Persistence of disease in territorial animals: insights from spatial models of Tb

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Abstract: Early models of directly transmitted wildlife disease focused on rabies transmission as a travelling wave, usually in a homogeneous density of wildlife. Such models of epi-enzootic diseases paid little attention to local-scale disease prevalence. Historical data on bovine tuberculosis (Tb) in cattle indicates that very localised areas can suffer from frequent repeat breakdowns, indicating that some environmental factors might be the cause. There are a number of different ways to simulate such local disease 'hotspots' in wildlife, and these resultant hotspots may mean that, overall, wildlife disease prevalence is very low. However, spatial and temporal persistence of this hotspot is more difficult to model. This heterogeneity in disease prevalence is difficult to produce in non-spatial models, and is one of the reasons why such models gave poor predictions of disease dynamics in the field. For example, Nigel Barlow struggled with finding a way to produce this spatial heterogeneity in mathematical models, culminating in his 2000 paper in *Journal of Animal Ecology*. This gave a phenomenological treatment, but not a causative solution. I take a look at the various causative methods of producing disease heterogeneity in simulation models of Tb, a chronic wildlife disease. These include (1) chance, (2) model artefacts, (3) population (e.g. demographic, genetic) heterogeneity and (4) environmental heterogeneity. I further argue that only (4) can be predicted over a medium timescale, and propose methods to assess the contribution of (1) and (2) in a model. I also discuss how spatial heterogeneity may affect Tb management.

Keywords: badgers; bovine tuberculosis; disease prevalence; *Meles meles*; spatial heterogeneity; spatial model; territorial behaviour

Introduction

Disease outbreaks and spread are, by definition, spatially heterogeneous. For directly transmitted diseases new infections are local, and animals are discrete. Despite this, early disease models, which assumed homogeneous mixing, density-dependent transmission and real numbers, were very powerful predictors of disease spread in animals and humans (e.g. Anderson and May, 1979; 1991). Recent work has highlighted the difference between these general non-spatial models and models that have a spatial structure (Keeling, 2005). The now classical models of Anderson and May use simple differential equations to model each compartment of the host population: susceptible, exposed, infectious, and sometimes an immune or recovered category (SEI or SEIR models).

Many early wildlife disease models focused on rabies transmission, and represent disease spread as a travelling wave, usually in a homogeneous density of wildlife (Lambinet *et al*., 1978; Anderson, 1982). Such models of epi-enzootic diseases paid little attention to local-scale disease prevalence. Attention soon shifted to modelling chronic enzootic diseases such as bovine tuberculosis (Tb: caused by *Mycobacterium bovis*) by the same approach (e.g. Anderson and Trewhella, 1985). These simple models help us understand how a system works. They tend to be general in construction, and are therefore often imported relatively unchanged, except for parameter values, from other areas of epidemiology, biology, or even physics. They are often analytically tractable, and give insight into the importance of particular parameters, regardless of the specific system under study. These simple models are 'mean-field', or population-level, models, where each parameter of the model is measured for the whole population (e.g. mean death rate, mean litter size). These models are usually based on population density, permitting the use of real numbers.

These early models utilised density-dependent transmission (McCallum *et al.*, 2001). Thus, if host density doubled, then the transmission of disease doubled. One of the first analytical results derived from these models is the basic reproductive ratio, R_0, which is the number of new cases of disease caused by a single infected individual in a population of susceptible individuals (Anderson and May, 1991).

Since transmission increases linearly with density, it is important to note that any measure of R_0, must be for a specific host density. The assumption that underlies this linear density-dependence is that of homogeneous mixing. This assumes that any infected animal is equally likely to contact, and thus infect, any other animal, i.e. there is no spatial structure. Strictly speaking, linear density dependence can arise from spatially localised homogeneous mixing, if within a homogeneous environment (Begon *et al*., 2002). Once a transmission rate has been determined then, for a particular species, disease dynamics depends almost entirely on population density. For any territorial species, homogeneous mixing cannot hold true. It is therefore likely that these homogeneous mixing models become less and less 'correct' as the amount of mixing (extra-territorial movements such as dispersal) decrease. An attempt to deal with the problem of homogeneous mixing is the use of frequency-dependent transmission. Here the number of transmissions is held constant as density changes (McCallum *et al.*, 2001). Frequency-dependent transmission can occur if animals adjust their territory size, rather than social group size, since the number of neighbouring territories would remain constant. If, however, both social group size and number of territories can change, then the resultant disease dynamics would be neither density-dependent nor frequency-dependent. Although I refer to territorial animals throughout, the arguments also apply to non-territorial animals with defined home ranges.

Historical data on Tb in cattle (*Bos taurus*) (Krebs *et al*., 1997), badgers (*Meles meles*) (Delahay *et al*., 2000) and possums (*Trichosurus vulpecula*) (Hickling, 1995) indicate that disease foci can be localised over time and space. Such disease clusters can be either ephemeral, or static in time and space, the latter indicating that spatial factors (e.g. environmental) may be the cause. Such spatial correlation in the structure implies that the simple models are not adequate. Predictions from the simple density-dependent badger/Tb model included linear correlation between host density and disease prevalence and marked suppression of host density (Anderson and Trewhella, 1985). Neither of these has been found in the wild (Smith, 2001). Simple models are also not capable of correctly simulating the low prevalence and relatively quick recovery of Tb in possum populations (Barlow, 1991). However, these models rarely consider the possibility of re-seeding of infection from other wildlife, for example ferrets (Caley and Hone, 2004) or deer and other species (Delahay *et al*., 2001). Spatial models of Tb in wildlife (e.g. Smith *et al*., 2001a) can simulate repeat cattle herd breakdowns, spatial correlation, lack of a relationship between host density and disease, and limited suppression of host density. Thus they simulate reality much more closely, but at the cost of much larger data requirements. The questions we must ask are (1) are these spatial models actually necessary or more accurate, (2) what general aspects relating to spatial heterogeneity do spatial models predict and (3) which is the best such model?

Modelling spatial heterogeneity

There are a number of different ways to simulate a temporally persistent local disease hotspot in wildlife, and this resultant hotspot may occur despite very low overall disease prevalence. While hotspots due to chance should emerge from any stochastic model, the difficulty is in defining what mechanisms may underlie persistent spatial heterogeneity. This heterogeneity has been difficult to produce in non-spatial models, and explains why such models gave poor predictions of Tb disease dynamics in the field (Smith, 2001). For bovine Tb, spatial aggregation of disease was first modelled with a simple two-patch SEI model, which assumed that increased mortality caused by disease in one patch was balanced by immigration from the disease-free patch (Barlow, 1991). However, there was no mechanistic explanation for the maintenance of this heterogeneity, although both stochastic effects and spatial heterogeneity in the carrying capacity (K) were hypothesised as a cause. A secondary effect of this model was to remove the potential for temporal disease oscillations, which were predicted by the homogeneous models (Anderson and Trewhella, 1985; Bentil and Murray, 1993), and for which there is now no field evidence (Barlow, 2000). Although dramatic changes in disease prevalence have been recorded (Coleman *et al*., 1999; Delahay *et al*., 2000), these may well be related to extrinsic environmental factors rather than intrinsic epidemiological factors. A later adaptation spread the SEI model over a grid of 1-km squares (Barlow, 1993), and showed that chronic disease, or lack of juvenile dispersal, gave the slowest spread of disease. These factors would therefore lead to the greatest spatial heterogeneity of disease. Indeed, in a high-density population of the badger it has been shown that dispersal rates are very low and annual movement rates are correlated with subsequent disease incidence (Rogers *et al*., 1998). Further modelling involved non-linear contact rates (Roberts, 1996) and heterogeneous mixing and non-linear contact rates (Barlow, 2000). These models gave a phenomenological treatment, but not a causative solution. In none of the above examples was the reason for spatial clustering of disease presented.

In a spatial individual-based stochastic model White and Harris (1995) demonstrated spatial heterogeneity in badger Tb, within a homogeneous badger population. These patches were randomly located and shifted in location over time depending upon the relationship between within- and between-

group infection rates. The actual cause of this spatial heterogeneity was not explicitly stated but appeared to be due to stochastic chance.

I will use an established individual-based model of Tb in the badger (Smith *et al*., 2001a, 2001b; Wilkinson *et al*., 2004) to look at the various causative methods of producing disease heterogeneity in simulation models of disease. There appear to be four possible reasons for this heterogeneity:

(1) Since animals are discrete and located in space (limiting social contacts), random stochastic chance will give rise to spatial heterogeneity in stochastic but not deterministic models. This heterogeneity can occur in a true homogeneous environment, even when seeded with a homogeneous distribution of disease, and it appears to be the cause of the spatial heterogeneity in White and Harris (1995). This form also occurs under homogeneous conditions with the model of Smith *et al*. (2001b). Undoubtedly this form of heterogeneity occurs in real life, but by definition the spatial distribution cannot be predicted as it occurs by chance. If this is the cause of spatial heterogeneity in a model then two things will follow from this: (i) disease foci will move over time, dependent on local host density, transmission rates, dispersal and disease-induced mortality and (ii) if disease prevalence is averaged over time, or multiple simulations, then the degree of heterogeneity will eventually decrease to zero, as all points will have the same likelihood of disease presence.

(2) Model construction may give rise to spatial heterogeneity in both stochastic and deterministic models. This became apparent in the model of Wilkinson *et al.* (2004), which was a grid-based stochastic model with reflecting boundaries. Plotting the prevalence of disease spatially showed that disease prevalence declined towards the edge of the grid. Social groups actually at the edge had a reduced number of neighbours, and this resulted in a small decrease in disease prevalence. However, this decrease radiated three social groups into the simulation grid, so that the outermost three rings of social groups had a detectable decrease in disease prevalence. This model artefact was removed when the model was run on a torus (the top of the grid was linked to the bottom, and each side to the other). Another possible model artefact that could induce spatial heterogeneity is the order in which grid cells are interrogated and adjusted during each time step of a simulation for any spatial process (e.g. dispersal) (Ruxton, 1996; Smith and Bull, 1997). The latter means of heterogeneity will not occur in real life, although effects similar to the former may occur near reflecting boundaries such as coastline or rivers. If this is the cause of spatial heterogeneity in a model then two things should follow: (i) disease foci will be static and (ii) plotting the spatial distribution of disease (averaged across simulations for stochastic models) over a homogeneous landscape will show a distinct pattern. The existence of static disease heterogeneity in homogeneous models should therefore lead one to investigate possible artefacts.

(3) Population heterogeneity, e.g. intrinsic demographic or genetic variation, may also give rise to spatial heterogeneity of disease. There are a number of potential causes: (i) true individual-based models may allow some individuals to consistently produce larger litters resulting in increased social group size and thus increased local disease prevalence, (ii) genetic inheritance of traits such as large litter size, or immunity to disease, will change local disease prevalence, (iii) differential pathogenesis or competing disease strains may also give rise to local variation in prevalence, and (iv) differential rates of spatial diffusion in multi-species models (e.g. Comins and Hassell, 1996; White and Gilligan, 1998). In the model of Smith *et al.* (2001b), allowing a small proportion of individuals to have immunity to disease, which can be genetically inherited, results in areas of reduced prevalence in an otherwise homogeneous environment. This form of heterogeneity will occur in real life and will be in addition to (1). Similar to (1) if this is the cause of spatial heterogeneity in a model then two things follow: (i) disease foci will move slowly over time (possibly taking generations) and (ii) if disease prevalence is averaged over time, or multiple simulations, then the degree of heterogeneity will eventually decrease to zero. However, it is possible to differentiate (3) from (1), since switching off the causative factor in the model will result in a reduced level of heterogeneity.

(4) Extrinsic spatial variation may produce spatial heterogeneity in disease. This may be caused by internal reflecting boundaries as in (2), variation in carrying capacity, edge effects between habitats, which may cause differential immigration, mortality (including that caused by man) or fertility, or spatial distribution of chemicals (e.g. pesticides) causing changes to population parameters. Habitat may also directly affect transmission rates by adjusting behaviour. Tb in badgers is known to cluster spatially (Delahay *et al*., 2000), and both prevalence and incidence of disease are related to the number of occupied setts in a social group, but not the number of badgers (Rogers *et al.*, 2003). The maximum number of breeding females in a badger social group varies between territories, and this was used in Smith *et al*. (2001b) to set the carrying capacity. A similar approach, used to simulate the historical pattern of disease at the Woodchester Park badger study site gave a high spatial correlation between model output and reality (Shirley *et al.*, 2003). Again, this form of heterogeneity occurs in real life and as in (2): (i) disease foci will be static and (ii) plotting the spatial distribution of disease (averaged across simulations for stochastic models) will show a distinct

pattern. As in (3), this form of heterogeneity can be distinguished from (2) by switching off the external spatial factor. It is important to note that any spatially varying control policy will act to increase disease heterogeneity. An extreme example of this is the increased cattle herd breakdown rate associated with reactive culling in the Krebs trial in the UK (Donnelly *et al.*, 2003).

In some circumstances a combination of (1) and (2) can occur where the initial conditions of a spatial model are randomised (e.g. territorial configuration). This can become evident if these initial conditions are used for all simulations. For example, in the model of Smith *et al.* (2001b) it is possible to examine an epidemic outbreak of Tb where qualitatively different results occur depending upon the exact spatial starting conditions. This is actually a stochastic result, which can occur in real life. In this case the epidemic depended upon a minimum number of neighbouring social groups, which occurred in some simulations but not others. However, it is also a model artefact, as it depends upon the frequency of calling a randomisation procedure to initiate the starting conditions.

Although (1), (3) and (4) occur in real life, (1) can never be predicted and (3) can only be predicted where the causative variation in intrinsic structure (e.g. genetic profile) is known for the whole population. Therefore only (4) can be predicted over a medium timescale.

Disease prevalence is not always related to population size or density. In spatially heterogeneous patches, for a model of Tb in possums, it has been noted that disease prevalence may actually be higher in patches with a lower carrying capacity (Fulford *et al*., 2002), due to migration. It is possible that this is only a special case where individual patches need to be above a certain size to maintain disease (e.g. greater than a single social group of badgers), as higher prevalence is not found in smaller badger social groups (Rogers *et al*., 2003), and the patch with the higher prevalence needs to be a preferred site with a higher immigration rate. Local mixing of individuals, rather than homogeneous mixing as assumed in the early models, also appears to be responsible for a lack of relationship between host population size and disease prevalence (Smith *et al*., 1995). For badgers, the amount of extra-territorial movement in previous models (Smith *et al*., 2001a) may, however, have been underestimated, as a small but significant proportion of cubs are fathered by males living more than one social group away (Carpenter *et al*., 2005). Indeed to correctly simulate the recovery time for culled populations, it is necessary to allow badger movements over more than one social group distance (Wilkinson *et al*., unpublished data). These pieces of evidence suggest that the localised mixing of badgers, at least, may not be as extreme as initially thought.

This potential lack of a relationship between population density and disease prevalence makes control more difficult. In terms of disease eradication, increased spatial variation in host density gives rise to an increased risk of disease extinction (Caraco *et al.*, 1998). However, the optimal immunisation approach in spatially aggregated populations occurs when the number of susceptible individuals is uniform (May and Anderson, 1984), thus control should be focused on higher-prevalence areas, rather than higher-density areas. However, the maintenance of Tb in badger populations may depend upon a minimum group size of some 6-8 badgers (Smith *et al.*, 1995; White and Harris, 1995). Badger social group size can be predicted by the number of active setts (Rogers *et al.*, 2003), by using faecal DNA fingerprinting (Wilson *et al.*, 2003) or potentially by using remotely sensed data (French and White, 2004). This suggest that control can still be successfully applied to higher-density areas in the absence of good-quality information on disease prevalence.

Which is the best model?

Very often the exact choice of which parameters to include in a model, and which to omit, is made by individual modellers, based on experience. This is why modelling is often called an art. The fact is, computer modelling has not yet elevated itself on a par with statistics, which is able to examine various topics without having to defend itself from first principles. There is no clear consensus on when to use different types of models (e.g. differential equations, reaction-diffusion equations, interacting-particle models, cellular automatons or IBMs) and the majority of authors appear to stick to a single type of model over many years, and over different topics. I would argue here that this is tantamount to always using a chi-square test, regardless of the data structure. The choice of the best model structure will depend on the availability of data and the nature of the question(s) being asked. It is vital that the question(s) asked of the modeller are well thought out. If the initial question is not concerned with spatial differences, then the resulting non-spatial model may not be able to answer a later, and more important, question which involves spatial structure.

Information-theoretic approaches are being increasingly used to choose between different statistical and capture-recapture models (e.g. Burnham *et al.*, 1995; Anderson *et al.*, 1998) but this approach is also applicable when choosing between different population models (e.g. White and Lubow, 2002). Although other approaches are available, the most commonly applied in biology is Akaike's Informations Criteria (AIC). This is in effect a measure of goodness of fit with a penalty for the number of parameters in the model, and

is analogous to fitting the most parsimonious least squares linear regression. This approach can be used for fitting the most parsimonious population model(s) to multiple sources of data (similar to fitting a regression) (White and Lubow, 2002). However currently, the comparison of models with different levels of spatial structure is not straightforward and does not appear to have been performed to date. For non-spatial models, or for models with identical spatial structure, I would like to suggest that information-theoretic approaches (e.g. Akaike's Information Criteria) are evaluated against available field data. This does however, evaluate a model against the data used to construct it and says little about a model's ability to 'correctly' predict in other spatial or temporal locations. There is thus a need to consider how to choose between competing models, of different structure or complexity, that make predictions of, for example, disease prevalence for which field data is available. In many circumstances field prevalence may be the only biology data available — data on the underlying population parameters are probably not collected. The ability to choose between models with different structures may be important if these models predict that different levels of management are required to eradicate disease.

Conclusions

I have argued above that spatial models are necessary to capture the complexity of disease heterogeneity that arises from the local contact structure that occurs for bovine Tb in both the possum and the badger. Only spatial models are capable of simulating the causative function(s) that produce spatial heterogeneity of disease. I have further suggested that there are four different reasons for such heterogeneity to appear in models, and that only one (extrinsic heterogeneity) can be predicted. Recent work in information-theoretic approaches have begun to be used to choose between population models, but there is much work to be done before this approach can be applied to models with different spatial structure.

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