Chapter 4
Modelling Disease Dynamics and Management Scenarios

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4.1 Introduction

Mathematical modelling now plays an important role in developing scientific understanding of complex biological processes such as epidemics. Model-based risk assessments make such studies relevant to policy makers and resource managers. However, in providing such advice it is important to ensure that model predictions are robust to alternative plausible assumptions, and also that any predictions arising from such models correctly reflect the uncertainty in current knowledge and any intrinsic variability of the system under study. To see why this is so, contrast a point estimate of the efficacy of a given disease control measure with a prediction which gives the probability associated with varying degrees of success, and crucially, failure. The former gives a false sense of confidence, whilst the latter allows the decision maker to carry out a more complete risk assessment of the proposed strategy. In all cases, model predictions should be interpreted in the light of model structure and assumptions.

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In this chapter we are going to look at how modelling should be used to investigate disease in wildlife, with a strong focus on using models to make management decisions. We will largely avoid the vast area of purely theoretical modelling and concentrate on finding practical solutions to real world problems. Nevertheless, it is worth noting that theoretical analysis can, and has, provided profound insights into key aspects of system behaviour. One notable and particularly relevant example is the extensive range of theoretical results showing the importance of the basic reproduction number (R_0) as a threshold parameter in epidemics, starting with the work of Kermack and McKendrick in the 1920s (see Kermack and McKendrick 1991). However, this chapter is not about complex mathematics, but about defining the types of models available, describing the pros and cons of different approaches, and helping managers to determine the strengths and weaknesses of each in particular circumstances.

The objective of this chapter is not to turn the reader into a modeller, so there is no need to have a high level of understanding of mathematics, but to appreciate how models should, and should not, be used and interpreted. We will not give an exhaustive description of types of models, but concentrate on more commonly used approaches. Any model that is used to propose a management decision needs to be critically examined and our objective here is to give an understanding of modelling terminology, and the tools with which to question the model and the modeller.

4.1.1 What Is a Model?

As a matter of definition, no model is right in the philosophical sense of representing truth, but some models may be useful. All models are a simplification of reality. George Box (1979) stated "*All models are wrong – but some are useful*" and Oreskes et al. (1994) wrote *"… the establishment that a model accurately represents the 'actual processes occurring in a real system' is not even a theoretical possibility"*. Models are simplified logical constructs of what we believe to be true, and in the context of this chapter are used to explain disease patterns in space or time, and to predict their future patterns. We construct models in our minds all the time, for example to assess the likely traffic flow of alternate routes on our way home or which queue to join in the supermarket. We know that these models only work in limited circumstances, and we should be equally willing to accept this as true for mathematical models, which are the focus of this chapter. The only real difference with these conceptual models is that mathematical models are a *formal* abstraction of our thought processes expressed in terms of a series of equations. Indeed, the act of constructing such a model, forces us to consider the problem in detail, and in a logical fashion. A mathematical model is simply an extension of a conceptual model into a mathematical framework.

Quantitative modelling activities can be broadly categorised into statistical (data driven) and mathematical (knowledge driven) models. An assessment of the

strength of the inferences that can be drawn from these approaches needs to take this into account. Data-driven modelling uses statistical approaches to derive quantitative relationships from datasets. One strength of these models is that they are based on directly measurable factors, but this is also a potential weakness as these factors are usually proxies for underlying biological processes that cannot be directly measured in a field study, although statistical approaches can be used to infer the value of unobserved factors indirectly from the available observations. Such models can be used to generate knowledge in relation to cause–effect relationships (see Box 3.2), but they are not usually dynamic and only predictive in a limited domain determined by the range of the data used to construct them; extrapolation of statistical models is perilous indeed. Mathematical (knowledge driven) models can be analytically tractable or simulation-based. It is often advantageous to express even simulation models in terms of a formal mathematical description (e.g. differential equations or stochastic processes i.e. processes with a random element) for a number of reasons, including clarity in model definition and independence of the model from a particular implementation (i.e. easier translation to different simulation software, which is useful for model verification). Such models are based on existing understanding of the biological relationships within a system, and in principal, to the extent that such knowledge is correct, can be used to extrapolate predictions to novel situations. The strength of knowledge-driven modelling lies in the ability to represent the dynamics of complex biological systems. For an infectious disease this is particularly important as propagation of infection is inherently a time-dependent phenomenon, in that the number of new infections at a particular time depends on the number of infectious and susceptible individuals at preceding points in time. It is often possible to identify key factors within such a system. This group of models may include factors or quantities that cannot be directly measured, and are defined on the basis of measured proxy variables or hypothesised relationships. Such models may also have ‘emergent properties’ that are the unexpected result of the interactions between multiple effects represented in the model. Knowledge-based models can also be used to test the impact of changes in a system. Some of the information included in developing knowledge-driven models is generated through data-driven models, and in some cases the distinction is further blurred by the use of statistical methods to infer parameters in knowledge-driven models, but such models may also include expert opinion. In the rest of this chapter we will concentrate on these knowledge-driven (mathematical) models.

4.1.2 Why Model?

The question ‘why model?’ is important to address. If models are simplifications of reality and are always wrong then why bother? The answer hinges on the extent to which we understand the disease we are looking at. Models are a reflection of our understanding of the ‘real world’ in that they provide a structure in which to consider the complex biological interactions within a disease system. They allow us to explain

or predict effects, whether these are the result of interactions of numerous factors or emergent properties of a system that evolve over time. Different approaches can be used to categorise them, one being to group them into qualitative and quantitative models. The models discussed here are all quantitative (knowledge-driven) models. Models are needed where mental simulation is not able to represent multiple causal links within a system (Lempert et al. 2003). According to Klein (1998) the limit is usually reached with three key variables and six transitions from one state to another. If we do not have full understanding of the underlying mechanisms and processes of disease, then modelling can allow us to investigate how the disease system as a whole functions. It can also reveal how weak our understanding is. This can be used to direct research to gain knowledge on the disease and the ecology of the host. Conversely, when we have more knowledge it can also be used to reveal how the disease system will respond to management interventions and to compare different approaches. Modelling thus provides either a strategic tool for increasing our understanding of disease or a tactical way of dealing with it. From this it should be apparent that we do not subscribe to the view that models should not be constructed until all suitable data are available. Rather the act of model construction itself forces us to formalise our ideas on the processes and mechanisms that we believe occur in the system under study; a process which often yields valuable insights.

Here we focus on the development of models that can be used to explore disease control strategies. As such, the models should capture the biological processes driving the disease and be able to simulate some management intervention whether that be at the host population level (e.g. population reduction) or the individual host level (e.g. restrict animal behaviour to prevent exposure to disease).

We can also use the output of models to inform field research. From the results of sensitivity analysis (see Section 4.4) we can extract those parameters that have a large influence on the output. In particular, we should differentiate between parameters that have known variability, and those that have uncertainty. Once we have identified the important uncertain parameters with significant influence on the system, we can then use this list to decide on research priorities for further data collection. This is discussed further in Section 4.4.

4.2 Basic Approaches

The modelling process usually starts with a question and is followed by the development of the underlying biological framework, mathematical model development, model testing and ultimately, predictive modelling to answer the question.

4.2.1 Approaches to Modelling

If a model is analogous to a scientific experiment, then the original question to be asked of the model is analogous to the hypothesis to be tested. There are three basic steps in constructing any model. These steps are so basic we often overlook the first

two. But only after answering all three can we start to choose what sort of model would be most useful.

1. What is the question we wish to answer and are we aiming to increase our understanding of disease or develop methods for control?
2. What is the scope of the problem we wish to include?
3. What is our understanding about the mechanisms under study?

The first question we have to answer is what are we modelling for? Do we wish to use modelling conceptually or strategically, to increase our understanding about the underlying disease, or do we want a practical or tactical model for disease management. Emerging diseases such as the recent introduction of bluetongue virus to Northern Europe are a good example of where we might want to use modelling to investigate the potential spread of disease among wild and domestic ruminants, or identify key factors in the disease process that we do not understand in its 'new context'. Investigating the dynamics of bluetongue and its interaction with its vector species in the north European countryside with a strategic model would be a first step to understanding the magnitude of the problem for Northern European countries. Recent models have highlighted the possibility of bluetongue spread in northern Europe by climatic matching of vector species (*Culicoides* midges) with recent records of disease (Purse et al. 2007), demonstrating the potential involvement of novel midge vectors. Where we have greater understanding of the disease process, such as in rabies in wildlife, or bovine tuberculosis, then a tactical modelling approach would be more appropriate. In most cases the strategic versus tactical argument is easily defined at the outset, usually on the basis of our underlying knowledge of the disease.

It is impossible to undertake modelling without a context. This is fundamental to producing a useful model, and we will look at rabies in wildlife to illustrate the process. A request to "model the dynamics of rabies in wildlife" may be interpreted differently by almost every modeller. In this simplified example, no particular output is requested; so one person may model genetic changes to the virus over each viral generation, while another may construct a multi-species model of the evolution of rabies over centuries. The question needs to be carefully constructed, and a good modeller will help the manager to define the question. Even extending the question to "what is the best way to eradicate rabies from a focal outbreak in a naive population of red foxes?" does not precisely define the question. Do we mean the quickest, or most cost effective? Clearly by now we must realise that the question needs to be asked in such a way that it specifies the answer we expect to get from the model.

We move now to the second point, which is one of scale. In an isolated population, such as red foxes (*Vulpes vulpes*) in Britain, geographical scale has a maximum bound imposed by the surrounding sea. But should we model all the foxes in Britain, or just those within some distance of the outbreak? There are an estimated 240,000 foxes in Britain (Harris et al. 1995), so at this scale we could probably assume the population is infinite. But if in the case of an outbreak of rabies in the Ethiopian wolf (*Canis simensis*) with an estimated total world population of 500 individuals (Randall et al. 2004), then the issue of low numbers and chance events arises. Also, we need to examine the temporal scope of a question. For example, we

may wish to ensure the survival of the Ethiopian wolf over decades or centuries. Consequently, with respect to the threat of rabies, the only way to ensure this is to eliminate the disease completely from the domestic dogs (*Canis lupus familiaris*) in the surrounding area.

Lastly we need to specify the mechanism we are interested in, and indeed what mechanisms we are not interested in. Biological systems are effectively hierarchical. At the lowest level we have underpinning biochemical processes such as the level at which individual drugs act in a veterinary context (e.g. Acetylcholinesterase inhibitors). Above this we have whole organ responses (e.g. renal failure) and above this whole animal responses at the level of the individual (e.g. alterations in behaviour, morbidity and mortality). Going higher still we come to inter-individual interactions (e.g. disease transmission) and to population level behaviour where we come into the realms of epidemiology. At even higher levels we have multi-species epidemiology and then the effect on food webs and biodiversity. Clearly, it is not practical to model at all levels in this biological hierarchy, so whilst we might be interested in looking at developing a model system to investigate the spread of bluetongue or rabies, we would not want to be involved with modelling the biochemistry of the immunological response to exposure to the infective agent. One could argue that a key component in the historic success of modelling in epidemiology is the assumption that the complex processes occurring within an individual whose immune system has been challenged by a pathogen can often be adequately (e.g. for the purpose of population and community epidemiology) summarised by a series of transitions between a small number of distinct states (e.g. Susceptible, Exposed, Infected and Recovered: SEIR), despite the true internal state of the individual being more precisely described by something closer to a continuous range. However, if the key concern is the behaviour of a diagnostic test applied to individuals then a model of within-organism response may be more appropriate. In the context of rabies spread we are interested in inter-animal transmission and subsequent impacts on disease spread. In most cases, we would not model individual animal behaviour and we might not need to consider age or the sex of the animal (or just consider females). But how sure are we on issues such as sex- or age-biased infection? Generally we should only add model components (e.g. age or sex) when there is evidence that they impact on disease dynamics either directly, or indirectly. Note however, that they may impact on the management of disease even if they have no significant impact on (unmanaged) disease dynamics.

When constructing a model it is necessary to choose what to incorporate, and crucially what to leave out. Some elements of the model are dictated by the goal of the study, for example understanding the dynamics of sexually transmitted diseases is likely to require modelling both sexes! However, decisions whether or not to treat certain aspects come down to pragmatic considerations including current knowledge, resources and the data available for the project. As a general rule, models should be as simple as possible to describe the phenomena of interest (but not too simple). A commonly encountered problem when modelling biological systems is the explosion of model complexity, leading to poorly understood model behaviour and potentially low predictive ability due to

over-fitting of the available data. In statistical models information theoretic approaches (e.g. AIC) are widely used to formally control the growth of model complexity. Pragmatically, model complexity can be limited by developing models for a particular purpose and incorporating only those features that are critical to that end. Like a map, models are an abstraction of reality and are at their best when they incorporate the appropriate level of detail, as too much detail can obscure the most important features. Of course, not enough detail means that the model may not be able to achieve the original goal, but this may just be an accurate reflection of current knowledge.

Thus, having defined the question, the scope, and our understanding of the system, we now need to decide how to model it. In mechanistic terms models can be classified in different ways on the basis of how they are constructed mathematically. Again we have three decisions to make. Should the model be continuous or discrete in time, spatial or non-spatial, and deterministic or stochastic.

The first is often a matter of personal choice. Continuous time models are usually differential models or stochastic processes, which are generally preferred by mathematicians, while discrete time models are difference equation models, which are generally preferred by biologists. Indeed there are often clear biological reasons for choosing a discrete-time model, for example in modelling populations with highly synchronous (e.g. annual) reproduction. However, it is important to note that time related parameter values (e.g. for birth and survival: are rates in continuous models and probabilities in discrete time models) need to change between these two models. A mortality rate/probability (s) in a discrete time model of interval length t, is related to the continuous-time differential equation mortality rate (μ) by

$$\mu = -\ln(s)/t \tag{4.1}$$

where discrete time models are chosen it is important to consider the time step used. This is generally set to one of the shortest events that occur in the system. With simple models (e.g. numerical solutions to differential equations) it may be possible to check that the time step is adequately short by making it shorter and checking that no differences occur in the output. However, this is not practical for most models. A simple way to determine if the time step is too long is if too many competing events occur within one step (e.g. if both primary and secondary infections could occur within one step). For example, in discrete-time models of rabies dynamics, the time step is often about one month (the average incubation period of rabies) on the assumption that the period of infectiousness (a few days) is regarded as an instantaneous event. However, in this case the number of individuals which are rabid on any one date will not be recorded since infectiousness is always followed by death and thus these individuals will be removed from the model. Such considerations typically do not arise in continuous time models, although algorithms used for numerical solution of differential equations will typically determine a short time-step to be used, this is relatively automatic and does not require any reformulation of the model. It is often the case that continuous-time models are structurally simpler, and thus conceptual whilst discrete event models are more complex and designed to be more practical. However, even most moderately realistic

continuous-time models are not solvable using present-day mathematics, but nonetheless there are a range of approximate mathematical approaches that can provide valuable insights into model behaviour.

Another crucial, yet often over looked aspect of modelling disease dynamics is the issue of waiting time distributions. Consider an individual that becomes infected with say a virus, the *latent period* is the time it takes for the virus to become established and the individual to become infective i.e. to start shedding the virus. The latent period will vary between individuals, but across the population is described by a latent (waiting) time distribution. Particular waiting time distributions typically describe other transitions e.g. from infected to recovered or susceptible. The details of such waiting times are crucial in determining disease dynamics, for example at the start of an epidemic, particularly for emerging diseases, uncertainty about the latent period can result in large uncertainty in the predicted size of an outbreak: HIV-AIDS and variant CJD being two notable examples in humans. Models may fail to account correctly for waiting times due to a lack of information, but also because widely used mathematical formalisms such as deterministic ordinary differential equations, and stochastic Markov processes are based on exponential waiting times. However, such shortcomings can be addressed and, for example using individual-based stochastic methods, it is relatively easy to account for any required waiting time distribution.

It is essential to be aware that models should strive to capture the key ecological processes that drive disease dynamics, and be capable of including proposed management options.

4.2.2 Deterministic or Stochastic

Most of the early mathematical modelling of disease in human, livestock and wildlife populations was undertaken with continuous time – differential models. These modelling approaches were based on calculus, originally developed by Isaac Newton. This approach is deterministic in the sense that, for any set of inputs to the series of equations used in the model, the output is determined and fixed. This approach was used to predict the motions of the planets around the sun. However, one of the most obvious features of biological systems is that they show inherent, but often unexplained variation. Many biological systems, including epidemics, exhibit a high degree of variability. For example, the introduction of a single infected animal into a population may or may not result in a disease outbreak, and the size of any resultant outbreak will likely vary between populations. This leads to the adoption of stochastic modelling methods in which there is randomly induced variation between different model-runs (even where all parameters are held constant). In theory, the output of such models is represented by a probability distribution, which can be estimated from simulation, as a histogram across many model runs. Therefore stochastic models are more computationally demanding than deterministic models. However, a key advantage of this approach is that it represents

variability parsimoniously with relatively few parameters and without necessarily increasing the number of variables needed to represent the state of the system. Since for every iteration, model output will be different, many (hundreds or thousands of) iterations are required for stochastic models to produce a representative distribution of possible outcomes. A major advantage of stochastic models is that they are able to capture emergent properties of a system arising from stochastic or rare events. This ability may be considered especially useful when quantifying the effects of population reduction as a means of disease control. Box 4.1 describes an example where the use of population reduction is explored as a means of paratuberculosis control in rabbits (*Oryctolagus cuniculus*). The observation that the success of single one-off population reduction events comes largely, not from the probability of removing all of the infected individuals in the population, but from the failure of the disease to spread from the infected animals that remain, highlights one advantage of stochastic over deterministic models.

Deterministic models are therefore best used early in any biological investigation, to improve our understanding of the processes being modelled. They can lead to useful insights, but generally stochastic models are more valuable if the objective is to make a management decision. It is important to realise that the introduction of stochastic effects into a previously deterministic model can alter predicted outcomes both quantitatively and qualitatively. For example, with low levels of stochasticity model outputs are typically distributed around a mean value corresponding to the deterministic model prediction (the stochastic model predicts system mean *and* variability). At intermediate levels of stochasticity the mean prediction of the model is typically different to the deterministic case, and where stochastic effects dominate they can drive a transition not observed in the deterministic model (e.g. stochastically induced disease extinction where the deterministic model predicts disease persistence). Stochastic effects are typically most important for relatively small populations (or sub-populations), however heterogeneity can also amplify stochastic effects.

4.2.3 Non-Spatial Models

Non-spatial models were the first to be developed, and generally treat the whole population as homogeneous: without having to consider space or any social interactions, they are relatively simple. Such homogeneous mixing models based on differential equations are relatively amenable to mathematical analysis, although typically most recent models are not solvable mathematically. Nonetheless, mathematical analysis of such models has led to important insights into system dynamics and this is where many of the theoretical developments in epidemiology have been produced. These developments have included insights based on R_0, the average number of new infections that a single infectious animal will produce during its "infectious lifetime" when placed in a completely susceptible population (see Box 3.3 on estimating R_0). This ratio depends on the density (and other factors, such as spatial organisation and behaviour which are essentially ignored in non-spatial

Box 4.1 Modelling population reduction to control wildlife disease: rabbits and paratuberculosis

Reduction of wildlife population density is a common method used to control wildlife disease. Given the financial and logistical difficulties in experimentally testing the efficacy of wildlife control programmes, modelling is often employed to explore wildlife population reduction as a means of disease control. Here, stochastic modelling offers a significant advantage over deterministic modelling as it can capture both the likelihood of the population reduction event removing all the infected animals and also the probability that stochastic fluctuations prevent the persistence and subsequent recovery of the infected population following population reduction. This was demonstrated by Davidson et al. (2008) when modelling the control of paratuberculosis (*Mycobacterium avium* subsp. *paratuberculosis*; *Map*) in rabbit *(Oryctolagus cuniculus)* populations. They used a spatially-explicit stochastic simulation model of *Map* dynamics in rabbit populations to quantify the effects of rabbit population control on disease persistence. The model was parameterized from empirical studies on rabbit population dynamics and on rabbit-to-rabbit *Map* transmission. Single population reduction events targeting up to 96% of all individual animals did not result in any noticeable chance of disease extinction, while culls at the (even more) unrealistically high levels of 98% and 99%

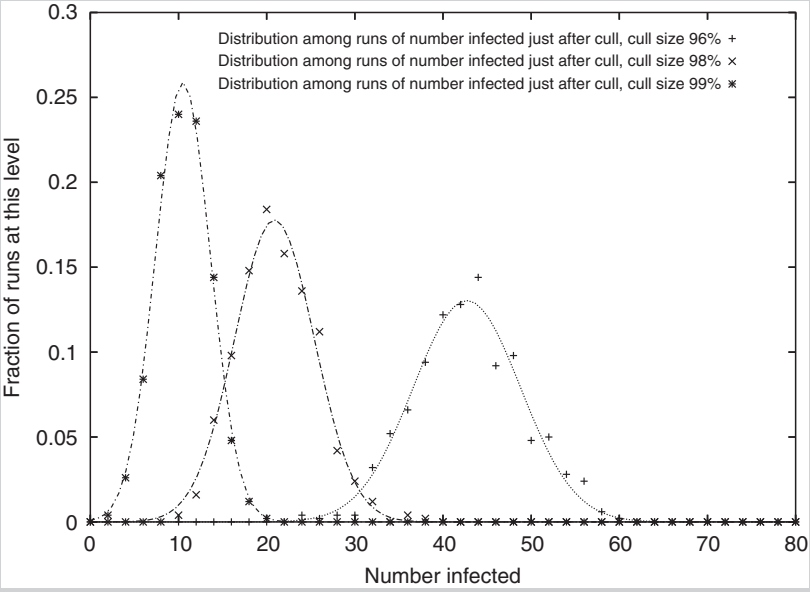

Fig. 4.1 The distribution among realizations of the number of infected individuals immediately after a cull event. Gaussian curves have been fitted to the data points. Three levels of culling are shown – 96%, 98% and 99% (from Davidson et al. 2008)

of the population yield disease extinction probabilities of just 0.08 and 0.34 respectively. These results can also be seen in Fig. 4.1, where the distribution of the number of infected animals among simulations *immediately* after a population reduction event is shown. Although no simulations were disease-free straight away, even with the 98% and 99% culls, many simulations were left with a small number of infected individuals (e.g. a mean of 11 infected individuals in the case of a 99% cull), which resulted in chance eradication in the subsequent recovery period due to small populations being more susceptible to stochastic effects.

The study demonstrated that high rabbit population reduction levels (greater than 96%) are necessary if a one-off rabbit cull strategy is to have even a small probability of eradicating the disease. At these high reduction levels the main contribution to this small eradication probability emerges not from the probability of removing all infected individuals at the cull (which is highly unlikely), but from subsequent fluctuations while the disease remains for a short time with a reduced incidence brought about by the cull i.e. the failure of the infection to spread post-cull. This effect can only be captured with a stochastic model.

homogeneous-mixing models) of the host population. If the value is above unity then the disease will *probably* produce an epizootic, whereas a value of less than one means that the disease will die out, although stochastic factors may mean that a relatively large number of animals will become infected beforehand.

Other important insights include estimating the threshold density at which the disease will die out (i.e. when R drops below unity), or the proportion of a population that needs to be vaccinated to eliminate the disease (i.e. an alternative way for R to drop below unity). A large literature exists which presents the mathematics of disease dynamics (see for example Anderson and May 1991) and simple disease modelling is mentioned in most ecological texts. Whilst these models have generic value in understanding disease dynamics in systems that are adequately captured by the free-mixing assumption, they are less useful where the animal-pathogen system shows heterogeneity. This heterogeneity can occur at different levels which range from differences in the susceptibility of individual animals to disease, variations in the pathogen, or more commonly, heterogeneity that arises from the distribution of hosts in time and space and determines levels of population mixing (e.g. territoriality in some wild mammals). In addition, animal behaviour may change as population density is reduced through interventions such as culling (Chapter 7), which gives rise to the more correct concept of a threshold contact rate, rather than a threshold density (Sterner and Smith 2006). Early non-spatial homogeneous mixing models assumed linear density dependence in transmission as density is reduced (often referred to as βSI). A refinement assumed instead a fixed contact rate between individuals regardless of density (referred to as $\beta S(I/N)$), such as may occur with sexual contacts, since

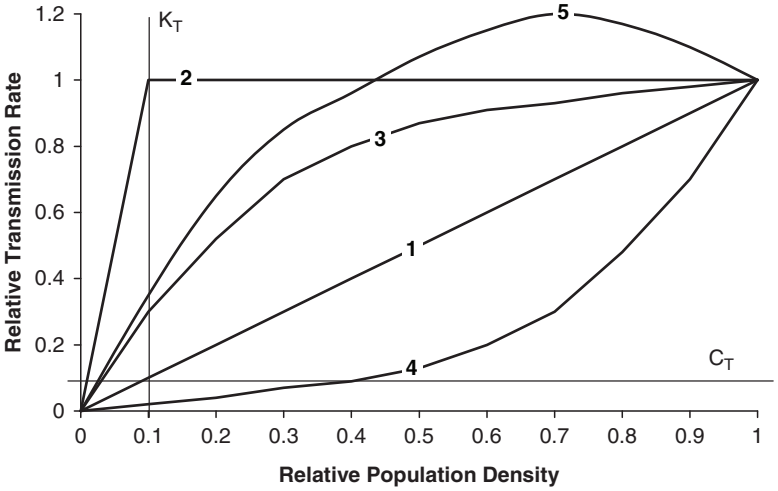

Fig. 4.2 A variety of relationships have been hypothesised between (susceptible) host density and the transmission rate. The earliest (line 1) is linear density dependence (βSI), which gave rise to the idea of a threshold density (K_T) below which the disease will die out since R_0 declines to below unity. Alternative relationships include frequency dependence (line 2), which technically cannot be a constant since the relationship must go through the origin, convex up (line 3) and convex down (line 4). Line 5 represents social perturbation discussed in detail in Chapter 7. From these lines it can be seen that K_T should be replaced by a critical contact threshold (C_T), although this is much harder to measure

these do not normally scale with density. However, empirical evidence often suggests a non-linear response with density (Caley et al. 1998; Ramsey et al. 2002). These relationships are shown in Fig. 4.2.

Non-spatial models have come a long way since simple linear relationships, and can now adequately model spatial heterogeneity (e.g. Barlow 2000), although the mechanism causing this non-linear relationship is not specified. However, by using a simple model, Keeling et al. (2000) showed that such non-linear relationships could be interpreted as the effects of spatial heterogeneity. Box 4.2 illustrates a widely used approach in which a deterministic model is constructed (using a technique known as closure) as an approximation to a fully stochastic and spatial model in a manner that captures some spatial effects. The accuracy of such pseudo-spatial models should be tested, but they are typically an improvement on non-spatial homogeneous-mixing models also illustrated in Box 4.2. Closure-type approximations of this type have been used to capture spatial effects in a computationally efficient manner, for example to model the UK 2001 Foot-and-mouth epidemic (Ferguson et al. 2001b). It is also worth noting that it is often possible to identify cases, e.g. high rates of migration or cross-infection, where deterministic homogeneous mixing models, moment-closure type approximations, and stochastic spatial models coincide. Such limits are useful both in developing understanding and in verifying correct implementation of models.

Box 4.2 Assessing the importance of stochastic and spatial effects in determining disease risk exposure in grazing systems

Many of the most pervasive disease challenges to livestock, and other herbivores, are transmitted via the faecal-oral route, from mycobacterial pathogens such as *Mycobacterium avium* subspecies *paratuberculosis* (the causative agent of Johne's disease) (Judge et al. 2005a), to nematode parasite infections such as *Haemonchus contortus* and *Teladorsagia circumcincta* (Hutchings et al. 2003). Marion et al. (2005, 2008) developed an agent-based modelling framework, based on a series of empirically observed rules of thumb, governing the grazing and faecal avoidance behaviour of grazing animals, which can be used to assess disease risk to livestock from faecal contacts. The key features captured by the model are (i) animals only have limited local knowledge e.g. they can visually assess swards from some distance but only smell faecal contamination at short ranges; and (ii) there is a trade-off between faecal avoidance and the desire to maximise intake which controls the risk of exposure to faecally transmitted disease.

Marion et al. (2005) demonstrated how to develop an analogous non-spatial deterministic model which ignores both spatial and stochastic effects. In the limiting case of large movement rates these models give equivalent predictions. However, their comparison is useful in quantifying the importance of stochastic and spatial aspects of the model. Not only is this useful in developing a better understanding of the system at hand but for example, if the two models agree then it would make more sense to use the deterministic version which is simpler, quicker to run and potentially more amenable to analysis. In general, deterministic models can be thought of as differential equations for the mean value of quantities in the stochastic case. However, a formal mathematical derivation of equations for such mean values shows that they depend on higher-order statistics of the stochastic model like variances and co-variances, which are simply ignored in deterministic models. The only exception to this is a completely linear model, but biologically plausible models will usually contain some non-linearity in which case the deterministic model is not guaranteed to match the mean of the stochastic model. Unfortunately, although it can usually be easily simulated on a computer it is typically not possible to solve the stochastic model analytically, although various approximate methods are available. For example, so-called closure approximations that attempt to model both mean values and some higher-order statistics, such as variances and co-variances, have been widely applied in epidemiology. Figure 4.3 shows the total intake rate across all animals for continuously occupied pasture versus the density of animals (stocking rate) for each of the three model formulations: deterministic; stochastic spatial; and moment-closure based. The peak-value identifies the optimal stocking density and comparison of the three curves shows that both the deterministic and moment-closure models underestimate the optimal stocking density and overestimate the associated intake rate, in comparison with the stochastic spatial model.

(continued)

Box 4.2 (continued)

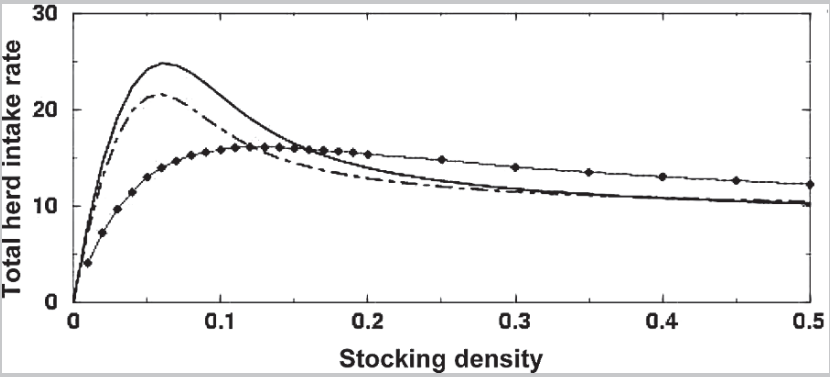

Fig. 4.3 Total intake rate across all animals versus stocking density for non-spatial deterministic (solid curve), stochastic and spatial (black dots), and moment-closure based (dot-dashed curve) models (taken from Marion et al. 2005)

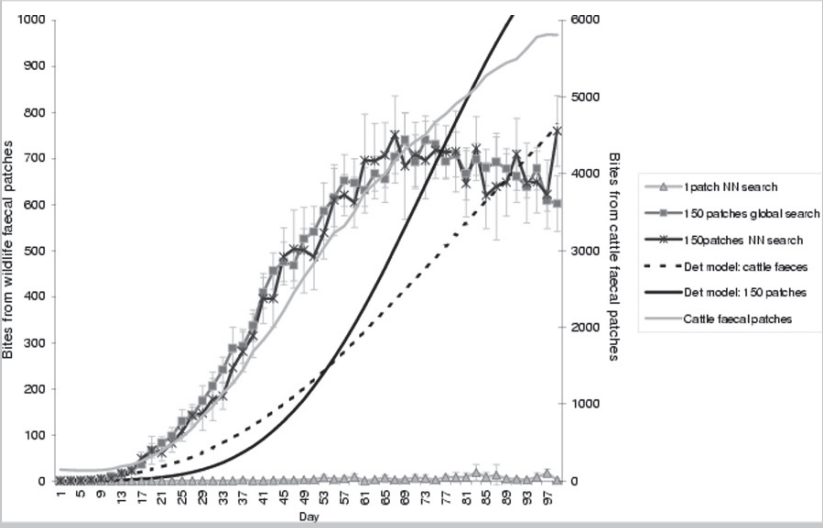

Fig. 4.4 Effect of wildlife faecal defecation pattern ('1 patch' corresponding to a latrine & '150 patches' to dispersed faecal distributions) and search distance (global and local, or NN) on the number of bites taken by cattle from wildlife faecal contaminated patches (mean over 10 realisations +/−1 standard deviation for the stochastic model). The deterministic model outputs relate to the case of dispersed wildlife faeces as indicated. The scale on the right refers to the daily bite rate on livestock faecally contaminated patches (with standard errors omitted for the stochastic outputs) (taken from Marion et al. 2008)

Marion et al. (2008) extended the original model to explore the risk of exposure to faecally mediated disease, now comparing the spatial stochastic version of the model to a non-spatial deterministic model parameterised to represent a set-stocked scenario in a temperate beef herd. Figure 4.4 shows the bite rate from dispersed and highly clumped (representative of wildlife latrines) distributions of wildlife faeces, and from a dispersed distribution of livestock faeces for the first 100 days after cattle are turned out into the pasture. The search distance of herbivores is currently unknown and difficult to measure (Phillips 1993), and therefore the robustness of their conclusion to this poorly determined parameter was assessed. For the case of dispersed patterns of wildlife faeces, Fig. 4.4 contrasts strictly local searching, and global searching in which moves are simulated (at least potentially) across the entire pasture. Similar robustness to search distance was observed for both wildlife latrines and livestock faeces. In addition the results show that the non-spatial deterministic version of the model initially underestimated disease risk and crucially predicts the peak in risk much too late (the deterministic model predicts a peak well after the 100 days shown in the figure).

4.2.4 Spatial and Network Models

It has been a useful starting point to model disease spread within a population by assuming that all individuals within it mix evenly with each other (variously known as mean-field, mass action, homogeneous or complete mixing). However, spatial heterogeneity in wild mammal populations is an important determinant of contact patterns between individuals, with potentially profound implications for disease dynamics (Chapter 2). Hence, the introduction of heterogeneity in modelled contact structures typically produces a more realistic model. The impact of spatial heterogeneity, where contact patterns between individuals is a function of the distance that separates them, has been studied extensively. Another scenario of spatially heterogeneous contacts is where individuals mix uniformly with others in some localities (e.g. within a group territory), but only occasionally make longer-range contacts (e.g. with residents of other territories). Where further information is available it is sometimes possible to develop more detailed models of the network of contacts between individuals (e.g. social and sexual contacts: see Box 2.3), and indeed spatial contact processes themselves can also be thought of as a special class of contact networks. This duality is most simply demonstrated by a lattice where hosts are placed at the nodes and connections are allowed only to the four nearest neighbours; a structure can be viewed as a spatial neighbourhood model and a network. The mathematical study of networks is a rapidly developing field with recent results demonstrating the profound impact that different contact network structures have on disease dynamics (Chapter 2). For example, Pastor-Satorras and Vespignani (2001, 2002) showed that for a contact network with a power-law distribution (i.e. a few individuals have very many contacts) there is no critical

threshold density below which the disease will be eradicated. However, in such circumstances targeting highly connected individuals is an effective strategy. Durrett (2007) however, suggested that such extreme power-law contact networks are rarely observed in practice. Nonetheless, given the possibility for such profound effects, it is important not only to study the effect of observed network structures, but also to explore the robustness of any results obtained with respect to uncertainties in such contact structures. There is a growing literature on the estimation of complete contact networks from (inevitably) partial observations. Where data such as the mean observed number of contacts, or higher-order network statistics, are available, likelihoods can be constructed for so-called exponential random graph, or p^*, models (Frank and Straus 1986), and then computational statistical methods can then be used to generate complete networks consistent with available data (Handcock and Jones 2004). Closure type approximations have also been applied to epidemics on networks (Boots and Sasaki 1999; Keeling 1999) and can make direct use of measured network statistics without the need to model the network directly (Keeling and Eames 2005).

Models can be further refined by introducing variation between individuals, or across space, for example by specifying variation in the susceptibility of individuals. Intuitively, such heterogeneity and variability tends to sub-divide the population into smaller, partially connected clusters, enhancing the importance of stochastic effects in the spread of disease. Even in cases where there is no intrinsic or initial difference between sites or individuals, such heterogeneity in contacts interacts with stochasticity to generate heterogeneity within the system, often resulting in qualitative differences compared to the analogous homogeneous deterministic model. Such differences are typically smaller in situations where the contact network is highly connected and the population relatively homogeneous in nature.

The extent to which space is important as a modelled feature depends to a large extent on the mechanisms of disease transmission, how animals are distributed, or interact within it and the scale at which you model. If we are interested in investigating the dynamics of disease in a herd of dairy cattle then the animals can be considered to be homogeneously mixed, and to frequently come into close contact. In these cases the time domain for inter-animal contact is short relative to that of the transmission process. Disease spread under these conditions would not need to incorporate a spatial component. On the other hand, if we were interested in the spread of infection between herds and across farm holdings then space might be important. However, if two competing strains of disease were present, then space may even be important in the first example, since the homogeneity may be disrupted by the presence of the second outbreak. However, it is not certain if herds of wild mammals will mix homogeneously within any particular time frame.

Spatial models often provide a tactical context for managing disease. They can be used to simulate explicit/hierarchical contact networks between individuals, groups or sub-populations, even in specific geographical regions. In these models specific spatial locations are required, which may or may not be linked through Geographical Information System (GIS) software.

The use of spatial models has led to a number of findings that illustrate the importance of space in disease dynamics. Non-spatial badger (*Meles meles*)-TB models

predicted substantial population reduction when the disease was present (Anderson and Trewhella 1985). The development of spatial models, along with a thorough analysis of the data (Delahay et al. 2000a), has allowed the simulations to become more accurate with a relatively small population reduction and a poor relationship between population size and prevalence (Smith et al. 1997). These effects appear to arise because the disease moves slowly between social groups, which themselves change in size, and thus the disease never reaches equilibrium in all groups. This has demonstrated the importance of territoriality for disease spread in wildlife. Early non-spatial models of rabies in foxes suggested that approximately 70% of the population needed to be vaccinated to eliminate rabies (Anderson et al. 1981), and this has been taken as the target level ever since. However, spatial modelling indicated that this threshold density may be too high (Eisinger and Thulke 2008), because local remnants of rabies infection are unable to spread in the vaccinated population and so die out. For infected foxes the probability of encountering a susceptible host is less than that predicted from the overall density because spatial structure results in less susceptible animals in their contact neighbourhood. Since disease spread is a local phenomenon, many of the local foxes will already have been infected.

Spatial models are often run on a grid (x, y coordinates) with each cell representing a unit area, or a territory. Animals are then assigned to each cell as required. Such grids have received some discussion, since in a square grid each cell may be considered to have either four (called a Von Neumann neighbourhood) or eight (a Moore neighbourhood) neighbours. In reality, territorial animals often have an average of about six neighbouring territories. The original reason for using simple grids was related to the limitations in computing power. However, it is now easy to combine small cells to produce territories (e.g. Smith and Harris 1991), or to utilise a modelling framework based on the underlying geographical structure (using a GIS). This not only allows spatial heterogeneity in territory size and shape, but has recently been shown to remove significant potential bias related to movement of individuals, disease or other information in regular model landscapes (Holland et al. 2007).

4.3 Parameterising Models

An area of considerable importance is the parameterisation of dynamic knowledge-driven models (see McCallum 2000). A given dynamic model often exhibits a range of interesting and plausible behaviours, which can be explored via analysis where possible, but more commonly via numerical simulation and sensitivity analysis. It is usually necessary to determine parameter values in order to apply the model to a particular system, and this is critical if the model is to be used tactically for quantitative risk analysis or management purposes.

The parameters in dynamic models are typically biologically meaningful and therefore have often been measured directly or inferred from empirical studies. The values of such parameters are often quoted as a mean and standard deviation,

or in some cases as a distribution of values. If the parameter distribution is skewed (i.e. not symmetrical: e.g. lognormal) then quoting a mean and standard deviation can be misleading. In addition, inherent variability, for example between regions, sites, or even between times at the same site, often leads to apparently inconsistent parameter estimates between different studies. It is important to differentiate between inherent variation and uncertainty in parameter estimates. Mortality rates may be regarded as variable (between years or places), if a number of measurements are available. Disease transmission rates are often uncertain, since few studies have attempted to estimate or measure them, and they are often inferred.

Thus, there is usually uncertainty in our knowledge about some parameter values, which can be expressed as a range or probability distribution of possible values. In order for model outputs to reflect variation and uncertainty it is possible to randomly sample values for each parameter (independently) and then run the model for each set of parameter values thus generated. This builds up a histogram of model outputs reflecting the uncertainty. The computational cost of such a scheme can be reduced by employing an intelligent sampling scheme such as Latin Hypercube sampling (Vose 2001). However, since we typically know nothing about the correlation between model parameters, many parameter sets generated contain combinations of values that are unlikely. However, if system response data (e.g. the number of clinical cases observed over time during an epidemic) are available, a relatively limited, but rapidly developing, set of tools allows statistical parameter inference (i.e. unknown or poorly determined parameters can be estimated from data). Methods of Bayesian statistics can be used to combine both top-down system level data and bottom-up data on parameters, in which the distributions for each parameter are used. This process results in parameter distributions from which means, variances and *correlations* between different parameters can be deduced. Parameter combinations for which the model predictions are far from the observed data receive a correspondingly small probability.

In order to apply such methods it is necessary to define a *likelihood*, which, conditional on the model itself, determines the probability that the observed data was generated for each possible set of parameter values. In the case of stochastic models the true likelihood follows from the definition of the model and any assumptions about the accuracy of the observations e.g. Gaussian errors. Such an approach is arguably the most statistically rigorous, but is often difficult to implement and requires computationally intensive methods such as Markov chain Monte Carlo (MCMC). For example, Streftaris and Gibson (2004) use MCMC in a Bayesian framework to fit stochastic models for the transmission dynamics of a certain type of Foot and Mouth disease (FMD) virus to data from an experimental setting. These authors illustrate a key benefit of such an approach by not only inferring parameter values, but also missing data in the form of the hidden transmission history of the epidemic. Such techniques can be used to infer contacts in a real epidemic (Demiris and O'Neill 2005). In the case of deterministic models, parameters are typically determined by least-squares which implicitly assumes Gaussian measurement errors and ignores correlations in time.

What happens if we cannot agree on a single structure for a model? For many exotic diseases we may not even have enough information to decide what the mode of transmission is (for exotic vector-borne diseases we may have no evidence for how effective local vector species are). In such cases we can build two or more alternative models. Then, as more data becomes available we may be able to exclude (invalidate) some models. Where the models are relatively simple we may be able to choose between them using a multi-model inference approach (Burnham and Anderson 2002). Alternatively information theoretic criteria can be used to select between models sequentially (Spiegelhalter et al. 2002). If the alternative models are more complex we can still use any data ("patterns") at hand to qualify the good and the bad representations according to their ability to reproduce all the information simultaneously (for example after specifying the latent phase in our model, one could compare the resulting temporal epidemic curve emerging from different assumptions (fixed time vs. fixed rate) to field data on an outbreak. While the data may only show the temporal trend of virus positives, in the model we can manipulate the inputs and observe the outputs to compare it with the available data. Another approach is to produce one model that includes all structures and iterate the model repeatedly, with the number of iterations of each structure depending on the weight of evidence for that structure (see Smith et al. 2008). However, this approach is generally not possible if different research groups produce the models. Where no one model can be identified as significantly better than all others it is appropriate to employ a model averaging approach; each model is run and a combined output is formed by weighting the output of each model by some measure of our prior belief in the model combined with a measure of the extent to which it accounts for the available data. In such cases, uncertainty in model structure is combined with uncertainty in parameters and any intrinsic variation in the model to produce probabilistic outputs reflecting all these sources of uncertainty.

4.4 Quality Control

After constructing a model we then need to interrogate it. We should bear in mind that strategic models should be used to answer questions on improving our understanding, and tactical models should be used to answer questions of the form "what if". When deciding whether to consider model outcomes for policy development, the aim should be to determine whether a model is good enough rather than whether it is correct. But how do we assess the quality of the output and how do we deal with individual objections? There are three main objections used against models: (1) the "I don't believe it" approach, (2) "the model is not validated!" and (3) the model is "too complex" or "does not include some critical component", for example it only includes one sex. The first objection stems from a lack of understanding of the formal structure of modelling. In some cases unbelievable results will stem from errors in the coding, or structure, of a model. However, since the objective of a model is to gain *new* insights, we should not be surprised by unexpected results.

If the criticism can be more specific than "I don't like the answer", then it moves into the second objection category. If not, then this objection is irrational.

When considering the use of model outputs for informing policy development, it is crucial to evaluate their uncertainty (precision, random error) and validity (bias, systematic error). For knowledge-driven models, assessing the validity of outputs can be complex, since models are typically based on quantitative relationships, which have usually been derived from different studies, or may even be based on expert opinion. Validity is usually assessed by comparing model behaviour with the behaviour of the observed 'real world'. Since often 'real world' data does not exist, or the available study has been used to parameterise the model, it is often necessary to consider the plausibility of quantitative outcomes resulting from varying inputs. It should be emphasised that this is not the same as a full sensitivity analysis.

Usually the validity will have to be assessed in a qualitative fashion, whereas uncertainty can be quantified. Validity is therefore particularly difficult to assess, requires a good understanding of the biological system being studied and the methods used to study it. The uncertainty is a reflection of the natural variability in the 'real world' system and of lack of knowledge with respect to causal relationships. Both uncertainty effects are often difficult to separate or measure, but clearly any model prediction should also include an estimate of the uncertainty associated with the predicted outcomes. Policy makers may perceive scientific enquiry as a means for reducing the uncertainty associated with decision-making. However, this may not always be the case as research leading to the advancement of knowledge often results in the realisation that uncertainty has actually increased. Pielke (2003) wrote: "*Ignorance is bliss because it is accompanied by a lack of uncertainty*".

The question of model validity is a important one. By definition, no model can be valid for all circumstances. As we stated at the beginning of this chapter, all models are wrong. Equally, no model can be truly validated – like hypothesis testing, model validation can continue until a model is falsified, and even then it could remain useful in some circumstances. A model that predicts well in the short-term may predict badly in the medium to long term, but we should still consider it valid for short-term predictions. However, some important steps can and should be taken before using the results of a model. Firstly, a model should be verified. This means that its structure should be tested to ensure that the processes are modelled logically and that the output of interest changes in a plausible manner when input values are adjusted. A model should not generate results that are unfeasible, although judging what is feasible is not always straightforward. Nevertheless, there is clearly a problem if model outputs are negative when they should be positive or if it generates numbers that are larger than the total number of atoms in the universe! It is important to distinguish errors of logic from errors of coding. For this purpose it is useful to have a hierarchy of models based on different mathematical approaches e.g. deterministic non-spatial homogeneous mixing to stochastic and spatial, within which results can be compared. For nationally important management decisions, two similar models could be constructed by different teams using the same data and agreed mechanistic processes. From this, verification can occur by cross-model analysis of output.

For discrete-time models there is an additional verification step; examination of all processes (subroutines) that can occur within a single time step. The order of all subroutines within a time step should be clearly stated. One misguided approach that has been taken is to randomise the order of subroutines in each time step. However, all subroutines are either continuous (e.g. mortality) or effectively instantaneous (e.g. changing age categories, disease transmission), and the latter should usually all occur together either at the start, or the end, of each time step, and the order of all subroutines should be checked for logical consistency. If we can assume that the model is logical and verified, and there are no coding errors, then there are two other key processes that have to be considered before it can be used in anger, namely sensitivity analysis and model validation.

Sensitivity analysis assesses how sensitive the model is to its input parameters. There are a number of ways of assessing model sensitivity. The most common approaches include adjusting each parameter by a fixed value (say ±10%), or adjusting each parameter to its maximum and minimum bound, and re-running the model. The former approach is often called local sensitivity analysis and is a form of model verification that tests the sensitivity of the model structure to change. The latter, tests the sensitivity of the uncertainty or variation in the system under study and is used to determine the most important drivers of a system. As an example, a model of population control of a fossorial mammal may indicate that a 10% increase in mortality of young (i.e. pre-emergence from their underground lair) reduces the population more than a 10% increase in mortality of adults. However, the cost of increasing juvenile mortality by 10% may include finding and digging into the lair, whereas a 10% increase in adult mortality could be achieved for far less effort. Thus, from a management perspective the 'best' management option may be to increase adult mortality rates. Thus, local sensitivity analysis by changing values by a fixed percentage should not be used to inform management decisions. It is also important to distinguish between parameters that have large natural variability (e.g. juvenile mortality) and those that are relatively unknown (e.g. disease transmission rates or their surrogate, individual contact rates). A key feature of sensitivity analysis is to provide insights into which features of the model have the greatest effect on the output. This is important particularly if there is any imprecision or over-simplification of fundamental processes within the model. The sensitivity analysis is then used to identify areas where the model requires more precise data. This can be of considerable significance in modelling disease spread because key processes such as transmission are often poorly understood or quantified. This approach can be used to identify those parameters or processes that have the greatest influence on the outcome, and if amenable to human influence, provides insight into management and control. Sensitivity analysis is also useful for identifying parameters or processes that have limited impact on the model outputs. If a model is insensitive to a variable or a process that is incorporated in the model then it is quite legitimate to remove the process from the model completely.

Model validation is the next step in model assessment. During this process, the outputs of the model are compared with real data. These data should come from a

system different to that which was used to create the parameters used as inputs in the model. In effect the modeller is attempting to replicate what happened in another system. Models may also be validated against secondary predictions, in other words with data not used during model parameterisation, but nevertheless taken from the same system. If the verification, sensitivity analysis or validation fails in some respect, then the model has to be redesigned, or refined, until it passes the tests. Once it has 'passed' the tests it could then be used to inform management decisions. Ideally, the requirements for model validation should be specified in advance, since it is often easy to find some aspect of model output that does not fit well with the available data, or belief.

4.5 Using Models to Inform Policy Decisions

If we therefore assume that we have a model that has been subjected to verification and validation, and has not failed these tests, it can be used to help make management decisions. However, it should be noted that models do not produce decisions, but simply extrapolate under a number of "what if" scenarios. The consequences of these management options need to be considered in a wider context. Pielke et al. (1999) stated "*Predictions must be generated primarily with the needs of the user in mind. For stakeholders to participate usefully in this process, they must work closely and persistently with the scientists to communicate their needs and problems*". Thus there should ideally be constant dialogue between the modeller(s) and the user (decision maker), although in our experience this is rare.

Models generally assume that all parameters remain constant (or for stochastic models that the variation does not change with time), except for the parameter being changed (e.g. the management option). In many cases however we expect that some aspects of the model assumptions may change with time (e.g. landowner behaviour), thus, model 'predictions' need to be interpreted in the light of our expected changes in the system.

It is also critical that the user understands the uncertainties in the model, and how they may affect the outcome of different policy options. Lempert et al. (2003) describe the use of quantitative models in policy development as follows:

> *Under conditions of deep uncertainty, we suggest that analysts use computer simulations to generate a large ensemble of plausible scenarios about the future. … The goal is to discover near-term policy options that are robust over a wide range of futures when assessed with a wide range of values.*

When using models to provide management advice it is desirable to take account of uncertainty in our knowledge of, as well as the intrinsic variability in, the system under study. As discussed above, variability can be accounted for by introducing a stochastic element into the behaviour of the model, and uncertainty in knowledge may be accounted for by using statistical approaches. For example, the estimation of parameter values from data is uncertain, and statistical methods provide a distri-

bution of estimates or at the least a mean and standard deviation. It is often the case that a range of models are available and there is therefore uncertainty associated with the choice of model. Accounting for either, or both, system variability and uncertainty in our knowledge about the system leads to a probability distribution across the predicted response of the system. This profoundly changes the advice arising from the model from unequivocal, to for example the relative probabilities that a given disease reduction strategy will be successful or fail (by some criteria). In addition to such quantifiable uncertainty it is also critical to communicate the qualitative limitations of different model formulations as these are likely to be critical to interpreting results.

A recent UK government review into infectious diseases concluded that useful models would in the future need to include stochasticity, individual and population level heterogeneity and spatial structure. It stated "*Combining these refinements into ever more complex … models provides a better chance of accurate prediction. This will be invaluable in … deciding on control options*." Further, the report suggested how models could be used to assess new technologies: "*The development of rapid tests to detect infection earlier could, in theory, help isolate infectious individuals and stop disease spread. However, a model is needed to estimate the potential of such diagnostics and to show* [how] *they might best be deployed*" and also pointed to a new area for consideration in modelling "*To be really useful, however, future models must embody more understanding of human behaviour*".

Modellers need to understand that the results of their model will not be used without being put into a policy context, and users need to understand that model results should not be used without critical interpretation. How models have developed over time, for the UK wildlife rabies contingency plans, are shown in Box 4.3. This development is also instructive in informing policy makers, or budget holders, where to direct further research.

4.6 Model Limitations

All models are subject to a number of assumptions. Much like for statistical tests, some assumptions can be broken without affecting the validity of the answer, and there is no clear definition of which assumptions are of over-riding importance. For example, many models that do not include sex, or age, or season, can result in robust results. In any written presentation, a list of model assumptions should be given, including those that seem obvious to the modeller. Indeed it is worth noting that important caveats concerning the model can easily be lost when crossing between one discipline (epidemiology) and another (policy-making). It is only by examining a list of model assumptions that model output can be interpreted correctly. The failure to provide an adequate list of assumptions often leads to 'overselling' the model.

One of the most important limitations for wildlife disease models is that the disease transmission rate can rarely be measured directly. This is such an important parameter

Box 4.3 The development of rabies modelling for contingency planning in the UK

The simplest mathematical model of rabies spread in red foxes (*Vulpes vulpes*) was a deterministic non-spatial model (Anderson et al. 1981). Although not designed or parameterised for the UK, this simple model could be used to calculate the level of culling (or vaccination) required to eliminate a rabies outbreak, as a function of fox density. Although structurally overly simple, the model relied on assumptions about the threshold density below which fox rabies does not persist (i.e. $R_0 < 1$), which was estimated at one fox per square kilometre. However, rabies is known to persist in foxes in Canada at far lower densities (Voigt and Macdonald 1984), so the generality of this assumption is uncertain. This model was then parameterised for the UK and a spatial dimension was added in the form of a diffusion term, which assumed that disease spread was caused only by the itinerant movement of rabid foxes (Murray et al. 1986). A map of fox density in England and Wales was then used, on which the equations were numerically solved, producing time series pictures of rabies spread in England and Wales. In a first attempt to utilise a model to evaluate the local introduction, spread and control of rabies, an existing simulation model (the 'Ontario Rabies Model': Voigt et al. 1985) utilised a grid where each cell represented a fox home range (Smith and Harris 1989). This model simulated a large range of fox densities, and being stochastic, could evaluate the probability of disease elimination for any given level of control. It permitted disease spread by neighbour-to-neighbour contact and fox dispersal, and the threshold for disease persistence was an emerging function of biological parameters, and was not pre-determined. This latter model also demonstrated that low levels of fox culling would result in extending the duration of the epidemic. However, it was known that fox density in local areas of English cities could exceed nine foxes per square kilometre (Harris 1981), whereas in nearby rural areas it was likely to be less than one fox per square kilometre (Macdonald et al. 1981). Therefore, a revised simulation model was constructed based on 500× 500 m grid cells, which were combined to form fox home ranges of different sizes (Smith and Harris 1991). This not only permitted the incorporation of heterogeneity in fox density, but had the added advantage of removing the bias inherent in regular geometric simulation models (Holland et al. 2007). Refinements of this model were used to investigate fox vaccination (Smith 1995) and fertility control (Smith and Wilkinson 2003), and the model was integrated within the UK contingency plan for dealing with an outbreak of wildlife rabies (Smith and Fooks 2006).

in the models that we dedicated a whole chapter to estimating it (Chapter 3). However, this is not an insurmountable problem, since, if the structure of the model is correct, and a prevalence estimate has been measured in the field, a limited range of transmission

rates will produce this output. This is similar to having one unknown in an equation – only one value (of the transmission rate) will make the equation balance. In two-species models there are four transmission rates (two within-species and two between-species rates), which makes estimating these values with limited field data difficult. Few attempts have been made to formally parameterise two-species disease models for practical use (but see Morgan et al. 2006). Some theoretical work has been done in this area (Dobson 2004), particularly with parasite/parasitoid models (e.g. Preedy et al. 2007). With three-species models there will be nine transmission rates, thus making accurate estimation nigh impossible.

Given that modelling outcomes will always be associated with varying degrees of uncertainty and validity, the decision to use them for informing policy making will have to be based on opinion and judgment. One recent advance is the inclusion of the economic dimension within computer models to help managers to make informed decisions.