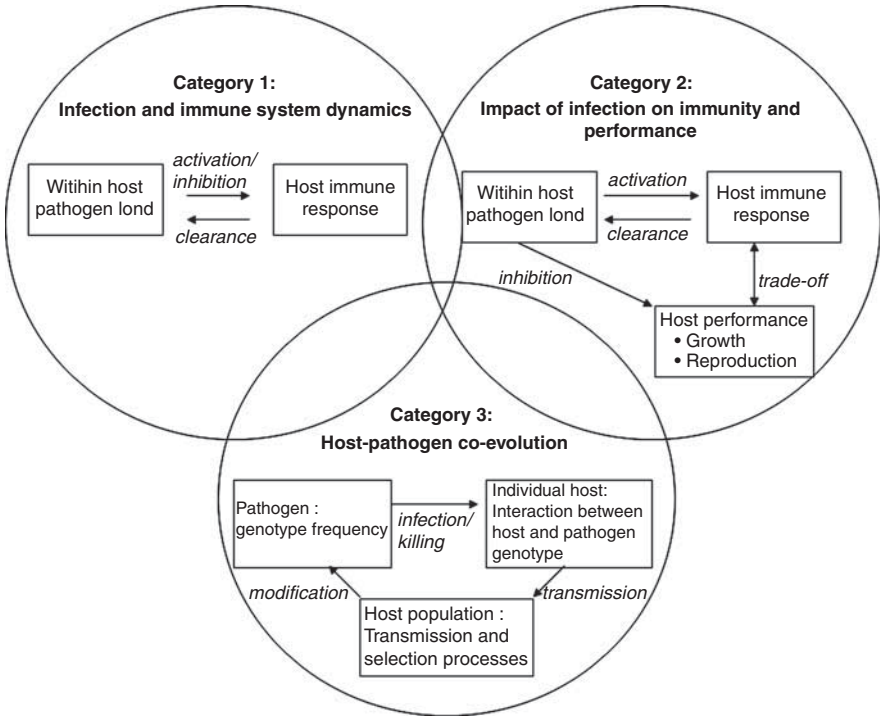

Figure 1 Schematic diagram of the three alternative categories of existing host–pathogen interaction models. The categories differ in the questions addressed by the models, the biological principles incorporated, the choice and representation of model components and in the methodology. The categories generally correspond to different research disciplines, although methodologies may overlap.

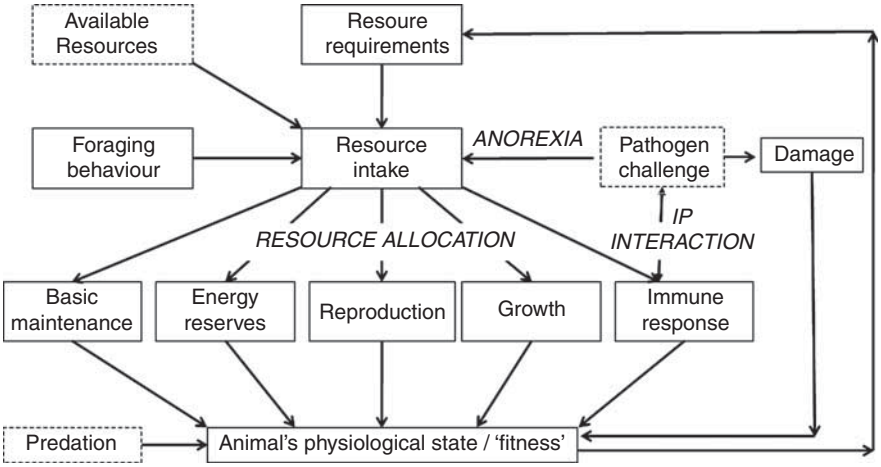

Figure 2 Schematic diagram of processes included in host–pathogen interaction models belonging to category 2. Not all processes/attributes are included in each model. Solid boxes refer to attributes of the animal and dashed boxes refer to attributes of the animal's environment. *ANOREXIA, RESOURCE ALLOCATION* and *IP INTERACTION* refer to biological processes represented in (some of) the models. For further explanation, see text.

which has resulted in the emergence of anthelmintic-resistant parasites and increased host susceptibility (Sangster, 1999; Jackson and Coop, 2000). The methodology for models belonging to category 3 differs from those of the other categories, as they concentrate less on the dynamic processes during infection of an individual host, but more on the transmission of pathogens and resulting evolutionary processes in the population. These models are more closely related to epidemiological models and merit a review on their own (e.g. Woolhouse *et al.*, 2002). In this review, I will focus on models that describe the host–pathogen interaction within individual hosts, that is, models belonging to the first two categories.

Category 1: models of infection and immune system dynamics

Overview of published models for animal diseases

In contrast to the vast amount of epidemiological models that describe the spread of infection between animals and predict disease prevalence and severity in the population, models that study the dynamics of infections in individual animals are relatively scarce. Although most epidemiological models incorporate expressions for the disease progression within animals (e.g. from latent infected to diseased to recovered state in compartmental models for micro-parasitic infections or more explicit descriptions of the life cycle of macro-parasites within and outside the host (Anderson and May, 1991)), they will not be considered here as they aim to address questions concerning disease prevalence in the population rather than in individual animals. Published models that concentrate on the within-host dynamics of infections exist for nematode infections in ruminants (Louie *et al.*, 2005; Vagenas *et al.*, 2007a and 2007b), gut and mammary gland infections in cattle caused by *Escherichia coli* and other bacterial infections related to mastitis in cattle (Oltenacu and Natzke, 1976; Detilleux, 2004; Detilleux *et al.*, 2006; Wood *et al.*, 2006a and 2006b; White *et al.*, 2010) and porcine reproductive and respiratory syndrome (PRRS) in pigs (Doeschl-Wilson and Galina-Pantoja, 2010).

PRRSV (virus) infection (see Example 1). Given the great economic importance of PRRS in many pig producing countries worldwide, PRRSV infection dynamics have been studied extensively in field and laboratory experiments (Zimmerman *et al.*, 2006). However, many fundamental questions remain unanswered that prevent the development of effective disease control strategies. The wealth of experimental evidence offers a great opportunity for mathematical models to combine the accumulating knowledge into a holistic quantitative framework.

A first step towards this goal, that is, a simple model for PRRSV infection dynamics, is outlined in detail in Example 1. The model describes how pathogen load, severity of infection and target cell numbers change over time in the absence of an immune response. For a more comprehensive model of PRRSV infection that includes immune response mechanisms, see Doeschl-Wilson and Galina-Pantoja (2010). The example presented here not only aims to show how findings from various empirical studies can be combined into a quantitative model (Table 1, point 1) but also illustrates that even very simple mathematical models can produce valuable scientific insights. In particular, discrepancies between model predictions and empirical observations point towards missing system components of great importance that warrant further experimental investigations and model development (Table 1, points 4 and 10).

Example 1: modelling host–virus interaction for the PRRSV infections in pigs

Questions arising from empirical studies

PRRS is an endemic viral pig disease causing reproductive failure in pregnant sows and respiratory disease with an often fatal outcome in growing pigs. A hallmark of PRRSV infection and reason for lack of efficient control to date is the

unusual pathogenesis and the atypical immune response it invokes (Murtaugh *et al.*, 2002). PRRSV targets primarily a subpopulation of macrophages in the lung and other tissues that have reached a specific stage of differentiation that renders them permissive to the virus (Duan *et al.*, 1997; Gaudrealt *et al.*, 2009).

PRRSV infection is characterised by an atypical pathogenesis consisting of a prolonged acute phase lasting for 1 month or longer, with peak virus levels in the blood and lung between 7 to 14 days post infection and followed by a persistent infection in the lung and lymphoid tissues that clears for most animals within 150 days post infection (Allende *et al.*, 2000), but can last in some (especially younger) pigs for several months or years (Lopez and Osorio, 2004; Figure 3a).

Compared with other common viruses, PRRSV fails to elicit any of the typical innate immune response mechanisms (van Reeth and Nauwynck, 2000; Murtaugh *et al.*, 2002), and the adaptive immune response is delayed and weak (Molitor *et al.*, 1997; Mulupuri *et al.*, 2008; Figure 3b).

The results of empirical studies thus raise the following question that (together with other questions) has been addressed by the mathematical model of Doeschl-Wilson and Galina-Pantoja (2010) and is described below.

What causes the decline in virus load during the acute phase of the infection before the onset of the adaptive immune response?

The mathematical model. The model describes the interaction between a replicating virus and host alveolar macrophages, the primary site of PRRSV infection, during the acute phase of infection, before the onset of the adaptive immune response (i.e. no VN antibodies and cytotoxic T-cells). The basic model for host–virus interaction contains four variables: uninfected, non-permissive macrophages z, uninfected permissive macrophages x, infected macrophages y and free virus particles v. It is assumed that uninfected non-permissible macrophages z are produced at a constant rate λ, become activated towards a PRRSV permissive state at a rate $\delta_1 z$ and die at a rate μz. Permissive uninfected macrophages x return to a non-permissive state at a rate $\delta_2 x$, die at a rate μx and become infected by PRRSV at a rate βxv. Infected cells die at a rate αy, with $\alpha \geqslant \mu$. Free virus is produced by infected cells at rate a κy and decays at a rate ϕv. These assumptions are graphically captured in Figure 4 and lead to the following system of ODEs (1).

$$\begin{aligned} \dot{z} &= \lambda - (\delta_1 + \mu)z + \delta_2 x \\ \dot{x} &= \delta_1 z - (\delta_2 + \mu)x - \beta xv \\ \dot{y} &= \beta xv - \alpha y \\ \dot{v} &= \kappa y - \varphi v. \end{aligned} \tag{1}$$

Mathematical stability analysis at the system's steady states shows that there are two possible outcomes for system (1 for system (1) (described by two equilibrium points): either the infection will not be able to establish itself in the host or it will converge to a persistent state with positive viral load (although viral load may be too low to be maintained in reality), as shown in Figure 5a and b. The characteristic of most interest to the first question above is that a decline in virus load to low levels as shown in Figure 5a and observed in empirical studies is only possible if the total number of macrophages decreases substantially. This, however, contradicts empirical findings, which suggest that macrophage numbers in infected tissues remain constant during the time course of infection (Labarque *et al.*, 2003; Xiao *et al.*, 2004). Applying the additional constraint that macrophages are replenished at a rate corresponding to a constant number of macrophages leads to a new persistent equilibrium. However, it is straightforward to prove that this equilibrium corresponds to a high virus load (Figure 5a). Hence, the model predicts that a decline in virus load, as

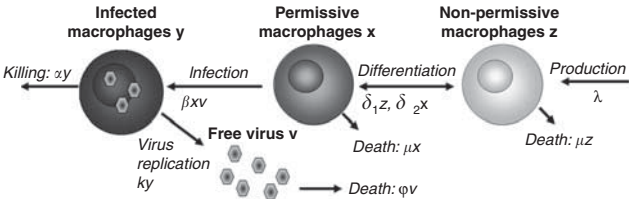

Figure 4 Schematic representation of the host–pathogen interaction model of porcine reproductive and respiratory syndrome in Example 1. For further explanation, see text.

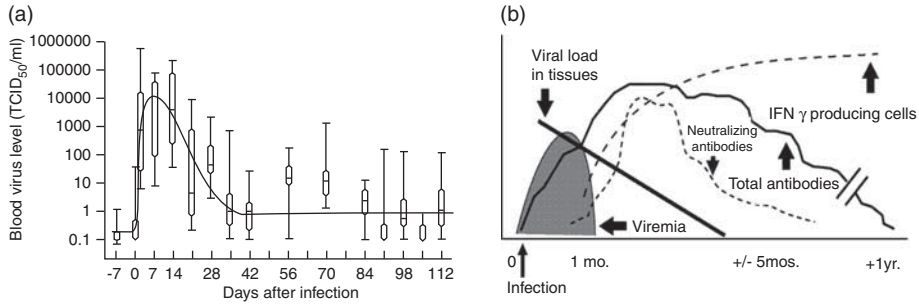

Figure 3 Time trends for virus load and immune responses observed in empirical studies. (a) Blood virus levels in pigs ($n = 16$) infected with a virulent strain of PRRSV in the experiment of Mulupuri *et al.* (2008). The horizontal bars in the box-whisker plots represent the mean, boxes represent the 75th percentile and whiskers extend to minimum and maximum values. (b) Scheme of temporal sequence of events after infection with PRRSV, adapted from Lopez and Osorio (2004); PRRSV = porcine reproductive and respiratory syndrome virus.

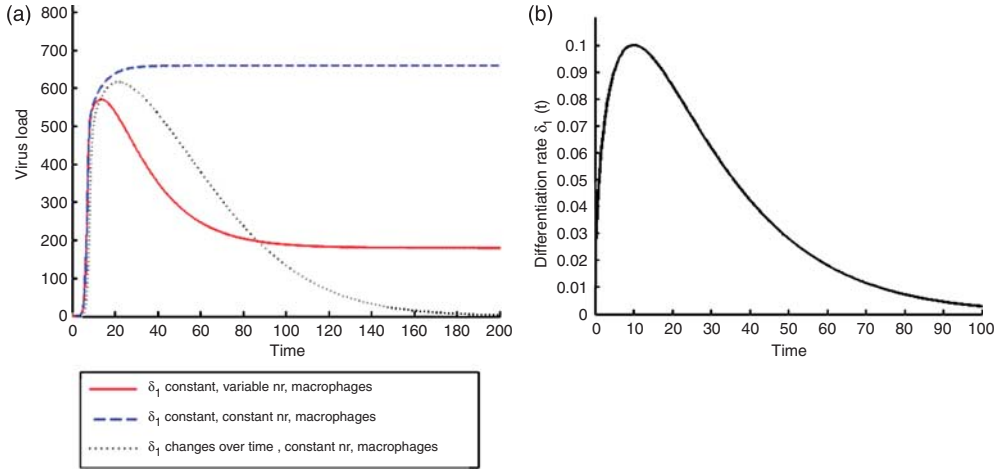

Figure 5 Predicted virus load profile for the PRRS model (1) with different assumptions concerning macrophage differentiation rate and total number of macrophages (a) and plot of the differentiation rate of lung macrophages, when assumed that it changes over time (b). Implementing this function into model (1) produces the dotted line for virus load shown in panel a.

observed in empirical studies, would not be possible under the assumptions incorporated in our model, that is, in the absence of immune response and a constant influx of new macrophages to maintain macrophage numbers constant. The results thus suggest that there are other important system components that need to be included in the model.

One possible mechanism that may affect the trend in virus load during the acute phase of infection is that macrophages may become less permissive during the time course of infection. Macrophage permissiveness over time has indeed been assessed in an *in vitro* infection experiment (Gaudrealt *et al*., 2009), but was found to increase within the first 5 days post infection. However, this time frame corresponds to the early stage of acute infection in which virus load still increases. Up to now, no published experimental study has investigated macrophage permissiveness over a sufficiently long time period to detect whether permissiveness decreases over a longer time period. The advantage of mathematical models is that they allow assessment of the outcome of hypothetical scenarios. Replacing the constant differentiation rate δ_1 in model (1) by the function $\delta_1(t) = at^b\exp(-ct)$, with parameters a, b and c describing fast differentiation rates at the early stages and slow differentiation rates at the later stages of infection (Figure 5b), indeed produces a reduction in virus load similar to those observed in experiments (Figure 3a).

This hypothesis is currently assessed in a laboratory study and stimulated a fruitful collaboration between mathematicians and molecular scientists. Preliminary results from the *in vitro* experiment confirm the hypothesis that macrophage permissiveness initially increases and declines after about 6 days post infection, and they also provide further insights into the underlying mechanisms responsible for this decline from which more accurate estimates for the differentiation rate $\delta_1(t)$ in the above model can be derived (Reyes-Umana, 2010).

Gastrointestinal parasitism in ruminants. An approach different from the PRRS infection model has been adopted for host–pathogen interaction models of gastrointestinal parasitism in ruminants, which, like all (epidemiological) macro-parasitic infection models, describe the life cycle of the parasite within the host from the intake of larvae to their establishment in the gastrointestinal tract and finally the production and excretion of larval eggs (Bishop and Stear, 1997; Louie *et al*., 2005; Vagenas *et al*., 2007a and 2007b). The model of Vagenas *et al*. (2007a and 2007b), presented in detail in Example 2, describes the impact of parasitism on both host immunity and performance, and therefore belongs to category 2. However, as infection and immune system dynamics have been modelled in a similar way as in all of the above models, the model is also partly considered here. In particular, host–pathogen interactions are described by the impact of larval challenge on the acquisition of immunity of the host (which are simple functions of the cumulative larval intake in the above-mentioned models), as well as by the influence of the host genotype and physiological or immune status on larval establishment, worm mortality and fecundity. Rather than containing explicit descriptions of individual immune processes, the models describe the effects of the host immune response on different stages of the parasite life cycles.

Model application consists of assessing the influence of diverse factors on the outcome of infection and of identifying key biological uncertainties for which field data are required. For example, Louie *et al*. (2005) established that parameters determining larvae establishment have the greatest influence on peak parasite burden, whereas parameters affecting mortality and fecundity had greater influence on the duration of the infection. Vagenas *et al*. (2007a) also identified larval establishment rate (E) as a key parameter determining the time trend of infection. In addition, they quantified the impact of different challenge doses, nutritional regimes (ranging from protein-rich to protein-scarce diets) and of the host genotype on parasite burden and other traits of interest.

Despite differences in the actual model equations, existing models of gastrointestinal parasite infections in ruminants are

similar in that they are hypothesis driven. In other words, they aim to provide an understanding of the influence of various factors on the infection dynamics, rather than to provide quantitatively accurate representations of individual immune processes. Obtaining accurate estimates of the model parameters and fitting the models to existing data may prove challenging as many key model parameters are defined on conceptual grounds (e.g. genotypes for growth or resistance) rather than representing measurable entities.

Example 2: modelling growth and immune response to gastrointestinal parasite challenge in immunologically naive lambs

In order to assess the influence of host genetics and nutrition on gastrointestinal parasitism in lambs, Vagenas *et al.* (2007a) developed a deterministic, dynamic simulation model that describes the growth and immune response of initially naive lambs facing pre-defined levels of nematode challenge. A schematic diagram of the basic concepts and rules for the host–pathogen interaction is shown in Figure 6. Inputs to the model are (genetically controlled) growth and resistance attributes of the host, feed quality, various parasitological parameters and daily larval intake. The model is built upon a nutritional framework, that is, all biological processes represented by the model are described in terms of nutrient requirements and nutrients allocated to the individual processes. For example, the host's growth genoytpe determines the desired nutrient intake, whereas the intake of parasitic larvae and established adult worms are assumed to result in nutrient loss for the host. The host counteracts this loss by mounting an immune response, which affects, in addition to the nutrient loss caused by larvae, the establishment rate of incoming larvae, mortality rate of adult worms and fecundity of female worms. Nutrient scarcity and the dilemma in nutrient allocation arises as a consequence of anorexia, which is modelled as a function of worm mass. Outputs include feed intake, growth rate and body composition, as well as worm burden and FEC.

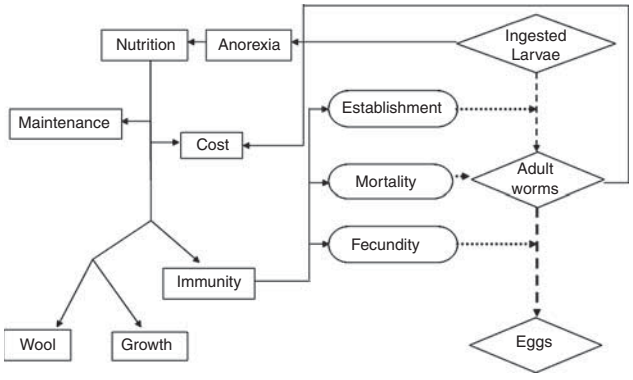

Figure 6 Schematic diagram of the host–parasite interaction model. Rectangular boxes indicate the fate of the ingested protein, rounded boxes indicated host–parasite interactions and diamond boxes indicate key quantifiable parasite life cycle stages. Dotted lines refer to the parasite life cycle. The figure was published in Vagenas *et al.* (2007a).

The model consists of a large number of mathematical equations describing changes in the model variables according to heuristically derived relationships. The time trends in the model variables are then described by first-order difference equations (i.e. $X(t+1) = X(t) + \mathrm{d}X^{*}\Delta t$), where a time step Δt of 1 day was used. Critical equations are those describing the rates of host-controlled establishment, fecundity and mortality of adult worms. These are sigmoidal functions of cumulative larval intake and relate the biological processes to nutrient requirements. For example, larval establishment (E) is described by

$$\mathrm{E} = \left(\varepsilon_{\max} \cdot \mathrm{e}^{-\mathrm{K_E} \cdot \left(\frac{\mathrm{PAC_{Imm}}}{\mathrm{PRQ_{Imm}}}\right) \cdot \sum_{t} \mathrm{LI}^{*}} \right) + \varepsilon_{\min},$$

where $\varepsilon_{\min}$ and $\varepsilon_{\max}$ are minimum and maximum rates of establishment, respectively, and $\mathrm{PRQ_{Imm}}$ and $\mathrm{PAC_{Imm}}$ are protein required and allocated to immunity, respectively, $\mathrm{K_E}$ is a scaling parameter and $\sum_{t} \mathrm{LI}^{*}$ is the scaled larval intake.

The model, and its extension to a population level, satisfied many of the functions listed in Table 1 (Vagenas *et al.*, 2007a, 2007b and 2008; Doeschl-Wilson *et al.*, 2008). By describing all biological processes in a nutritional context, the interactive effects of host genetics and nutrition on gastrointestinal parasitism, which are difficult to study experimentally, could be explored *in silico* (Table 1, points 1, 5, 6 and 7). The host–pathogen interaction model for individual animals was used to assess the time trends and severity of gastrointestinal parasitism in sheep of different growth and resistance characteristics, and kept in environments that vary in the provision of nutrients and exposure to parasites (Vagenas *et al.*, 2007b). One of the benefits of this model is that it provides time trends for observable output traits (e.g. growth rate and FEC), thus allowing assessment of the impact of different control factors at different stages of the infection (Table 1, points 11 and 12).

E. coli infections in the gut and mammary gland of cattle

Reflecting on the huge impact of *E. coli* on cattle health and milk production, and in some cases also on human health (for *E. coli O157*), several mathematical models exist for the within-animal infection dynamics of *E. coli*. Wood *et al.* (2006a) developed a stochastic simulation model that describes the ingestion process and the resulting bacterial population dynamics through simple birth–death and migration processes between different compartments in the bovine gut. Intensive literature search for parameter estimates and model fitting to experimental data showed that a variety of experimental features could be reproduced by the model (e.g. shedding duration and bacterial distributions in different gut compartments), but it also revealed important knowledge gaps that prevent the accurate prediction of bacterial time trends. Despite some uncertainties in the parameterisation, the model results suggest that although ingestion events in individual animals are expected to be rare, a small number of ingestion events would be sufficient to maintain the infection within

an animal. This insight was used in a subsequent paper in which the model was used to explore the efficacy of diverse control strategies (Wood *et al*., 2006b).

A more data-driven approach was adopted by Detilleux *et al*. (2006), who modelled the acute inflammatory response to *E. coli* of the bovine mammary gland. Their deterministic model consists of three relatively simple ordinary differential equations (ODEs) that describe the interactions between bacteria, milk somatic cells and blood leucocyte densities. By fitting the model equations to data from challenge studies, accurate estimates for the model parameters were obtained, and the influence of different experimental conditions (e.g. vaccinated and non-vaccinated animals, different bacterial strains) on the model parameters was assessed. The model also provided a threshold measure for the minimum milk cellular density necessary to protect the gland against *E. coli.* A similar approach (albeit a different model) had been applied in an earlier model of the same lead author to obtain an estimate of the minimum concentration of blood neutrophils necessary to decrease the concentration of other bacteria in mastitic milk (Detilleux, 2004). These studies show that even relatively simple models can produce accurate quantitative predictions and provide valuable insight into the role of different key parameters. However, simple models may not be able to capture all relevant phenomena observed in real studies. In this case, infection dynamics were adequately described for the acute stage of the infection but the model did not capture the persistent stage.

A model that is able to describe infection processes at any stage of mammary *E. coli* infection was recently developed by White *et al*. (2010), with the objective to determine the processes that lead to either transient or persistent infections. Their model includes a more detailed description of bacteria (distinguishing between intracellular *E. coli* and *E. coli* in milk), immune response mechanisms (including pro-inflammatory and inhibitory cytokines and concentrations of macrophages and polymorphonuclear cells) and environmental factors (impact of lactation on cell numbers) than other models. More complex models generally require more parameters. Parameter estimates were derived by using a combination of literature studies and fitting the model to data from individual cows with transient and persistent infections. On the basis of the results of the fitted models, the authors established the most likely causes of divergent outcomes (i.e. clearance or persistence).

In summary, there are relatively few models describing the within-host infection dynamics for specific diseases in animals. Existing models vary in their approach and in the level of detail in which biological processes are represented, but most models implement a very crude description of the host immune response and its effect on within-host–pathogen load.

Overview of published models for basic immune processes relevant for diseases in humans

In contrast to the few mathematical models that describe the dynamics of infections in animals, the application of mathematical modelling in the study of immune system dynamics in general and applied to human diseases is well established. The abundance of published immune response models can be partly attributed to the recent explosion of available experimental data, combined with the recognition that an in-depth understanding of the immune system with all its dynamic interactions cannot be deduced from experiments alone (Yates *et al*., 2001). In immunology, mathematical models have adopted the role of providing the (quantitative) theoretical framework for interpreting the wealth of available immunological data. In addition, the value of mathematical models in advancing the understanding of the immune system and in the development and *in silico* testing of treatment strategies has been convincingly described by models of human immunodeficiency virus (HIV) and some other infections in humans that emerged in the 1990s (see reviews by Morel, 1998; Perelson, 2002; Davenport *et al*., 2007). The success story of the early models has sparked much collaboration between mathematicians and immunologists since.

The extreme complexity of the immune system and the vast variety of available data representing different system components are mirrored by the great diversity of available mathematical models. Detailed information about various types of models of immune system dynamics published in the immunological and mathematical literature is beyond the scope of this review, but can be found in several excellent reviews (e.g. Morel, 1998; Nowak and May, 2000; Yates *et al*., 2001; Perelson, 2002; Louzoun, 2007; Kirschner and Linderman, 2009).

Existing models of immune system dynamics vary between those addressing basic immunological phenomena, such as antigen recognition or development of immune cells and effector mechanisms (e.g. Perelson and Wiegel, 1981; Antia *et al*., 2005; Souza-e-Silva *et al*., 2009), models that are generic for virus or bacterial infections (e.g. Antia and Koella, 1994; Antia *et al*., 1996; Nowak and Bangham, 1996; Kleinstein and Seiden, 2000; Pugliese and Gandolfi, 2008) and models that focus on a particular (mostly human) disease of interest (e.g. Marchuck *et al*., 1991; Wodarz, 2003; Kosmrlj *et al*., 2010; Smith and Ribeiro, 2010). Models differ widely in the level of detail and the temporal and spatial scales at which immune processes are represented as well as in their methodologies. Many (in particular, early) immunological models are more conceptual, focusing on a phenomenological description of the time course of infection that results from the interaction of a relatively small number of components (e.g. antigen with antibodies, T-cells or memory B cells; Perelson and Wiegel, 1981; Wodarz *et al*., 1999; Wodarz, 2003; Pugliese and Gandolfi, 2008). In these models, the description of the individual system components and their interactions can be simple (e.g. constant proliferation rates, ignoring time delay or spatial distribution) and model variables and parameters are often unscaled or described in arbitrary units (as in Example 1). Nevertheless, the dynamic properties of the simplistic model systems often mimic the complex dynamics observed in the real world, demonstrating the fact that complex behaviour can emerge from simple interactions between few components.

Increasing acquisition of data that produce detailed insight into the fine building blocks of the immune system, together with the shift from a reductionist to a systems view of biology (Kitano, 2002), also raises the demand for a shift in mathematical modelling. Traditional conceptual approaches are replaced by more data-driven approaches and mathematical systems with few components giving way to large networks. Citing Louzoun (2007), 'mathematical modelling in immunology is becoming more and more molecular'.

One hallmark of mathematical modelling of immune system dynamics is the incredibly rich repertoire of mathematical methodology applied, which has evolved over time in synchrony with the acquisition of new data. The advances in the collection, storage and analysis of biological data are also applicable to livestock diseases. Some of the most common approaches, which are relevant to the development of host–pathogen interaction models for livestock diseases, are outlined in the section 'Overview of mathematical methodologies used in host–pathogen interaction models'.

Category 2: models that consider the impact of infection on health and productive functions

An accurate understanding of the immune system dynamics is vital for the development of pharmaceuticals, but for the sustainability of livestock production a deep understanding of the relationship between health, reproduction and production traits is equally important. These questions are the focus of models belonging to category 2, which arise mainly from evolutionary ecology and livestock production science. Evolutionary ecologists are interested in understanding the factors influencing an animal's 'decision making', in particular when investment in immunity competes with investment in reproduction or other survival traits (Medley, 2002; Houston *et al*., 2007). Ultimately, the understanding will provide insight into the evolution of immune and survival functions in animal species. In contrast, livestock production scientists are more interested in predicting the influence of infection on productive traits (Lescourret and Coulon, 1994), in anticipating the consequence of genetic selection on animal health and production and in determining the role of environmental factors (e.g. pathogen challenge and nutrition) on the health–production relationship. Their ultimate aim is to obtain the necessary understanding for minimising the detrimental effects and side effects of disease on animal health and other traits of interest.

Basic principles of models in category 2

A common assumption underlying the majority of host–pathogen interaction models of category 2 is that immunity, like all biological processes, requires resources (e.g. protein and energy). Resource scarcity, either resulting from environmental conditions (e.g. food shortage due to seasonal effects) or from infection-induced anorexia (Exton, 1997; Ayres and Schneider, 2010) causes a trade-off between diverse resource-demanding functions. The observed response of an animal in terms of immunity, reproduction and/or production is then the outcome of an individual's distribution of resources between different competing processes.

The schematic diagram of Figure 2 illustrates how the above-described nutritional framework is incorporated in the host–pathogen interaction models belonging to category 2. Despite the common conceptual approach, models differ in the actual components included in the models (e.g. no model considers all of the listed body functions in the nutrient allocation simultaneously and only a few models included infection-induced anorexia), in the representation of pathogen challenge (e.g. pathogen dose, incoming larvae and infection pressure) and resources (e.g. energy or protein), in the resource allocation rule and in the description of the interaction between pathogens and the host's immune response.

Host–pathogen interaction models of category 2 in evolutionary ecology

Host–pathogen interaction models in evolutionary ecology aim to determine the optimum host defence strategy (mainly allocation of resources) corresponding to minimum resource requirements (Shudo and Iwasa, 2001), maximum chance of survival (e.g. McNamara and Buchanan, 2005; Houston *et al*., 2007) or maximum number of offspring (e.g. Medley, 2002). They assess how optimum allocation depends on various factors such as nutrient availability, pathogen challenge or the physiological status of the host, with the aim to explain contrasting phenomena observed in field studies.

Examples of evolutionary ecology models applying the principle of trade-offs to host–pathogen interactions for an individual animal include the model of Medley (2002), who showed that the optimal defence strategy of a host exposed to a constant parasite challenge may be to tolerate rather than to clear parasites. The model also investigates how the optimum level of parasites to be tolerated depends on host resource acquisition, on parasite pathogenicity and on host exposure level to the parasite. The model provides theoretical support for the hypothesis emerging from field observations that non-zero parasite burden could be beneficial to the host (Behnke *et al*., 1992), and also offers some explanation for the observed variations in parasite burdens between hosts and parasite species.

Houston *et al*. (2007) applied the principle of nutrient allocation to examine the trade-off between accumulating energy reserves to avoid starvation and investing in immunity to avoid death by disease for animals exposed to changing environmental conditions. Their model suggests that the optimal host strategy at a given time depends largely on the host's energy reserves and on the frequency of changes in food availability.

Trade-offs occur not only between immunity and other fitness functions or production, but also between different immune processes, such as between immediate or delayed responses (Segel and Bar-Or, 1999) or between cellular and humoral immune responses (Bankroft *et al*., 1994). For example, mouse experiments showed that different doses of the same pathogen or pathogens with different virulence

could lead to divergent differentiation of Th0 cells into either Th1 or Th2 cells activating cellular or humoral immune response mechanisms, respectively (Janeway *et al*., 1999). This motivated Shudo and Iwasa (2001) to develop a mathematical model to investigate whether different dominance patterns between immune response mechanisms could be inferred from energy costs associated with different defence strategies. Weighting the energy cost of defence associated with different types of immune responses against inflicted damage, their model showed that response mechanisms that require no or little time delay would be beneficial over delayed response if pathogen dose and virulence are high, thus supporting the experimental findings.

Although the processes implemented into these models differ, the models share the underlying principle of trade-off arising from resource scarcity and partitioning. In addition, all of these models are represented as systems of ODEs (see section 'Overview of mathematical methodology' below).

Host–pathogen interaction models of category 2 in livestock science

Generic models for micro-parasitic infections. Host–pathogen interaction models in livestock production science are aimed more at determining the optimal control than optimal host strategy. The underlying assumption of these models is that the host genotype largely determines the nutrient requirements and/or nutrient allocation between different biological processes and that the partitioning rules are known. The models are then used to assess how changes in the animal's genotype (e.g. through genetic selection) or changes in environmental conditions (e.g. different pathogen challenge, nutrient availability or diet composition) affect nutrient intake and allocation and consequently also the observable phenotypes related to health, reproduction and production (e.g. van der Waaij *et al*., 2000; van der Waaij, 2004; Vagenas *et al*., 2007a, 2007b and 2008; Doeschl-Wilson *et al*., 2008 and 2009a). In particular, the models aim to shed light on the ongoing debate about how genetic selection influences the relationship between disease resistance and (re-) production (Knap and Bishop, 2000; Houdijk and Bünger, 2006; Doeschl-Wilson *et al*., 2009b). It has been suggested that selection for increased production over the last decades has made animals on average more susceptible to disease as it may draw resources away from immune defence towards costly productive processes when nutrients are scarce (Sheldon and Verhulst, 1996; Lochmiller and Deerenberg, 2000). However, empirical evidence based on estimates of genetic correlations between health and production traits also exists for the contrary, as reviewed by Rauw *et al*. (1998).

As described by van der Waaij *et al*. (2000) and van der Waaij (2004), it is possible to assess the consequences of genetic selection on the animal's ability to cope with infectious challenge with models that do not include explicit expressions for host–pathogen interactions. Representing host–pathogen interactions simply by the extent to which genotypes for production and fitness can be realised (with high infectious pressure corresponding to low realised production), van der Waaij *et al*. (2000) showed that selection for observed production could result in increased disease resistance when animals are exposed to constant infection pressure. A later model (van der Waaij, 2004) then described how changes in resource availability and partitioning caused by genetic selection for observed production could affect both the sign and degree of genetic correlations between production and fitness traits.

More recently, Doeschl-Wilson *et al*. (2009a) used a generic model for host–pathogen interactions for micro-parasitic infections to explore genetic and nutritional influences on the production–disease resistance relationship over time. The underlying assumption of this model was that the host's genetic capacities for growth and immune response determine its nutrient requirements and preference of allocating nutrients to either process. In addition, nutrient availability (which is reduced due to infection-induced anorexia) and allocation stipulate the extent to which the genotypes are expressed if the animal is challenged by pathogens. The simulations demonstrate that a host's response to pathogen challenge is the result of a complex interaction between host genotypes and the nutritional environment, and that different outcomes to genetic selection could be expected if selection was performed under nutrient-rich or nutrient-scarce conditions (Doeschl-Wilson *et al*., 2009a). The model also reveals the importance of appropriate timing of measurements on which selection is to be based, as the same selection criteria applied at different time points could lead to different trends in genetic improvement. All models belonging to category 2 mentioned so far are non-specific to any particular type of pathogen and typically represent pathogen challenge, immune response, host genotype and nutrition through single entities with arbitrary units. The objective of these models is to explain general phenomena rather than to accurately predict the outcome for a particular disease.

A specific model for the influence of parasitism on sheep health and production (see Example 2). To the best of my knowledge, the only (mechanistic) host–pathogen interaction model that explores how pathogen challenge affects both production and health for a particular disease is the model for gastrointestinal parasitism in growing lambs by Vagenas *et al*. (2007a). As outlined in more detail in Example 2, the model adopts similar principles for nutrient requirements and distribution as the generic model of Doeschl-Wilson *et al*. (2009a) to simulate nutrient utilisation, growth, immune status and parasite burden of an infected sheep on a daily basis. One of the main benefits of a disease-specific model over generic models is that the model can provide quantitative predictions for observable growth and resistance traits (e.g. body weight and FECs), which can be compared with existing data. For example, extreme correlations between resistance and growth, similar to those derived from field studies (McEwan *et al*., 1992, 1995) could only be reproduced by the model of Vagenas *et al*. (2007a and 2007b) if underlying traits were genetically related (Doeschl-Wilson *et al*., 2008). The results thus point to pleiotropic or linkage

effects between underlying growth and resistance mechanisms related to parasitism. In addition, the model offered some explanations with regard to dietary effects on the growth–resistance relationship explored in various field studies (e.g. Greer, 2008; Zaralis *et al*., 2008). The model results suggest that infection-induced anorexia is more likely to be observed when nutrition is rich in dietary proteins (Vagenas *et al*., 2007b), and that genetic correlations between growth and resistance traits are stronger in protein-scarce than protein-rich environments (Vagenas *et al*., 2008).

Nutrient intake and allocation as key drivers in models of category 2

Nutrient intake and partitioning are key drivers determining the observed host response to infectious challenge in all models belonging to category 2 (Figure 2). Whereas nutrient intake is either provided as model input or can be predicted based on existing theoretical frameworks (e.g. Kyriazakis and Emmans, 1999; Sandberg *et al*., 2006; Kyriazakis and Doeschl-Wilson, 2009), all models rely on assumptions concerning how nutrients are partitioned between different body functions that are difficult to verify with experimental data (Friggens and Newbold, 2007). It is therefore not surprising that substantial differences exist between nutrient allocation rules adopted in different models. For example, van der Waaij (2004) assumed that nutrient partitioning is a genetic characteristic of the host, independent of the host's physiological status or level of infectious challenge. In the models of Vagenas *et al*. (2007a and 2007b) and Doeschl-Wilson *et al*. (2009a), nutrient allocation to growth and immunity is status- and genotype-dependent and based on the relative nutrient requirements for either process. In contrast, Medley (2002) proposed that the proportion of resources allocated to the immune response depends on the pathogen load and does not exceed a fixed proportion of the total resources available to the host. Given the importance of nutrient allocation for determining the health–production relationship, more research efforts to come up with a unified framework would be warranted. These could extend existing theoretical frameworks for predicting nutrient partitioning based on empirical observations (Coop and Kyriazakis, 1999; Houdijk *et al*., 2001; Friggens and Newbold, 2007).

Description of host–pathogen interactions in models of category 2

In contrast to the infection models of category 1, all models belonging to category 2 adopt a relatively simplistic description of host–pathogen interactions. In the simplest case, host–pathogen interaction is only indirectly described by the impact of pathogen challenge on the expression of the host genotype (e.g. van der Waaij *et al*., 2000; van der Waaij, 2004) or by the probability of death due to disease (Houston *et al*., 2007). Others describe host–pathogen interaction by the impact of pathogen challenge on the immune response alone, ignoring how the immune response affects the within-host pathogen load (e.g. Medley, 2002). Conversely, the interactions were also described by the impact of the immune response on the pathogen load (e.g. Shudo and Iwasa, 2001), assuming that the strength of the immune response is constant over the time course of infection and independent of the type or degree of pathogen challenge. Even models that incorporate explicit two-way interactions between the host immune response and within-host pathogen load (e.g. Vagenas *et al*., 2007a; Doeschl-Wilson *et al*., 2009a) only describe the immune response by a single or few entities representing, for example, the intensity of the immune response or the nutrient requirements for immunity.

Besides the risk of ignoring the role of essential system ingredients, the consequence of this simplistic representation of the immune system is that the models are restricted to exploring qualitative behaviour and trends with regard to the infection dynamics, and have limited predictive power. Currently, a number of models exist that predict the growth and body composition of animals relatively accurately when animals are raised in healthy environments (e.g. Knap, 1999; Green and Whittemore, 2003) or challenged with social stressors (Wellock *et al*., 2003). However, to this date, no model exists that can accurately predict how these traits are affected if animals are infectiously challenged (Kyriazakis and Houdijk, 2007).

Including a more detailed description of the immune response into these models would require specification of resource requirements and allocation corresponding to each individual immune process captured by the model. Several studies have shown that estimates for protein and energy requirements for immune processes in animals can be empirically derived (Lochmiller and Deerenberg, 2000; Houdijk *et al*., 2001; Klasing, 2007). The model of Romanyukha *et al*. (2006) illustrates that empirical estimation of resource requirements for specific immune processes is feasible and can lead to valuable model predictions: after deriving estimates of energy requirements for eight different immune processes relevant in pneumonia infections, their mathematical model could predict whether pneumonia infections will lead to acute or chronic conditions based on energy costs alone. The theoretical frameworks for predicting nutrient partitioning mentioned above may serve as a good basis for deriving quantitative estimates of nutrient allocation to the immunological and other biological processes considered in the models.

Alternative approaches to model the effect of infection on production traits

Not all models belonging to category 2 addressing the relationship between health and production traits are based on biological principles. For example, the two independent simulation models for predicting the impact of mastitis on milk production in dairy cows (Oltenacu and Natzke, 1976; Lescourret and Coulon, 1994) build upon the results of statistical analyses of mastitis and lactation data from commercial dairy herds rather than upon biological concepts. Although the data-driven models may provide a useful means to investigate the effect of changes in animal characteristics

and management on milk production (Lescourret and Coulon, 1994), their scope is limited as extrapolation of model results beyond the conditions captured by the available data is questionable.

Overview of mathematical methodologies used in host–pathogen interaction models

The spectrum of mathematical methodologies applied to model host–pathogen interactions, in particular to model immunological processes, is extremely rich. Different methodologies often generate different kinds of insight, and the choice of the most appropriate methodology for the question at hand may not always be obvious. This section of the review summarises the principles, strengths and weaknesses of the most widely applied mathematical tools in current host–pathogen interaction models.

Systems of differential equations (DEs)
Traditionally, dynamical systems in mathematics are represented by sets of DEs (ODE, if change of system with respect to time is studied and partial DEs, if a spatial component is included). The model in Example 1 is represented through ODEs, and most host–pathogen interaction models in evolutionary biology consist of ODE systems. Equipped with a robust set of mathematical tools to solve and analyse the behaviour of DEs developed by mathematicians over centuries, DEs (in particular, ODEs) have been used widely in models of immune reactions in previous years and are most likely to continue being used in the future for systems comprising a limited number of components. Despite their popularity, DEs have several important limitations: first, non-linearities in the system can cause difficulties in deriving (analytical or numerical) solutions of the DE systems, especially if the system contains a large number of variables, or if parameters are symbolic rather than actual values (which lend themselves to more thorough mathematical analysis). Second, as the variables of DE models describe generally a number or density of specific components (e.g. cells and virus particles), they rely on the assumption that entities are identical. Individual variation, brought on, for example, by genetic heterogeneities of hosts or pathogens or different life histories, is not easily captured by these models. Another limitation of DEs is that they are deterministic and thus only provide information about the average behaviour of a system rather than about the distributions of possible outcomes. In addition, model variables can adopt arbitrary small values that may not be realistic, such as pathogen loads corresponding to <1 pathogen particle, and the modeller is faced with making subjective decisions on how to interpret these values.

Mechanistic stochastic models
Many of these limitations can be overcome by introducing a chance element to the dynamic processes described by the DE models, using stochastic modelling approaches (e.g. Renshaw, 1991). A chance element can be introduced to the initial conditions (e.g. initial pathogen challenge, host status and time of infection) or to the occurrence of particular events captured by the models. All stochastic models therefore require the use of random number generators and, as every realisation of the model leads to a different prediction, multiple simulations to determine the expected range of behaviour. The models thus provide a distribution of outputs rather than single predictions of the average system behaviour. Stochastic models are particularly useful in scenarios in which chance fluctuations become important, as for example, when pathogen load or immune responses can be eliminated due to stochastic fade-out (Wood *et al.*, 2006a; White *et al.*, 2010). As these models are usually computationally demanding and more difficult to analyse than deterministic models, application of stochastic approaches to model host–pathogen interactions are at present relatively sparse.

Cellular automata (CA) and agent-based models (ABMs)
CA and ABMs are the biological alternatives to the mechanistic DEs and their stochastic equivalents. Rather than applying sophisticated mathematical methods to obtain (analytical or approximate) solutions to a given set of equations representing the entire system dynamics, CA and ABMs simulate (usually simple) local interactions between discrete 'cells' (or 'agents' in case of ABMs) (Wolfram, 1994; Bauer *et al.*, 2009). The dynamic evolution of the system is then completely described by the specified rules of interaction. The underlying assumption of these types of models is that complex patterns can emerge from relatively simple sets of interactions between system components, and the aim of these models is therefore to establish the rules that generate similar dynamic behavioural patterns as those observed in real systems. In contrast to the continuous DEs, CA and ABMs are discrete in both time and space.

Originally, CA models were deterministic and consisted of a regular grid of identical cells that assume a finite set of states, which solely depend on the states of the neighbouring cells (Wolfram, 1994). Although restrictive, the mathematical properties of these types of models were well characterised. Several types of CA models have been developed to model different aspects of the immune system (Celada and Seiden, 1992; Seiden and Celada, 1992; Morpurgo *et al.*, 1995; Zorzenon dos Santos and Coutinho, 2001; Shi *et al.*, 2008) of which the immune simulator IMMSIM (Kleinstein and Seiden, 2000) is probably the best known. However, most of these CA models involve essential modifications of the original concepts of CA (e.g. stochastic or continuous CAs and entities can move between sites, etc.).

ABMs are natural extensions of CA models, relying on the same principle that complex dynamic behaviour emerges from local interactions of discrete agents, but applying less restrictive rules. ABMs are stochastic, thus providing a distribution of outputs rather than single predictions of the average system behaviour. As the rules are still simple but less restrictive than the CA rules, ABMs can handle a large number of different immune system agents. Reflecting the trend of increasing data production in experimental immunology, ABMs of immune processes have emerged due to the desire to provide a more comprehensive description of the

complex immune network, comprising a large number of interacting entities together with their inherent stochasticity. Examples of existing ABMs of host–pathogen interactions and their pros and cons are discussed in the review of Bauer *et al.* (2009). The majority or CA or ABMs model 'generic' immune processes rather than specific diseases. ABMs are relatively new in mathematical immunology and to the best of my knowledge have not yet been applied to study the relationship between processes related to health and production.

The main advantage of CAs and ABMs over ODE models is that the components and processes are represented in biological language, thus lending themselves more easily to biological applications and interpretations (Kleinstein and Seiden, 2000). Despite their simplicity, they are able to generate a rich spectrum of complex dynamic patterns (Ganguly *et al.*, 2003; Bauer *et al.*, 2009). Integration of new biological insights into the model rules is relatively straightforward for these types of models compared with the mechanistic DE or stochastic models, which do not lend themselves easily to model extensions (Louzoun, 2007). However, several restrictions apply to CA and ABMs: first, the simulations are often sensitive to parameter changes, so that model validation requires a comprehensive sensitivity analysis (Louzoun, 2007). As the overall system behaviour emerges from local interactions, it can be difficult to discern whether an unexpected result is the reflection of a programming mistake or a surprising emerging property of the model. The simplicity of implementation and versatility of these models thus needs to be weighed against the difficulty in identifying the key mechanisms controlling the observed dynamics. Hence, whereas mechanistic DE or stochastic models may be time consuming to build and unfriendly to use, CA and ABMs are generally easy to code and use, but the generation and analysis of results can be time consuming and difficult.

Bioinformatics and systems biology

Growing information with regard to the pathogen genomes and molecular and biochemical pathways involved in the host immune response has shifted the demand of quantitative methods beyond the realm of mathematics towards bioinformatics and systems biology, which are focused on interpreting the large data sets emerging from genomic studies (Louzoun, 2007; Forst, 2010). Bioinformatics and systems biology are closely related. While bioinformatics is the science of using computer technology to gather, store, analyse and merge biological data (www.yourgenome.org/glossary/), systems biology aims at understanding the dynamic interaction between the identified system components. The underlying ethos of systems biology is that biological questions are addressed through integrating experiments with computational modelling, simulation and theory, in iterative cycles (Forst, 2010). Thus, in comparison to the above-described modelling techniques (DEs, CA or ABMs), they are much more data driven rather than built upon theoretical concepts. In addition, in contrast to the majority of existing mathematical host–pathogen interaction models, bioinformatics and systems biology operate (primarily) at a molecular level, for example, by using as input genomic sequences of pathogens and involving computational prediction algorithms to identify the pathogenic molecules to which the host immune response reacts (Lundegaard *et al.*, 2007). Adding genomic resolution has the benefit that resistance and susceptibility patterns between pathogens and genetically different hosts can be explored. However, in order to predict how molecular interactions determine the outcome of infection, the model has to operate on multiple scales ranging from the molecular to the whole organism. This is a major challenge that has been addressed only by a few studies. A framework for integrating bioinformatics with dynamic simulation models was first outlined by Rapin *et al.* (2006), who combined a simple ODE-based mechanistic model with bioinformatics to determine how the mutation process of HIV (as predicted by bioinformatic algorithms) affects the infection dynamics. More recently, Kosmrlj *et al.* (2010) solved one of the long-standing mysteries in HIV research by integrating bioinformatics and systems biology approaches with sophisticated ODE models (Katsnelson, 2010). Their model combined three approaches: (i) bioinformatic algorithms for quantifying peptide binding in host-specific cell-surface proteins that detect viruses and present them to T-cells, (ii) stochastic simulations to predict how these affect T-cell maturation and (iii) an ODE model for studying the effect of peptide binding in cell-surface proteins and T-cell maturation on the virus set point and the within-host evolution of HIV. This synthesis of methodologies led to a convincing quantitative explanation of why some people never develop AIDS after becoming infected with HIV (Katsnelson, 2010).

Integrating molecular information into dynamic simulation models is still in its infancy and has (to my knowledge) only been shown for HIV, for which extensive information on pathogen and human genome or proteome, and good estimates exist for proliferation, division and death rates of immune system components. Model implications discussed in the literature exclusively concern drug development or administration. Given the current trend in molecular research, the time will soon be ripe for exploring similar approaches to tackle animal diseases.

What is a good mathematical model?

After being presented with different types of mathematical models using different principles and mathematical methodologies, the question arises, which mathematical model is most appropriate for addressing specific issues concerning host–pathogen interactions in animals. The choice of an appropriate model depends primarily on the modelling objective: should the model be explorative or predictive? Are we interested in better understanding a particular phenomenon or in obtaining quantitatively correct predictions for the outcome of a certain treatment? To answer questions of the first kind (explorative and improved understanding), a simple model consisting of a small number of key components may be adequate, whereas a comprehensive model including as many known components of significant influence as possible may be required to provide accurate predictions.

Irrespective of the model complexity, the most important rule of thumb for creating any model is the principle of

Occam's razor, which states that one should choose from a set of equivalent models of a particular phenomenon always the simplest one. This implies that a model should not extrapolate too far beyond the current knowledge of the system, as this would require several assumptions that may not be met. Application of this principle has been exemplified by the progression of HIV models during the last decades. Starting with small sets of DEs with very few parameters in the initial stages of HIV modelling (e.g. Nowak and May, 1991 and 1993), the gradual accumulation of in-depth knowledge has evolved HIV modelling towards a combination of mathematical tools including computational algorithms in systems biology and extensive systems of DEs (Rapin *et al.*, 2006; Kosmrlj *et al.*, 2010). However, as illustrated by the early HIV models and by the numerous models outlined in this review, even simple models can provide useful insights with strong implications. In fact, one of the great dangers arising from the current generation of vast amount of data is that they may produce models that provide more accurate representations of reality, but do not enhance the understanding of the system. As Mata and Cohn (2007) warn: 'building a mathematical web around a random collection of observations does not in itself increase understanding.'

Another critical factor for choosing an appropriate model concerns model validation. Generally, 'the more assumptions that have to be put into a model, the harder it is to be confident about the conclusions' (Morel, 1998). A model that contains many parameters with unknown values is difficult to validate, as a comprehensive sensitivity analysis testing the outcome for all possible parameter combinations is virtually impossible. As discussed above, some modelling methodologies lend themselves better to model validation than others. For example, validation of DE models is generally more robust than validation of, for example, CA or ABMs due to the symbolic mathematical toolset (e.g. bifurcation and stability analysis) that exists for the more classical mathematical approaches. Model developers are often faced with a trade-off between ease of computing, of interpretation of results and model validation.

Conclusions and the way forward

As shown through numerous examples, mathematical models of host–pathogen interactions in animals are a valuable complement to empirical studies to improve our understanding of the processes underlying an animal's response to infectious challenge. This understanding is crucial for the control of livestock diseases and the sustainability of livestock production and human health. Given the important role of livestock production in feeding an ever-increasing human population, mathematical models of livestock disease are faced with the additional challenge compared with models of human disease that they should account for the impact of disease on animal health and performance and environmental impact simultaneously. The nutrient allocation framework has proved valuable for linking processes associated with immunity, reproduction and production but needs to be complemented with a more sophisticated representation of the biological processes involved in an animal's response to pathogen challenge that integrates the vast amount of information emerging from field and laboratory studies. To achieve this, animal scientists should follow the footsteps of immunologists in developing fruitful collaboration with mathematicians and adapt the established methodologies and insights gained from immunological models aimed at tackling human diseases to diseases in livestock. The model development should also take into account that compared to human diseases in which treatment focuses on the application of pharmaceuticals, a larger set of tools may be available to control disease in livestock. These include diverse changes in animal husbandry, breeding for disease resistance or other genetic control strategies. In particular, greater attention should be given to the role of host genetics and nutrition when modelling host–pathogen interactions in livestock.

In conclusion, there is work to do before we can exploit the benefits of mathematical models of host–pathogen interactions to their full potential when tackling disease in livestock. However, rather than being confronted with the difficult task of inventing new tools, the work entails a skilful assembly of existing building blocks.

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References

Allende R, Laegreid WW, Kutish GF, Galeota JA, Wills RW and Osorio FA 2000. Porcine reproductive and respiratory syndrome virus: description of persistence in individual pigs upon experimental infection. Journal of Virology 74, 10834–10837.

Anderson RM and May RM 1991. Infectious disease of humans – dynamics and control. Oxford University Press, New York.

Antia R and Koella JC 1994. A model for non-specific immunity. Journal of Theoretical Biology 168, 141–150.

Antia R, Koella JC and Perrot V 1996. Models of the within-host dynamics of persistent mycobacterial infections. Proceedings of Biological Sciences 263, 257–263.

Antia R, Ganusov VV and Ahmed R 2005. The role of models in understanding CD8+ T-cell memory. Nature Reviews Immunology 5, 101–111.

Ayres JS and Schneider DS 2010. The role of anorexia in resistance and tolerance to infections in Drosophila. PLoS ONE Biology 7, e1000150.

Bankroft AJ, Else KJ and Grencis RK 1994. Low-level infection with Trichris muris significantly affects the polarization of the CD4 response. European Journal of Immunology 24, 3113–3118.

Bauer AL, Beauchemin CAA and Perelson AS 2009. Agent-based modeling of host-pathogen systems: the successes and challenges. Information Sciences 179, 1379–1389.

Behnke JM, Barnard CJ and Wakelin D 1992. Understanding chronic nematode infections: evolutionary considerations, current hypotheses and the way forward. International Journal of Parasitology 22, 861–907.

Bishop SC and Stear MJ 1997. Modelling responses to selection for resistance to gastro-intestinal parasites in sheep. Animal Science 64, 469–478.

Celada F and Seiden PE 1992. A computer model of cellular interactions in the immune system. Immunology Today 13, 56–61.

Coop RL and Kyriazakis I 1999. Nutrition–parasite interactions. Veterinary Parasitology 84, 187–204.

Davenport MP, Ribeiro RM, Zhang L, Wilson DP and Perelson AS 2007. Understanding the mechanisms and limitations of immune control of HIV. Immunological Reviews 216, 153–163.

Department for Environment Food and Rural Affairs (Defra) 2010. 'Food 2030'. Retrieved June 28, 2010, from http://www.defra.gov.uk/foodfarm/food/strategy/.

Detilleux J 2004. Neurophils in the war against *Staphylococcus aureus*: predator–prey models to the rescue. Journal of Dairy Science 87, 3716–3724.

Detilleux J, Vangroenweghe F and Burvenich C 2006. Mathematical model of the acute inflammatory response to *Escherichia coli* in intramammary challenge. Journal of Dairy Science 89, 3455–3465.

Doeschl-Wilson AB and Galina-Pantoja L 2010. Using mathematical models to unravel some mysteries of host–pathogen interaction in mammals: insights from a viral disease in pigs. In Host–pathogen interactions: genetics, immunology and physiology (ed. A Barton), pp. 109–131. Nova Science Publishers, USA.

Doeschl-Wilson AB, Vagenas D, Kyriazakis I and Bishop SC 2008. Challenging the assumptions underlying genetic variation in host nematode resistance. Genetics Selection and Evolution 40, 241–264.

Doeschl-Wilson AB, Brindle W, Emmans G and Kyriazakis I 2009a. Unravelling the relationship between animal growth and immune response during micro-parasitic infections. PLoS One 4, e7508.

Doeschl-Wilson AB, Kyriazakis I, Vincent A, Rothschild MF, Thacker E and Galina-Pantoja L 2009b. Clinical and pathological responses of pigs from two genetically diverse commercial lines to porcine reproductive and respiratory syndrome virus infection. Journal of Animal Science 87, 1638–1647.

Duan X, Nauwynck HJ and Pensaert MB 1997. Effects of origin and state of differentiation and activation of monocytes/macrophages on their susceptibility to porcine reproductive and respiratory syndrome virus (PRRSV). Archives in Virology 142, 2483–2497.

Exton MS 1997. Infection-induced anorexia: active host defense strategy. Appetite 29, 369–383.

Forst CV 2010. Host–pathogen systems biology. In Infectious disease informatics (ed. V Sintchenko), pp. 123–147. Springer, New York.

Friggens NC and Newbold JR 2007. Towards a biological basis for predicting nutrient partitioning: the dairy cow as an example. Animal 1, 87–97.

Ganguly N, Sikdar BK, Deutsch A, Canright G and Chaudhuri PP 2003. A survey on cellular automata. Technical Report, Centre for High Performance Computing, Dresden University of Technology.

Gaudrealt N, Rowland RRR and Wyatt CR 2009. Factors affecting the permissivness of porcine alveolar macrophages for porcine reproductive and respiratorysyndrome virus. Archives in Virology 154, 133–136.

Green DM and Whittemore CT 2003. Architecture of a harmonized model of the growing pig for the determination of dietary net energy and protein requirements and of excretions into the environment (IMS Pig). Animal Science 77, 113–130.

Greer AW 2008. Trade-offs and benefits: implications of promoting a strong immunity to gastro-intestinal parasites in sheep. Parasite Immunology 30, 123–132.

Houdijk JGM and Bünger L 2006. Selection for growth increases the penalty of parasitism on growth performance in mice. Proceedings of the Nutritional Society 65, 68A.

Houdijk JGM, Jessop NS and Kyriazakis I 2001. Nutrient partitioning between reproductive and immune functions in animals. Proceedings of the Nutritional Society 60, 515–525.

Houston AI, McNamara JM, Barta Z and Klasing KC 2007. The effect of energy reserves and food availability on optimal immune defence. Proceedings of the Royal Society B 274, 2835–2842.

Jackson F and Coop RL 2000. The development of anthelmintic resistance in sheep nematodes. Parasitology 120, 95–107.

Janeway CA, Travers P and Walport M 1999. Immunobiology: the immune system in health and disease. Garland Publishing Co., New York.

Katsnelson A 2010. Well-trained immune cells keep HIV in check. Nature News. doi:10.1038/news.2010.219

Kirschner DE and Linderman JJ 2009. Mathematical and computational approaches can complement experimental studies of host pathogen interactions. Cellular Microbiology. 11, 531–539.

Kitano H 2002. Systems biology: a brief overview. Science 295, 1662–1664.

Klasing KC 2007. Nutrition and the immune system. British Poultry Science 48, 525–537.

Kleinstein SH and Seiden PE 2000. Simulating the immune system. Computing in Science and Engineering. 2, 69–77.

Knap PW 1999. Simulation of growth in pigs: evaluation of a model to relate thermoregulation to body protein and lipid content and deposition. Animal Science 68, 655–679.

Knap PW and Bishop SC 2000. Relationship between genetic change and infectious disease in domestic livestock. Occasional publications of the British Society of Animal Science No. 27, pp. 65–80, BSAS, Edinburgh, Scotland.

Kosmrlj A, Read EL, Qi Y, Allen TM, Altfeld M, Deeks SG, Pereyra F, Carrington M, Walker BD and Chakraborty AK 2010. Effects of thymic selection of the T-cell repertoire on HLA class I-associated control of HIV infection. Nature 465, 350–354.

Kyriazakis I and Emmans GC 1999. Voluntary feed intake and diet selection. In Quantitative biology of the pig (ed. I Kyriazakis), pp. 229–248. CABI, Wallingford, Oxon, UK.

Kyriazakis I and Houdijk JGM 2007. Food intake and performance of pigs during health, disease and recovery. In Paradigms in pig science (ed. J Wiseman, J Varley, MA McOrist and B Kemp), pp. 493–513. Nottingham University Press, Nottingham, UK.

Kyriazakis I and Doeschl-Wilson AB 2009. Anorexia during infection in mammals: variation and its sources. In Voluntary feed intake in pigs (ed. D Torrallardona and E Roura), pp. 307–318. Wageningen Academic Publishers, Netherlands.

Labarque G, Van Gucht S, Nauwynck H, Van Reeth K and Pensaert M 2003. Apoptosis in the lungs of pigs infected with porcine reproductive and respiratory syndrome virus and associations with the production of apoptogenic cytokines. Veterinary Research 34, 249–260.

Lescourret F and Coulon JB 1994. Modeling the impact of mastitis on milk production in dairy cows. Journal of Dairy Science 77, 2289–2301.

Lochmiller RL and Deerenberg C 2000. Trade-offs in evolutionary immunology: just what is the cost of immunity? Oikos 88, 87–98.

Lopez OJ and Osorio FA 2004. Role of neutralizing antibodies in PRRSV protective immunity. Veterinary Immunology and Immunopathology 102, 155–163.

Louie K, Vlassoff A and Macckay A 2005. Nematode parasites of sheep: extension of a simple model to include host variability. Parasitology 130, 437–446.

Louzoun Y 2007. The evolution of mathematical immunology. Immunological Reviews 216, 9–20.

Lundegaard C, Lund O, Kesmir C, Brunak S and Nielsen M 2007. Modeling the adaptive immune system: predictions and simulations. Bioinformatics 23, 3265–3275.

Mata J and Cohn J 2007. Quantitative modeling of immune responses. Immunological Reviews 216, 5–8.

Marchuck GI, Petrov RV, Romanyukha AA and Bocharov GA 1991. Mathematical model of antiviral immune response. I. Data, analysis, generalized picture construction and parameter evaluation for Hepatitis B. Journal of Theoretical Biology 151, 1–40.

McEwan JC, Mason P, Baker RL, Clarke JN, Hickey SM and Turner K 1992. Effect of selection for productivity traits on internal parasite resistance in sheep. Proceedings of the New Zealand Society of Animal Production 52, 53–56.

McEwan JC, Dodds KG, Gree GJ, Bain WE, Duncan SJ, Wheeler R, Knowler KJ, Reid PJ, Green RS and Douch PGC 1995. Genetic estimates for parasite resistance traits in sheep and their correlations with production traits. New Zealand Journal of Zoology 22, 177.

McNamara JM and Buchanan KL 2005. Stress, resource allocation, and mortality. Behavioural Ecology 16, 1008–1017.

Medley GF 2002. The epidemiological consequences of optimisation of the individual host immune response. Parasitology 125, S61–S70.

Molitor TW, Bautista EM and Choi CS 1997. Immunity to PRRSV: double-edged sword. Veterinary Microbiology 55, 265–276.

Morel PA 1998. Mathematical modelling of immunological reactions. Frontiers in Bioscience 3, 338–347.

Morpurgo D, Serentha R, Seiden P and Celada F 1995. Modelling thymic functions in a cellular automaton. International Journal of Immunology 7, 505–516.

Mulupuri P, Zimmerman JJ, Hermann J, Johnson CR, Cano JP, Yu W, Dee SA and Murtaugh MP 2008. Antigen-specific B-cell responses to porcine peproductive and respiratory syndrome virus infection. Journal of Virology 82, 358–370.

Murtaugh MP, Xiao Z and Zuckermann FA 2002. Immunological responses of swine to porcine reproductive and respiratory syndrome virus infection. Viral Immunology 15, 533–547.

Nowak MA and Bangham CR 1996. Population dynamics of immune responses to persistent viruses. Science 272, 74–79.

Nowak MA and May RM 1991. Mathematical biology of HIV infections – anitgenic variation and diversity threshold. Mathematical Biosciences 106, 1–21.

Nowak MA and May RM 1993. AIDS pathogenesis – mathematical models of HIV and SIV infections. AIDS 7, S3–S18.

Nowak MA and May RM 2000. Virus dynamics: mathematical principles of immunology and virology. Oxford University Press, New York.

Oltenacu PA and Natzke RP 1976. Mathematical modeling of the mastitis infection process. Journal of Dairy Science 59, 515–521.

Perelson AS 2002. Modelling viral and immune system dynamics. Nature Reviews Immunology 2, 28–36.

Perelson AS and Wiegel FW 1981. Theoretical considerations of the role of antigen structure in B cell activation. Federation Proceedings 40, 1479–1483.

Perry B and Grace D 2009. The impacts of livestock diseases and their control on growth and development processes that are pro-poor. Philosophical Transactions of the Royal Society B 364, 2643–2655.

Pugliese A and Gandolfi A 2008. A simple model of pathogen-immune dynamics including specific and non-specific immunity. Mathematical Biosciences 214, 73–80.

Rapin N, Kesmir C, Frankild S, Nielsen M, Lundegaard C, Brunak S and Lund O 2006. Modelling the human immune system by combining bioinformatics and systems biology approaches. Journal of Biological Physics 32, 335–353.

Rauw WM, Kanis E, Noordhuizen-Stassen EN and Grommers FJ 1998. Undesirable side effects of selection for high production efficiency in farm animals: a review. Livestock Production Science 56, 15–33.

Renshaw E 1991. Modelling biological populations in space and time. Cambridge studies in mathematical biology. Cambridge University Press, UK.

Reyes-Umana V 2010. Assessing key viral determinants for viral load decline. Honours degree thesis, University of Edinburgh, Scotland.

Romanyukha AA, Rudnev SG and Sidorov IA 2006. Energy cost of infection burden: an approach to understanding the dynamics of host–pathogen interactions. Journal of Theoretical Biology 241, 1–13.

Sandberg FB, Emmans GC and Kyriazakis I 2006. A model for predicting food intake of growing animals during exposure to pathogens. Journal of Animal Science 84, 1552–1566.

Sangster NC 1999. Anthelminitc resistance: past, presence and future. International Journal for Parasitology 29, 115–124.

Segel LA and Bar-Or RL 1999. On the role of feedback in promoting conflicting goal of the adaptive immune system. Journal of Immunology 163, 1342–1349.

Seiden PE and Celada F 1992. A model for simulating cognate recognition and response in the immune system. Journal of Theoretical Biology 158, 329–340.

Sheldon BC and Verhulst S 1996. Ecological immunology: costly parasite defences and trade-offs in evolutionary ecology. Trends in Ecology and Evolution 11, 317–321.

Shi V, Tridane A and Kuang Y 2008. A viral load-based cellular automoate approach to modeling HIV dynamics and drug treatment. Journal of Theoretical Biology 253, 24–35.

Shudo E and Iwasa Y 2001. Inducible defense against pathogens and parasites: optimal choice among multiple options. Journal of Theoretical Biology 209, 233–247.

Simm G 2010. Guest editorial: livestock and global climate change. Animal 4, 321–322.

Smith AM and Ribeiro RM 2010. Modeling the viral dynamics of influenza A virus infection. Critical Reviews in Immunology 20, 291–298.

Souza-e-Silva H, Savino W, Feijóo RA and Vasconcelos ATR 2009. A cellular automata-based mathematical model for thymocyte development. PLoS ONE 4, e8233.

Vagenas D, Bishop SC and Kyriazakis I 2007a. A model to account for the consequences of host nutrition on the outcome of gastrointestinal parasitism in sheep: logic and concepts. Parasitology 134, 1263–1277.

Vagenas D, Bishop SC and Kyriazakis I 2007b. A model to account for the consequences of host nutrition on the outcome o gastrointestinal parasitism in sheep: model evaluation. Parasitology 134, 1279–1289.

Vagenas D, Doeschl-Wilson AB, Bishop SC and Kyriazakis I 2008. In silico exploration of the effects of host genotype and nutrition on the genetic parameters of lambs challenged with gastrointestinal parasites. International Journal of Parasitology 37, 1617–1630.

Van Reeth K and Nauwynck H 2000. Proinflammatory cytokines and viral response disease in pigs. Veterinary Research 31, 187–213.

Van der Waaij EH 2004. A resource allocation model describing the consequences of artificial selection under metabolic stress. Journal of Animal Science 82, 973–981.

Van der Waaij EH, Bijma P, Bishop SC and van Arendonk JAM 2000. Modeling selection for production traits under constant infection pressure. Journal of Animal Science 78, 2809–2820.

Wellock IJ, Emmans GC and Kyriazakis I 2003. Predicting the consequences of social stressors on pig food intake and performance. Journal of Animal Science 81, 2995–3007.

White LJ, Schukken YH, Dogan B, Green LE, Döpfer D, Chappell MJ and Medley G 2010. Modelling the dynamics of intramammary *E. coli* infections in dairy cows: understanding mechanisms that distinguish transient from persistent infections. Veterinary Research 41, 13.

Wodarz D 2003. Hepatitis C virus dynamics and pathology: the role of CTL and antibody responses. Journal of General Virology 84, 1743–1750.

Wodarz D, Lloyd AL, Jansen AA and Nowak MA 1999. Dynamics of macrophage and T cell infection of HIV. Journal of Theoretical Biology 196, 101–113.

Wolfram S 1994. Cellular automata and complexity. Addison Wesley, New York, USA.

Wood JC, McKendrick IJ and Gettingby G 2006a. A simulation model for the study of the within-animal infection dynamics of *E. coli* O157. Preventative Veterinary Medicine 74, 180–193.

Wood JC, McKendrick IJ and Gettingby G 2006b. Assessing the efficacy of within-animal control strategies against *E. coli* O157: a simulation study. Preventative Veterinary Medicine 74, 194–211.

Woolhouse MEJ, Webster JP, Domingo E, Charlesworth B and Levin BR 2002. Biological and biomedical implications of the co-evolution of pathogens and their hosts. Nature 32, 569–577.

Xiao Z, Batista L, Dee S, Halbur P and Murtaugh MP 2004. The level of virus-specific T-cell and macrophage recruitment in porcine reproductive and respiratory syndrome virus infection in pigs is independent of virus load. Journal of Virology 78, 5923–5933.

Yates A, Chan CC, Callard RE, George AJ and Stark J 2001. An approach to modelling in immunology. Briefings in Bioinformatics 2, 245–257.

Zaralis K, Tolkamp BJ, Houdijk JGK, Wylie ARG and Kyriazakis I 2008. Changes in food intake and circulating leptin due to gastrointestinal parasitism in lambs of two breeds. Journal of Animal Science 86, 1891–1903.

Zimmerman J, Benfield DA, Murtaugh MP, Osorio F, Stevenson GW and Torremorell M 2006. Porcine reproductive and respiratory virus (porcine arterivirus). In Diseases of swine, 9th edition, (ed. BE Straw, JE Zimmerman, S l'Allaire and DJ Taylor), Wiley-Blackwell, UK.

Zorzenon dos Santos RM and Coutinho S 2001. Dynamics of HIV infection: a cellular automata approach. Physical Review Letters 87, 102–168.