PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B

Phil. Trans. R. Soc. B (2008) **363**, 741–759
doi:10.1098/rstb.2007.2181
Published online 7 September 2007

Sustainable agriculture and plant diseases: an epidemiological perspective

Christopher A. Gilligan*

Department of Plant Sciences, University of Cambridge, Downing Street, Cambridge CB2 3EA, UK

The potential for modern biology to identify new sources for genetical, chemical and biological control of plant disease is remarkably high. Successful implementation of these methods within globally and locally changing agricultural environments demands new approaches to durable control. This, in turn, requires fusion of population genetics and epidemiology at a range of scales from the field to the landscape and even to continental deployment of control measures. It also requires an understanding of economic and social constraints that influence the deployment of control. Here I propose an epidemiological framework to model invasion, persistence and variability of epidemics that encompasses a wide range of scales and topologies through which disease spreads. By considering how to map control methods onto epidemiological parameters and variables, some new approaches towards optimizing the efficiency of control at the landscape scale are introduced. Epidemiological strategies to minimize the risks of failure of chemical and genetical control are presented and some consequences of heterogeneous selection pressures in time and space on the persistence and evolutionary changes of the pathogen population are discussed. Finally, some approaches towards embedding epidemiological models for the deployment of control in an economically plausible framework are presented.

Keywords: epidemiological model; crop mosaics; genetical, chemical and biological control; population genetics; economic models

1. INTRODUCTION

Agriculture is changing fast and with it the landscape through which disease spreads. This imposes new demands on our understanding of epidemiology if we are to control disease efficiently, whether by genetical, chemical, biological or cultural means. The sorts of questions that need to be addressed (table 1) are focused on discovering the factors that influence the invasion and persistence of new pathogenic strains, how and why they outcompete resident pathogens and how to promote durable methods of control. This requires an understanding of what controls the variability of epidemics between one location and another and from one season to another, and how this impinges upon local, national and sometimes international crop loss. Can we do all this? Not yet but I shall argue here that we are beginning to be able to do so and illustrate some probable new directions. To help motivate the discussion, I summarize some illustrative questions in table 1 from which I conclude that we need to embed modern approaches to sustainable disease control within an epidemiological framework.

Why is agriculture changing so fast? What is the evidence? In large parts of the world, intensively managed farms are becoming larger, interspersed with smaller, organically and conventionally managed farms with diverse livestock and cropping patterns. Global warming is changing the national and international ranges of pests and disease (Coakley *et al.* 1999). Economic pressures and global trade are changing national cropping patterns. It is anticipated that the demand for cereals will increase by 20% by 2020 as world population grows (Rosegrant *et al.* 2001). The corresponding increase in demand for animal products is estimated to be 50%, in response to increasing affluence and urbanization, notably in southeast Asia (Evans 1998; Rosegrant *et al.* 2001). The recent accession of 10 new states into the EU along with reform of the Common Agricultural Policy is likely to change cropping patterns in Western Europe. Novel crops for biofuel, plastics and intensive specialized production of pharmaceutical crops under glass are probable. Meanwhile, our understanding of the genetical and chemical bases of disease control is accelerating following investment in molecular biology (Stuiver & Custers 2001; Strange 2003). The costs, though, for release of new varieties and for the development and registration of new chemicals have escalated. The quest for durable control itself rests on a paradox. Since most plants are self-evidently resistant to most pathogens, it seems perfectly reasonable to assume that advancing knowledge of the molecular and cellular bases of host–pathogen interaction will identify the means not only to engineer or to select durable resistance but also to produce effective and environmentally neutral forms of chemical control. Yet failures still occur, whether from the release of novel resistance genes (Brown & Hovmøller 2002) or from new pesticides and fungicides (Chin *et al.* 2001). Agriculture continues to be confronted with new and recurrent epidemics. Notable examples include recent epidemics of cassava mosaic virus in West Africa (Legg 1999), citrus canker in Florida (Gottwald *et al.* 2001; 2002*a*), rhizomania

*cag1@cam.ac.uk

One contribution of 15 to a Theme Issue 'Sustainable agriculture II'.

Table 1. Some illustrative questions that may be answered from an epidemiological framework that involves a synthesis of epidemiology and population genetics embedded in a biologically plausible economic framework for management of disease.

- How are invasion and persistence of agricultural parasites and the variability of epidemics affected by dynamical landscapes whereby the mosaic and connectivity of the landscape change due to:
  - cropping patterns within and between seasons?
  - spatial and temporal deployment of novel resistant varieties?
  - spatial and temporal deployment of chemical control?
- How are these processes affected by differences in: transmission, dispersal, recombination and intercrop survival typical of the principal classes of plant pathogens?
- How can epidemiological considerations of invasion, persistence and variability in heterogeneous temporal and spatial environments be introduced to economic models for management of resistance and decision making under uncertainty?
- What are the consequences for the optimal deployment of novel chemical, genetical and engineered biocontrol agents so as to minimize the risks of breakdown of control?
- Is there a critical density of susceptible crops below which a virulent race of the pathogen cannot invade?
- How is the risk of invasion affected by the geometry of the susceptible crops relative to the dispersal mechanisms of the parasite?
- How do differential fitness costs of invading and resident strains during the parasitic and saprotrophic or survival phases affect the probabilities of persistence?
- Can we predict durability of resistance and how is this affected by the deployment of resistance?
- What is the time to extinction or time to invasion of a novel pathogen strain?
- What are the consequences for the evolution of dispersal rates and switching between asexual and sexual phases?
- What will happen to the threat of disease in organic (pesticide-free farms) when there is less control on surrounding farms?

disease of sugar beet in the UK and Western Europe (Stacey *et al*. 2004), and the arrival and spread of Asian soya bean rust, caused by *Phakopsora pachyrhizi*, in South America and subsequent entry into the United States (Schneider *et al*. 2005). Similar problems arise in natural and semi-natural communities, where the effects are especially noticeable on forest and amenity trees: sudden oak death, caused by *Phytophthora ramorum* is spreading rapidly on coast live oak and tanoak in California (Rizzo *et al*. 2002), for which the probable strategy for control is sanitation and containment. Meanwhile, Dutch elm disease may recur in the UK (Swinton & Gilligan 1996) as may chestnut blight caused by *Cryphonectria parasitica* in the US (Milgroom & Cortesi 2004), for each of which there is continued interest in biological control by RNA viruses (Swinton & Gilligan 1999; Milgroom & Cortesi 2004).

Most forms of disease control are screened for effectiveness at the small scale. Often this is done at scales as small as the single plant for initial screening, though more usually it involves field plots and ultimately fields. Yet successful deployment, and the risk of failure, occurs at scales much larger than this, at the regional, national or even international scales. We can reconcile these scales using an epidemiological framework that allows us to predict how measurable changes in latent and infectious periods or transmission rate might affect the regional spread of disease. This, in turn, requires fusion of population genetics and epidemiology at scales extending from the field to the landscape and even to continental deployment of control measures. Progress in sustainable disease control measures also requires an understanding of economic and social constraints. These are all too frequently ignored in epidemiological models, while economic models are often biologically naive, failing particularly to allow for the dynamical nature of most epidemics (Gilligan 2003).

An epidemiological framework for sustainable disease control requires a suite of models to analyse and predict the effects of control on the spatial and temporal dynamics of disease, together with methods to parametrize the disease. One important switch of emphasis is from within-field to regional control of disease. Underlying this analysis is a shift in emphasis from private to public benefit (Geoffard & Philipson 1997), whereby optimization of control strategies may increasingly be exercised from a regional perspective over a population of growers rather than seeking to optimize control in each field. Many of the components for an epidemiological framework have been individually studied but not always at the same scale and often with little overlap. These include models from both medical and botanical epidemiology (to analyse and predict the effects of control strategies on the spatial and temporal dynamics of disease), population genetics (for the evolution of virulence and pesticide resistance), landscape ecology (for the spatial structure of susceptible host populations) and environmental economics (to allow for cost constraints and decision making under uncertainty). Progress in developing an epidemiological framework for sustainable control of disease also depends upon theoretical advances in mathematics and statistical physics (particularly for transient behaviour, spatially extended dynamics, percolation and network theory) as well as in probability and statistics (for stochastic dynamics and parameter estimation of nonlinear models using modern computer-intensive methods to explore large regions of parameter space). The relationships among some of these are shown schematically in figure 1. Here discussion is confined to strategic issues: mathematical details are not given but may be found in cited publications. Comprehensive treatments of model structure and analysis are also available in Gilligan (2002) for epidemics of fungal and fungal-like diseases and by Madden *et al.* (2000) for virus diseases.

2. EPIDEMIOLOGICAL FRAMEWORK

(a) *Scale: within-plant, field, farm, regional, national and continental scales*

Whereas, convention suggests that the plant is the natural unit to monitor epidemiological dynamics, this is not necessarily so for many diseases or for the

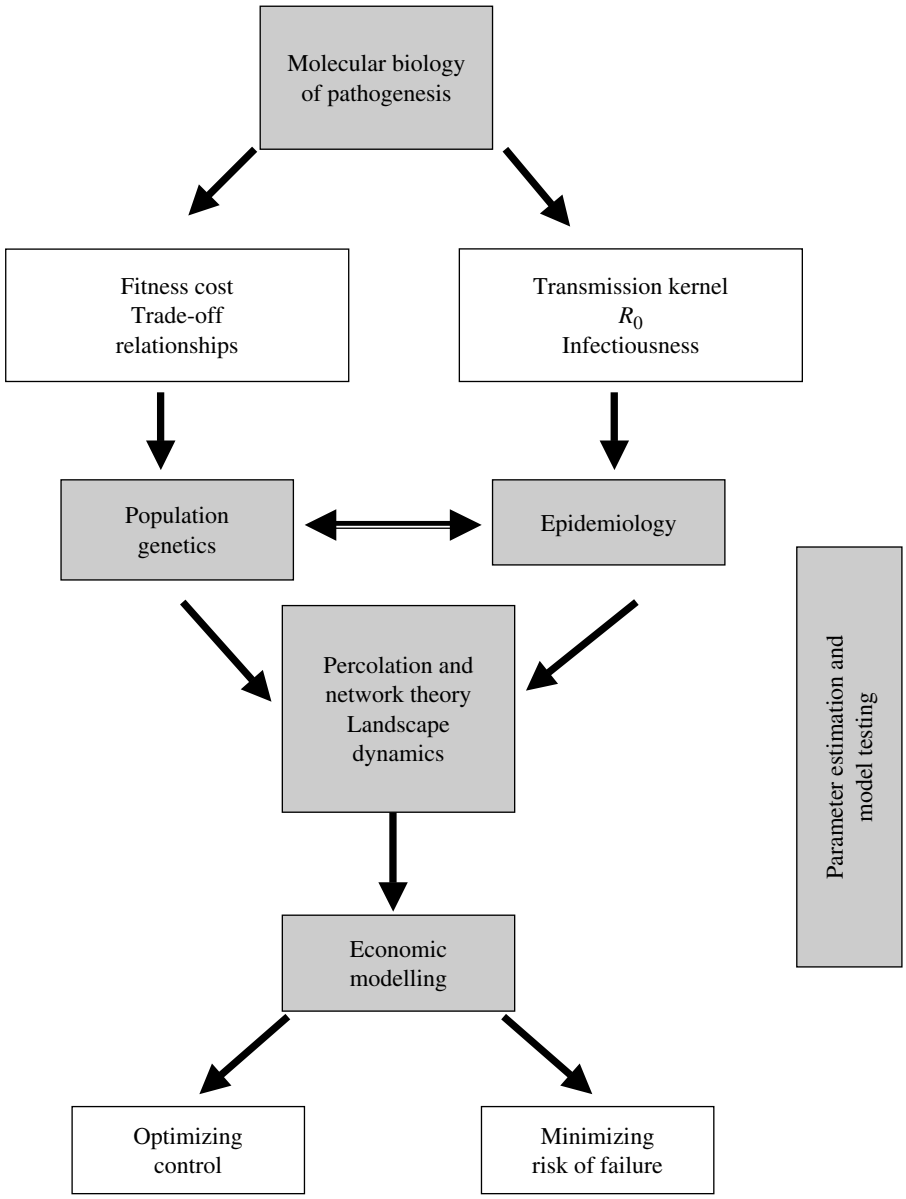

Figure 1. Schematic relationships of selected components of an epidemiological framework encompassing population dynamic, population genetic, landscape dynamics and economic approaches.

development of optimal control strategies. The appropriate scale of interest may occur both up and down from the level of the plant.

(i) *Within-plant dynamics, topology and crop ideotype*

For a crop plant, such as wheat, that can produce 10 or more leaves, 40 or more roots and several tillers, the single plant is frequently too crude a measure to understand the dynamics of infection. It is not unusual for all plants to be scored as diseased within a field (Werker & Gilligan 1990) yielding a spuriously asymptotic level of infection of 100%. This may have little impact on yield, when levels of infection within plants are low, while masking highly nonlinear changes in infection within plants and in the availability of susceptible tissue for infection. Although much attention has been focused on the molecular and physiological interactions at the host–pathogen interface and their genetical control, relatively little attention has been given to the importance for epidemics of the dynamics and topology of host growth within crops. The amount and location of susceptible tissue changes as leaves and roots are produced, expand and die. Accordingly, the individual leaf, root, tiller or stem may appropriately be considered the natural unit for infection and disease. Each unit is then categorized as to whether or not it is susceptible (S), infected (I) or removed (R, an epidemiological euphemism that encompasses dead, recovered or moribund tissue). This categorization leads to SIR models, common to human, animal and botanical epidemiology.

The availability of susceptible tissue modulates the invasion and persistence of epidemics, yet is often overlooked. For wheat infected by the take-all fungus, small levels of disease early on in an epidemic lead to an overcompensation of the plant in producing susceptible roots to replace diseased roots (Bailey & Gilligan 2004). The extra roots enable the plant to compensate for loss of tissue but the pathogen also benefits from the provision of new susceptible roots. The birth and death of roots therefore changes the topology of the system through which disease spreads. These function as

epidemiological 'stepping-stones' in bridging the gap between infected and otherwise susceptible roots, perhaps on adjacent plants, and so facilitate continued invasion by the pathogen. Only as the epidemic progresses and the average burden of diseased roots per plant increases, does the plant fail to compensate and the epidemic slow down (Bailey & Gilligan 2004; Bailey *et al.* 2006). Further analysis of this epidemiological response for disease escape by the host suggests that there is differential expression among cultivars (Bailey *et al.* 2006) from which selection may be initiated. Analogous properties hold for the dynamics and geometry of leaf growth and dispersal of aerial pathogens. Thus, Lovell *et al.* (1997) and Arraino *et al.* (2006) have shown how cultivars of wheat differ with respect to the orientation of leaves and propensity for splash dispersal of *Mycosphaerella graminicola* within and between leaves. We conclude from these and other studies that, in the renewed interest in re-constructing crop ideotypes (Denison *et al.* 2003), including reconstruction of genomes to bypass evolutionary bottlenecks, there is scope also for selection of traits that impinge on epidemiological dynamics.

(ii) *Beyond the field: treating fields as natural units for infection*

The switch of emphasis from within-field to regional spread of disease leads naturally to considering the field as the natural unit for epidemiological analysis. This can occur in two obvious ways. The first is simply to classify fields as susceptible, infected or removed, and to analyse the spread of disease through populations of fields using the same mathematical machinery as for epidemics within fields. The second is to allow for dynamics of disease within and between fields by considering fields as structured metapopulations (Gyllenberg *et al.* 1997; Park *et al.* 2001, 2003; Gilligan 2002). Epidemics now occur within fields but are subject to dual sources of inoculum from within and between fields (Park *et al.* 2001). In this case, there is therefore a transit time as a field first becomes infected until it begins to export inoculum that causes infection in other fields (Swinton 1998; Gilligan 2002). In each of these paradigms, the topological arrangement of susceptible crops within the landscape and the dispersal dynamics of the pathogen, or its vector, together determine the dynamics of disease spread. How far the infection spreads within and between fields is defined by the dispersal kernel. For many splash-borne pathogens, dispersal may be restricted to neighbouring fields, but for wind-dispersed pathogens dispersal may extend over several kilometres and exceptionally over hundreds of kilometres (Limpert 1999; Linde *et al.* 2002). For systems with large-scale dispersal, farms, counties or even larger regions may form the natural scales of interest (Stacey *et al.* 2004).

(b) *Simple models*

Epidemiological understanding of the sustainable deployment of disease control requires simple yet realistic models that capture not only the deterministic (average) behaviour but also stochastic dynamics within and between epidemics. The models can be used to compare alternative strategies for control by mapping the effects of disease control onto the model parameters (figure 2). Finding the appropriate balance between simplification and detail remains a serious challenge for epidemiological analyses of sustainable disease control. Another challenge is how to deal with temporal and spatial heterogeneities. Temporal heterogeneities occur due to fluctuations in environmental variables within seasons that can appear to start and stop epidemics (Truscott & Gilligan 2003). Fluctuations also impinge at the longer scale on the multi-seasonal dynamics of many botanical epidemics with periods of survival interspersed between periods of parasitic activity on susceptible crops (Gubbins & Gilligan 1997*a*,*b*). This exposes the pathogen to quite different selection pressures within and between seasons and is particularly acute for pathogens in which re-establishment each season from resident inoculum has a marked effect on subsequent epidemics (Bailey *et al.* 2004). Spatial heterogeneities arise from the mosaic of susceptible and non-host crops encountered by a pathogen as it spreads at the landscape or regional scales (Gilligan 2002). Surprisingly little attention has until recently been given to these important processes in understanding the dynamics of epidemics and the deployment of control.

Historically, there has been a tendency to focus on environmental variables, such as temperature and rainfall, often leading to multiple regression equations for disease progress (Kranz 1990). This reflected, in part, the ease with which abiotic variables could be measured relative to biotic variables such as infection and disease. Although these models may be useful as 'black-box' predictors of disease progress, they lack mechanistic interpretation of the epidemiological processes. Increasingly, therefore, mathematical models for botanical epidemics resemble those for animal and human diseases, centring upon the susceptible–infected–removed (SIR) framework, although the fine details may differ. Some common variants used for analysis of the dynamics and control of botanical epidemics are illustrated in figure 2. The balance between primary and secondary infection is particularly important for many plant diseases (Gilligan & Kleczkowski 1997). Primary infection is driven by ingress of inoculum from outside the system. For soil-borne pathogens, this often means infection from the reservoir of inoculum in soil; for aerial pathogens, it usually means allowance for inoculum coming from a different field or even a different region. Models for botanical epidemics also increasingly reflect seasonal dynamics accentuated by survival during intercrop periods. The emphasis on seasonal dynamics, together with the balance between primary and secondary infection, leads to SIX or SIR-X models for botanical epidemics in which X reflects the amount of 'free living' or simply surviving inoculum (figure 2). Detailed accounts of model structures for viral and fungal pathogens are given by Madden *et al.* (2000) and Gilligan (2002), respectively.

Just like animal diseases, many plant pathogens have a latent period between infection and sporulation and an incubation period between infection and symptom expression. Often these are short compared with the infectious period and can be ignored (Anderson & May 1991). The incubation period is

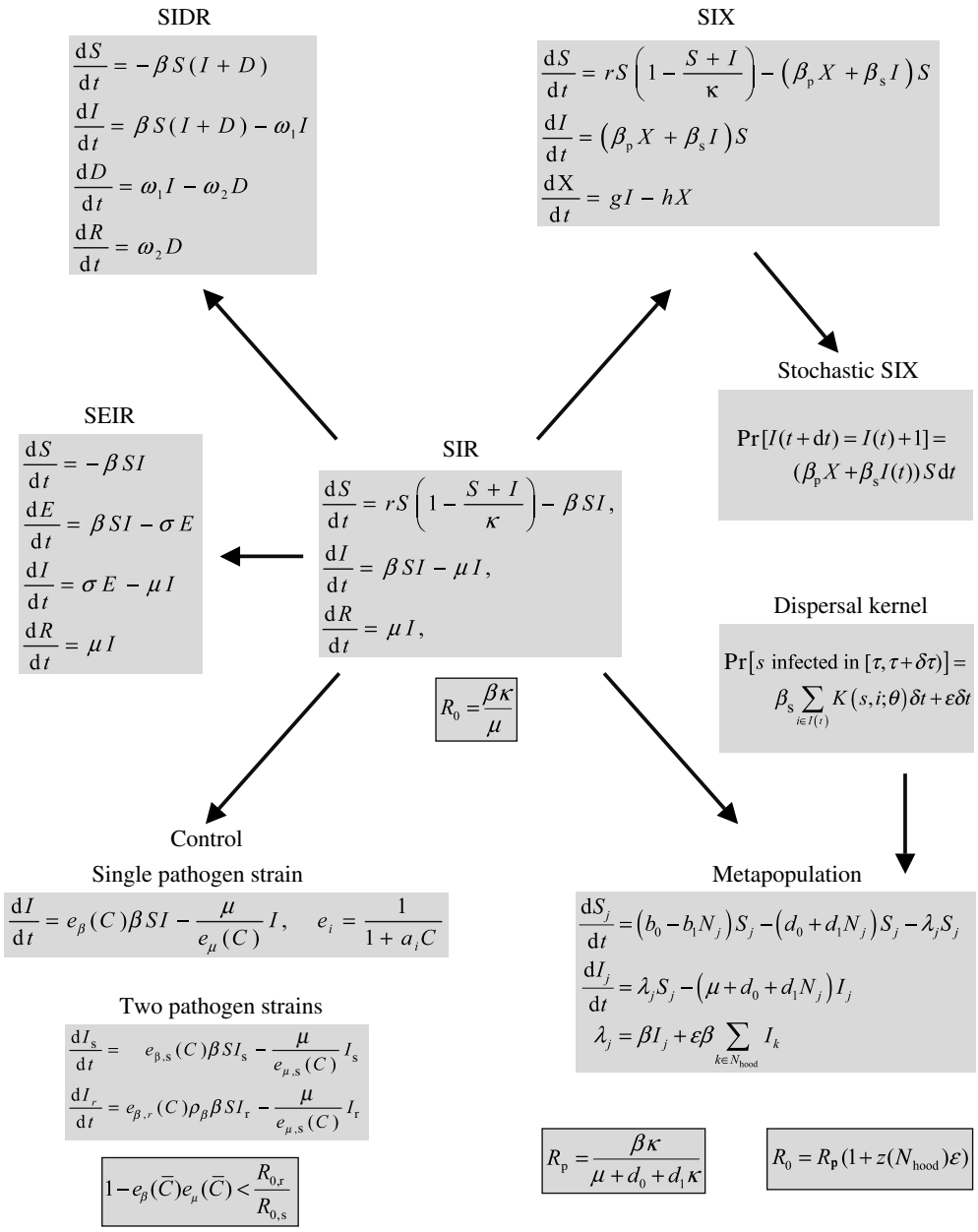

Figure 2. Some common epidemiological models. The principal state variables are: S (susceptible), E (exposed, i.e. latently infected), I (infected and infectious), D (detected, i.e. symptomatic and infectious), R (recovered or removed) hosts; X free-living inoculum. The following models are illustrated. SIR model with secondary infection, infectious period and net birth of susceptibles together with criterion for invasion (R_0). SIDR model with secondary infection, cryptic (ω_1^{-1}) and symptomatic (ω_2^{-1}) infectious periods with fixed host population size (Dybiec *et al.* 2004). SIX model with primary β_p and secondary β_s infection, net birth of susceptibles and decay of inoculum. Demographic stochastic version of SI model (Gibson *et al.* 1999). SEIR model with secondary infection, latent (σ^{-1}) and infectious (μ^{-1}) periods for fixed host population size. Dispersal kernel (with parameters, θ) for probability that susceptible (s) is infected by secondary infection from all infected hosts (i) within a neighbourhood N_{hood} and by a constant source of primary infection (ε) (Keeling *et al.* 2004). Metapopulation with transmission between subpopulations in a neighbourhood of interaction for a given strength of coupling (ε) in addition to transmission within subpopulations: model also shows separate density-dependent birth and death processes for susceptibles and criterion for invasion within a patch or subpopulation (R_p) and entire metapopulation (R_0) (Park *et al.* 2001). Effect of control agent on transmission rate and infectious period for a single pathogen strain and for two pathogen strains typified by a fungicide-sensitive (I_s) and a fungicide-resistant (I_r) strain with fitness costs ρ_β, ρ_μ, in which the efficiency is a function of fungicide concentration (C). A criterion for invasion of the resistant strain is given that links the ratio of reproductive numbers and the efficiency of control, for constant fungicide treatment (Gubbins & Gilligan 1999; Hall *et al.* 2004). Note that all of the deterministic models can be readily adapted to stochastic treatments: further details are given in the cited literature and a general mathematical treatment in Gilligan (2002).

important only when it is longer than the latent period, allowing cryptic infection to occur (figure 2). This happens with many virus diseases. The phenomenon of cryptic infection becomes important for almost all pathogens when the epidemiological unit of interest switches to large units such as trees or to entire fields. In each case, significant transmission of infection can occur between trees or fields before symptoms are detected. The delay is of immense practical importance when, as is usual, symptom expression triggers a

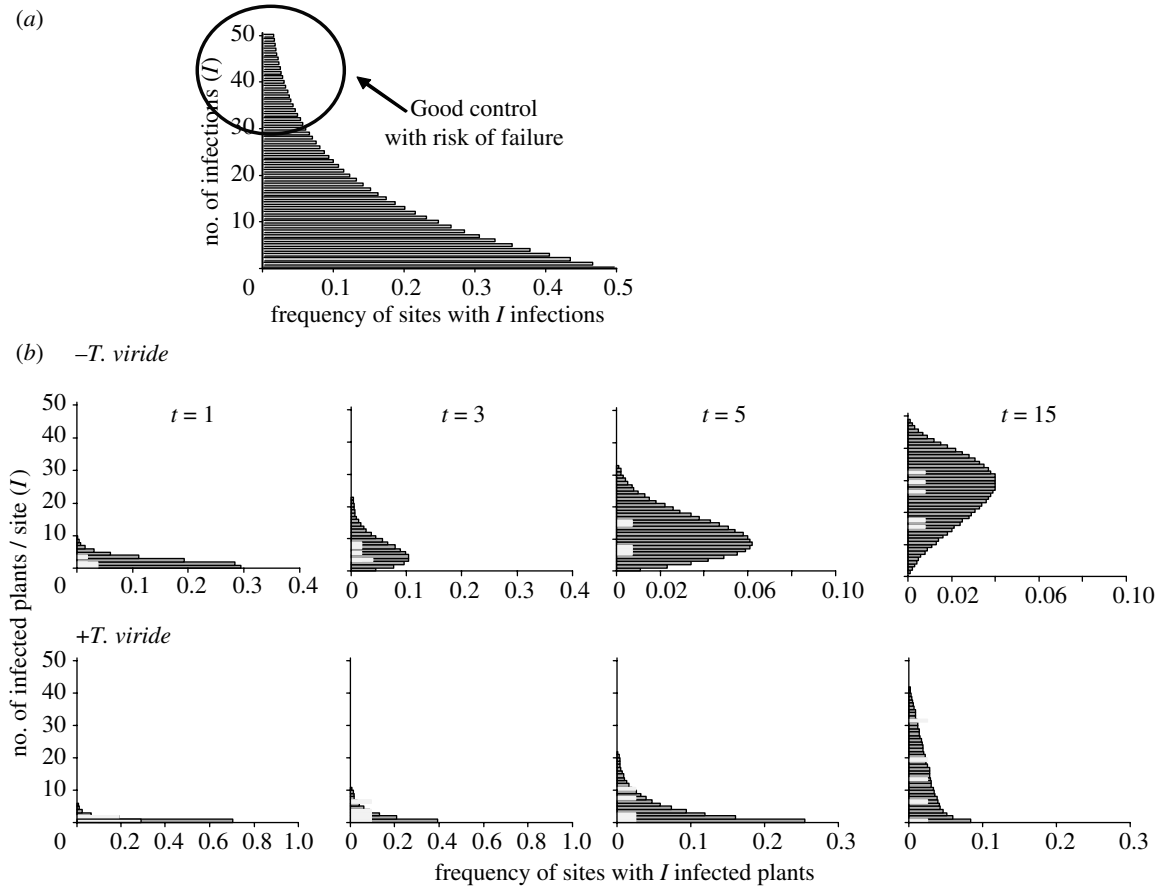

Figure 3. Use of stochastic models to analyse the dynamics and control of epidemics. (*a*) Probability distributions for final levels of disease at different sites showing skewness towards the origin for a good control agent but with a risk of some failures. (*b*) Evolution over time of the probability distribution for epidemics of damping-off disease caused by *R. solani* in the presence and absence of a biological control agent, *T. viride*. The pale bars represent data from a replicated experiment, the darker bars are model predictions for a large number of trials after fitting to the experimental data. Application of the control agent does reduce disease but there is a significant risk of failure at some sites. Further details are given in Gibson *et al.* (1999).

control response. This may be as diverse as the implementation of removal policies for trees infected with notifiable diseases such as citrus canker (Gottwald *et al.* 2001), or the implementation of a regional strategy for disease control, as in the recent attempts to control rhizomania disease of sugar beet in UK (Stacey *et al.* 2004). In each case, significant spread of disease occurred before control was implemented. Cryptic infection also means that control must be targeted at symptomless as well as infected sites if the epidemic is to be brought under control.

(i) *The role of variability*

Variability is an integral part of epidemics. It is manifest at a range of spatial and temporal scales. The timing, intensity and expansion of epidemics differ from one season to another: there are 'good' and 'bad' disease years for some pathogens, while other pathogens generate epidemics in most years. Even within the same season, the rates of spread of disease within and between adjacent fields sown to identical host varieties differ. Ideally therefore we would like to be able to predict not only the average trajectory of disease progress but also the variability. This centres on the estimation of the probability distribution for the probable occurrence of disease over time, and possibly also over space, in a population of susceptible sites. Individual sites can comprise entire farms, fields, orchards or glasshouses. By mapping the effects of alternative control strategies onto the probability distribution for disease progress, it is possible to predict not only the effect of treatment on the average amount of disease but also the risk of severe failure and in what proportion of fields or farms that failure might occur. The general approach is illustrated in figure 3*a* along with an example (figure 3*b*) for a model experimental system involving biological control of damping-off disease on radish by the hyperparasite *Trichoderma viride* (Gibson *et al.* 1999; Gilligan 2002).

There are two broad types of variability (Nisbet & Gurney 1982). Demographic stochasticity relates to differences among individuals. For epidemics, it simply reflects the probabilistic nature of transmission of infection between an infected and a susceptible host under identical environmental conditions. This leads to a series of stochastic events giving rise to different trajectories for different epidemics, even though the transmission and other parameters remain the same throughout the course of the epidemic. It is equivalent to saying that if epidemics were initiated in identical fields under the same initial conditions and exposed to identical environmental conditions, the resulting epidemics occurring in each field could still be markedly different. How different depends upon the inherent demographic stochasticity of the system. This is clearly difficult to demonstrate in the field, although extensive

data collection for the evolution of epidemics such as citrus canker in Florida (Gottwald *et al.* 2002*b*) and citrus tristeza disease (Gottwald *et al.* 1996), in which a complete census of the infection status of trees in replicate sites, comes close to this.

Analysis of demographic stochasticity allows us to identify the underlying variability of an epidemic, the so-called dynamical landscape (Gilligan 2002). Environmental stochasticity is superimposed upon this by changing model parameters in time and space. Historically, most attention has been given in botanical epidemiology to environmental stochasticity due to the obvious sensitivity of plants and micro-organisms to temperature, relative humidity and other environmental driving variables. Here the focus has been more on treating parameters as smoothed deterministic functions of environmental variables. Hence, the rate of transmission changes, for example with average temperature throughout the season (Webb *et al.* 2000). While this allows for seasonal forcing, it does not show how fluctuations in environmental variables affect the variability among replicate epidemics in a way analogous to the data in figure 3. Yet, owing to the inherent nonlinearity of epidemics, small differences in parameters, may become amplified or, conversely, large differences may be dampened. Some analytical work on this form of dynamically generated variability has been done for the *R. solani*–radish systems by Kleczkowski *et al.* (1996). Large numbers of experiments on this system have subsequently shown that variability among epidemics, whether driven by demographic or environmental variability, is as much a signature of the epidemics as is the intrinsic rate of increase. There is continual debate about how to quantify, distinguish, analyse and model the components of variability (Nisbet & Gurney 1982; Engen *et al.* 1998; Coulson *et al.* 2004). Future work in devising sustainable methods of control will continue to address these issues. The problems for data collection in the field are accentuated by sampling errors since complete census is seldom possible, though the prospects for remote sensing may improve this. Nevertheless, it will be increasingly important to quantify the variability within and between epidemics. This means that, wherever possible, we should exploit the availability of sampling and replicate data that so often in the past have been aggregated to produce averages that hide the natural variability.

(ii) *Spatial dynamics and mechanisms of spread*

Pathogens are dispersed through the landscape by abiotic agents and by invertebrate and other vectors. Dispersal also occurs by human intervention through movement of machinery and produce and by importation of seed. These features are increasing in importance in modern agriculture as farms become larger, with single ownership of multiple farms, shared machinery and cultivation by contractors operating over large regions. Disease spread occurs through an agricultural landscape that reflects these changes in commercial and agricultural pressures. This generates an epidemiological system with two or more scales of dispersal, a local scale, driven largely by abiotic and vector biology, and a global scale, driven by commercial arrangements. Depending upon the type of pathogen, the local scale operates at the within-field and between adjacent fields scales and the global scale operates at longer distances.

There are three ways in which to view this duality of dispersal scales. Long-distance movement may be seen as sources of primary infection, with local spread reflecting secondary infection. Dispersal though the heterogeneous landscape can be viewed as a network process, with nearest neighbour movement between adjacent fields and occasional, long-distance movements giving rise to small-world connections (Strogatz 2001). Finally, for some diseases where most dispersal occurs within fields (or farms) and movement between fields (or farms) is less common, the system can be regarded as a metapopulation in which fields (or farms) comprise more or less self-contained subpopulations. Strategies for the deployment of durable and sustainable control need to address these issues of how dispersal scales with the unit of interest and how to prevent invasion and persistence of pathogens in the landscape.

The conventional question concerning dispersal kernels is, how far can a disease spread? By this is usually meant, what is the furthest distance over which transmission of inoculum can give rise to infection and disease? This simple question, however, is confounded by very low probabilities of very long-distance dispersal. More enlightened questions are, how far is infection likely to spread? and how might the deployment of control strategies affect the dynamics of spread and the likelihood of disease invasion? The tail of the distribution for dispersal kernels is certainly important. Much thought and experimental ingenuity has been given to the distinction between exponential and thick-tailed distributions (Shaw 1994, 1995, 1996; Sackett & Mundt 2005*a*). Exponential kernels result in expanding waves about an initial focus, tending to a constant velocity of expansion after an initial period of build-up. Thick-tailed distributions give rise to distinct daughter foci and an entirely different spatial dynamic for epidemic spread (Shaw 1995; Sackett & Mundt 2005*a*) with dispersive spread in which the velocity of spread increases with time. Owing to the complications of controlling experimental conditions, most experiments to identify dispersal gradients have been confined to single foci spreading through single homogeneous field plots (Sackett & Mundt 2005*b*). Scaling-up to predict what happens at the larger scales (Frantzen & van den Bosch 2000) is still in its infancy for spread through heterogeneous landscapes. It is a major problem for emerging epidemics of new, rare or mutated forms of pathogens. Here we need to rely upon analogous results for related pathogens or to extract estimates for dispersal and other parameters from the emerging epidemic.

The challenge of estimating parameters for epidemics with multiple sites of initial infection has, with some notable exceptions, received little attention. Gibson & Austin (1996) and Gibson (1997) have made progress using likelihood-based and Markov chain Monte Carlo methods (MCMC) for citrus tristeza disease for which there was a complete census of infected and susceptible trees in citrus groves. The method involves taking successive snapshots of disease

and estimating the parameters of a dispersal kernel by inferring the temporal sequence in which individual trees became infected. Gibson & Austin (1996) and Gibson (1997) used a simple model for dispersal in which they compared an exponential with a power-law (thick-tailed) kernel with and without allowance for the entry of external infections from outside the groves. They showed that there was more evidence for the power-law model. By simulating the control of epidemics by removal of trees around infected trees, they showed that the critical removal distance of 14 m, previously advocated by Marcus *et al.* (1984), could lead to a serious risk of failure of eradication. Collection of census data is expensive and the number of temporal snapshots will often be limited. Exceptionally, progress is possible even when there is only one snapshot. By making certain assumptions about the status of an epidemic, Keeling *et al.* (2004) successfully inferred both spatial and temporal dynamics from single snapshots of disease, including the citrus tristeza example. These analyses showed preferential evidence for a power-law dispersal in common with the MCMC analyses of Gibson (1997) and with a similar estimate for the dispersal parameter. Importantly, however, this proved possible using just the first of two annual snapshots. Clearly, more work needs to be devoted not only to the methods of statistical analysis but also to efficient collection of data for parameter estimation of emerging epidemics. Prior knowledge helps, but experience from animal epidemiology militates for caution: it is striking how different were the dispersal mechanisms for the widespread 2001 foot and mouth epidemic in the UK from the previous major, but much more localized, epidemic in 1967 (Keeling *et al.* 2001). The difference partly reflects changes in pathogen strain but more significantly changes in agricultural practice, with much more frequent movement of animals over long distances occurring in 2001. Comparable large changes are evident in crop husbandry, with major changes in sowing dates, shorter intercrop periods, as well as changes in fertilizer and pesticide applications and the genotypes and frequency of crops being sown.

(iii) *Long-distance continental spread*

Historically, much attention has been given to the characterization of wave speeds for focal expansion through susceptible fields around isolated sites of initial infection (van den Bosch *et al.* 1988*a–c*, 1999). This still has an important part to play, especially in the continental-scale spread of disease in which it is reasonable to assume that there is enough crop to trap incoming aerially dispersed spores, without recourse to detailed analysis of the topological arrangement of susceptible crops on the ground.

Aylor (2003) constructed a stochastic dispersal model to estimate the rate and extent of seasonal incursions of two aerially dispersed diseases, stem rust of wheat and tobacco blue mould, from southern into northern areas of the US. The model treats the availability of the susceptible crop as a continuum in space, but one that changes over time, sandwiched in a seasonal 'green wave'. The leading northerly edge is determined by crop sowing date. The receding southerly edge is determined by an advancing wave of crop maturity.

Both wheat stem rust and tobacco blue mould appear to spread northward on average at about the same rate as the seasonal advance of the green wave of available susceptible host tissue. Aylor (2003) concludes that the concordance of the disease wave with the green wave underscores two important points. First, it suggests that disease spread over long distances may be limited more often by failure of the pathogen to establish than by the ability to be dispersed over long distances. The green wave also reduces the stochastic variability and speed of disease spread by presenting a barrier to potential long-distance, low-probability dispersal events. Second, it helps to focus attention on alternative pathways for disease spread and on possible unappreciated niches for overseasoning, both of which can have important implications for disease control strategies.

(c) *Mapping control strategies onto epidemiological variables and parameters*

Not surprisingly, the effects of different control methods may be mapped onto each of the epidemiological parameters (figure 2). Thus, genetical, chemical or biological methods may affect one or more of transmission rates, infectious periods, detection rates as well as latent periods. Control can also affect the dispersal parameters by interfering with vectors or by preventing long-distance movement. Removal of infecteds and susceptibles also allows control of epidemics by reducing the availability of infectious tissue and susceptible tissue. At the larger (field) scale, this is manifested by the application of protectant or eradicant chemicals, by changing cropping density or by introduction of resistant or partially resistant varieties. In the extreme, the target of most genetical and chemical control is to achieve immunity, so shifting plants from the susceptible to an unavailable class.

Once a control strategy can be interpreted within a model structure, it is possible to compare efficiencies of control for different strategies and intensities (table 1). In principle, this allows simple calculations about the ability of pathogen strains to invade by computation and analysis of invasion criteria such as R_0, a measure of the number of new infections per infected unit. It also allows computation of invasion and persistence times of resident pathogen strains that are sensitive to the control method, as well as fungicide-resistant or virulent strains. Here the temporal and spatial deployment of the control strategy in the landscape is important in determining whether virulent and avirulent strains coexist in the pathogen population, or if one is competitively excluded by the other. The consequences of this affect the durability of resistance (Vera Cruz *et al.* 2000; Parlevliet 2002). More importantly, it also begs the question as to how genetical control can be deployed in the population so as to promote the durability of resistance. Similar questions apply to the deployment of chemical control agents and to the fates of fungicide-sensitive and fungicide-resistant pathogen strains.

3. CROP MOSAICS, HETEROGENEITY AND TOPOLOGY OF CROPS IN THE LANDSCAPE

Much thought has been given to the construction and deployment of crop multilines and mixtures to slow the spread of disease within fields (Mundt 2002). Following early work by Browning & Frey (1969) on multilines and Wolfe (1985) on mixtures, interest in the strategies waned, partly due to resistance from processors. Recently, however, interest has been revived in China (Zhu *et al.* 2000) and Western Europe (Finckh *et al.* 2000). Slowing the increase of disease within fields may have a knock-on effect in slowing the spread of disease between fields and, hence, restricting invasion through the landscape. By thinking of fields as subpopulations in a structured metapopulation (Gyllenberg *et al.* 1997), the effect of mixtures in the landscape can conveniently be thought of as delaying the transit time between fields. We define the transit time as the time from when the first individual becomes infected in one field and starts an epidemic in another field. Most theoretical work on transit times in metapopulations has focused on persistence. Thus, Swinton (1998) showed that above a certain critical subpopulation size, the expected extinction time for a metapopulation scales with the number and size of subpopulations. There is a phase transition (i.e. a switch in behaviour from short to long extinction times) around the critical subpopulation size, N_C. Below N_C, the time to extinction is very short because the amount of susceptible hosts is not sufficient to maintain the epidemic before it spreads to the next subpopulation. As the population of susceptibles increases above N_C, there is a sudden transition to long extinction times. Increasing the numbers of subpopulations in the metapopulation delays extinction but does not affect the critical value of N_C at which the phase transition occurs (Swinton 1998). This has been demonstrated for animal disease (Swinton *et al.* 1998) and proposed for botanical epidemics (Gilligan 2002), with additional theoretical work on invasion as well as persistence (Park *et al.* 2001, 2003). It is now ready to be tested in the field.

How far and how fast a pathogen spreads through a landscape and, indeed, whether or not it persists and for how long, depends upon the crop mosaic within the landscape. Whether or not invasion occurs depends upon the relative magnitude of the modal dispersal distances and the scale of heterogeneity in the landscape (figure 4). Considering disease spread in this way is still at an early stage. A convenient starting point is to assume that disease spreads on a lattice and then to introduce gaps and so to advance to spread through a realistic population of fields. For a given pathogen, each field of a susceptible crop is classified as susceptible (i.e. healthy), infected or, if appropriate, recovered. Non-host crops are unavailable to the pathogen and are treated as gaps. The application of a protectant fungicide temporarily renders a susceptible field unavailable for infection (figure 4). Whether or not a pathogen invades now depends upon the spatial and temporal dynamics of the crop mosaic. A simple analysis based upon ideas from percolation, derived in statistical physics (Stauffer & Aharony 1994), illustrates an important relationship between dispersal kernels and invasion. When spread occurs between adjacent fields, i.e. by nearest-neighbour spread, the dispersal kernel then describes the probability distribution for transmission of infection between an infected field and its susceptible neighbour (figure 4). It follows from percolation theory that there is a critical probability above which disease spreads and below which it dies out. By increasing the distance between susceptible fields, it is possible to bring the percolation probability for a given lattice below the threshold and so prevent invasion (figure 4). These results are stochastic: it follows that there will be some spread when the percolation probability is below the threshold and occasionally invasion may occur but, on average, we would expect the strategy to work, albeit under these idealized conditions. Suppose now that the density of susceptible crops per unit area of land exceeds the threshold and invasion is expected. Introducing gaps into the lattice by the application of localized chemical control could switch an invasive into a non-invasive mosaic (figure 4). The fineness of the control and the precision of the phase transition is sufficiently striking (figure 4*d*) to lead us to question whether or not it is necessary to treat all fields in the landscape in order to prevent invasion. The answers from these theoretical investigations would suggest not. The ideas have yet to be tested in the field, however; something that presents significant challenges in large-scale testing of new approaches towards sustainable control. Meanwhile in order to gain more insight into these approaches and, in particular, to understand variability between replicate epidemics, we have tested some of the ideas in a series of microcosm experiments involving *R. solani* spreading between nutrient sites at different densities with and without gaps (Bailey *et al.* 2000; Otten *et al.* 2004). The results support the inferences proposed above.

As an epidemic spreads through a heterogeneous landscape, the dynamical contact structure, which measures the exposure of susceptible to infected sites, also changes. This too can slow down or speed up an epidemic and is a property of the topology of the system. So far, we have discussed susceptibles and gaps. What if there are differential susceptibilities for susceptible crops in a mosaic? This could reflect incomplete chemical control in treated fields or partial genetical resistance. By extending the model experimental system to include spread through mixed populations of radish and mustard in replicated microcosms, we simulated experimentally the spread through a heterogeneous landscape. Not surprisingly, the inclusion of a less susceptible host can slow the rate of spread of an epidemic compared with spread though a homogeneous mosaic (Otten *et al.* 2005). However, the rate of spread changes nonlinearly with the relative densities. If this holds for the large-scale transmission between fields, it follows that the introduction of a critical proportion of a less susceptible crop could slow the spread of infection through the landscape. Moreover, the differential rates reflect not only differences in susceptibility but also differences in infectivity. This means that for two types of host, four types of transmission rates occur, depending upon which host is the donor (infected) or recipient (susceptible). Otten *et al.* (2005) showed how to calculate transmission rates from empirical data which, in turn, can be used to

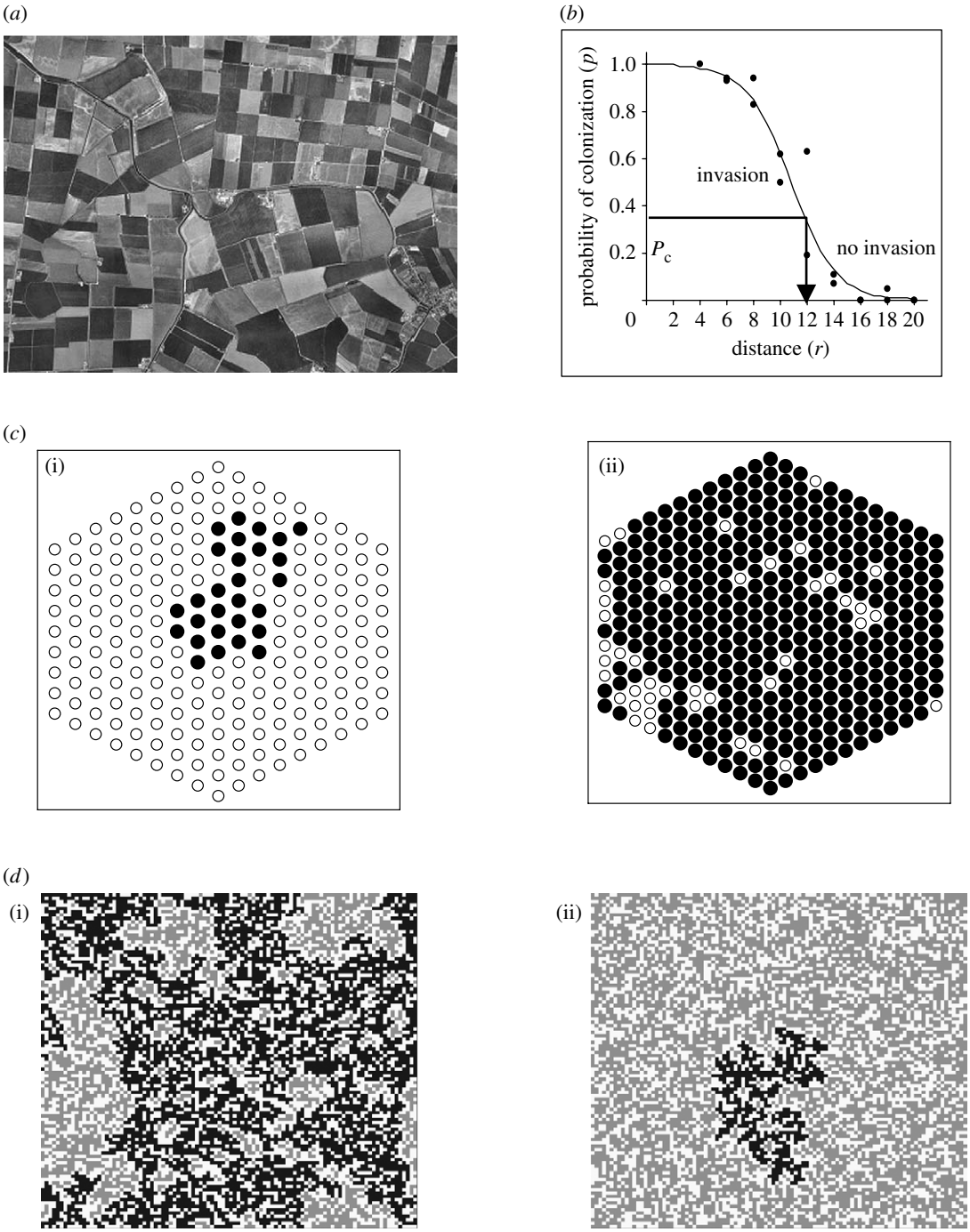

Figure 4. Spread through a landscape with nearest neighbour transmission between infected and susceptible sites. (*a*) Aerial photograph showing a typical example of a UK crop mosaic. (*b*) Probability distribution for transmission of infection to susceptible sites at different distances from the infected source showing the percolation threshold (P_c) for a triangular lattice. (*c*) Effects of a small change in the distance between susceptible (open circle) sites (i) above and (ii) below the threshold distance on the invasion of an epidemic measured by the spread of infected (filled circle) sites. (*d*) Effects of introducing gaps to simulate chemical control in the landscape upon a percolating system, showing the fineness of the control about a phase transition; white squares indicate control, light grey indicate susceptible and dark infected. (*b*,*c*) Derived from experimental microcosms (Bailey *et al.* 2000; Otten *et al.* 2004). (*d*) Derived from a computer simulation by kind permission of Dr J. Ludlam.

predict the effects of changes in the topology and composition of the mixture. By treating fields as units this approach can, in principle, be extended to gain insight into the effects of different levels and densities of partial control at the landscape scale.

(a) *Matching the scale of control with the epidemic scale*

The foregoing discussion suggests that control could be allocated to a proportion of fields in a landscape in order to prevent invasion. For some emerging diseases, in which initial foci are identifiable, local control may be implemented. This may involve removal of the infected site along with protection of surrounding susceptible sites. This is a classical example of ring vaccination that has been widely debated in animal (Keeling *et al.* 2003) and human (Ferguson *et al.* 2003) epidemiology. Obviously, by getting ahead of the infection, local 'vaccination' can bring the epidemic under control and prevent further spread. Problems

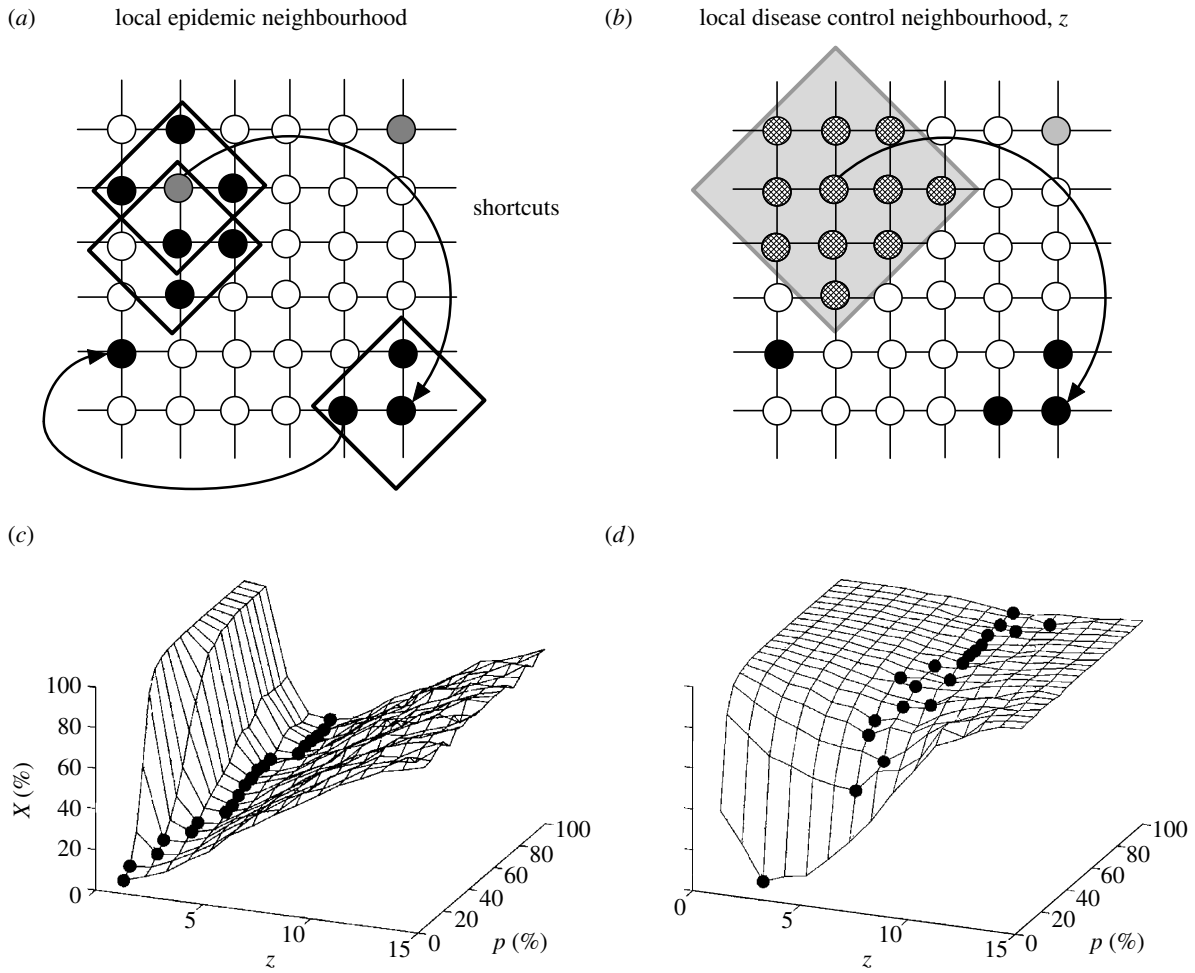

Figure 5. Matching the scale of control with the epidemic scale when there is cryptic infection. (*a*) Local epidemic neighbourhood. There are two scales of spread: local spread in which a region of cryptically infected sites surround a symptomatic site. Key: susceptible (white), cryptic (black), symptomatic (grey). (*b*) Example of a neighbourhood of control surrounding a symptomatic site; shaded sites have been treated. (*c*) Simulations show that there is a critical size for control neighbourhoods (z) that minimizes the cost of an epidemic (X, calculated as a simple weighted linear sum of treatment and infection costs) for spread on a two-dimensional lattice with nearest neighbour transmission and different probabilities, p (expressed as a percentage), for transmission between an infected and a susceptible site. (*d*) Equivalent results for a scale-free network. Further details are given in Dybiec *et al.* (2004).

arise, however, when there is cryptic spread of infection so that infectious fields export inoculum to adjacent fields before the disease is detected. This requires judgement of the size of the zone of cryptically infested fields around a symptomatic field. It is further complicated when local spread is augmented by global, long-distance movements. Taking a stochastic susceptible–asymptomatically infected–detectably infected–removed (SIDR) model (figure 2) on a two-dimensional lattice with long-distance movements, Dybiec *et al.* (2004, 2005) examined a series of control strategies of different sizes centred around a symptomatic site (figure 5*a*,*b*). They showed that for small to moderately severe incidences of infection with a small number of non-local links, it is possible to bring the spread of disease under control. The efficiency of a local control strategy is very sensitive to the choice of the radius. Importantly, it was also possible to show that there is a minimum radius associated with such a control neighbourhood leading to the lowest severity of the epidemic when costs of treatment and disease are taken into account (figure 5*c*). Below the optimal radius, the local strategy is unsuccessful; the disease spreads throughout the system, necessitating treatment of the whole population. Clearly, at the other extreme, a strategy involving a neighbourhood that is too large controls the disease but is wasteful of resources. Relatively little is yet known about the topology of networks for the transmission of crop disease, although this is an area of intensive theoretical investigation in animal and human epidemiology (Newman 2002; Keeling 2005). It is possible that transmission of some pathogens may be approximated by scale-free networks, in which there is marked variability in numbers of contacts, with the rich nodes equating to nurseries and wholesalers that inadvertently disseminate infected plants. This makes the local deployment of control more difficult, especially when there is cryptic infection. Dybiec *et al.* (2004, 2005) showed that it was not possible to stop an epidemic on scale-free networks by preventive actions, unless a very large proportion of the population is treated (figure 5).

A practical instance of the problem of controlling a disease in which there is cryptic infection may be seen

from experience with the control of rhizomania, a soil-borne disease of sugar beet in the UK (Stacey *et al.* 2004). The disease is transmitted by a plasmodiophoromycete vector, with spread between fields occurring principally on agricultural machinery. Prior to the availability of partially resistant varieties, control was effected by a mandatory containment policy whereby sugar beet could not be grown in fields that had shown symptoms of rhizomania. But by the time symptoms show, an infested field has already been exporting inoculum to other fields over several seasons (Stacey *et al.* 2004). Accordingly the containment policy was abandoned. Successful control of disease was shown to demand a farm scale, rather than a field-scale, response in which the scale of treatment more closely matches the scale of epidemic advance (Gilligan *et al.* 2007).

(b) *Durability of control*

The risk of failure, particularly of genetical and chemical control but also of biological control, within a few seasons is a major concern for sustainable control of endemic diseases in agriculture, not least due to the development and registration costs that can approach £500 M. For new diseases or pathogen strains, the concern is whether or not often untried methods can successfully contain the emerging epidemic. Although much experimental work has focused on the molecular and biochemical aspects of the breakdown of host resistance or of fungicide sensitivity in the pathogen, relatively little is known about the processes that underlie the durability of control at the population scale. Some resistance genes are known to have remained effective for a long time: resistance to cabbage yellows caused by *Fusarium oxysporum* f. sp. *conglutinans* has lasted for more than 90 years (Vera Cruz *et al.* 2000); resistance to leaf rust, *Puccinia triticina*, conferred by *Lr34* has lasted for 30 years (Kolmer 1996). Others are remarkably ephemeral, for example *Yr17* for the control of yellow rust on wheat, was rapidly overcome in two to three seasons by virulent isolates of *Puccinia striiformis* f. sp. *tritici* in the UK followed by Denmark, France and Germany (Bayles *et al.* 2000). The durability of various rice blast resistance genes is often less than 3 years (Kiyosawa 1982; Zeigler *et al.* 1994). Broad spectrum fungicides remained effective for long periods, but for those with single-site action the durability is often short. Following the introduction of strobilurins in 1996 to control a range of cereal pathogens, high frequencies of resistance in *Blumeria graminis* had been detected within 4 years over large areas of Germany, France and the UK (Chin *et al.* 2001). Clearly, the durability of control depends upon the selection pressure imposed upon the pathogen population and the fitness of virulent or fungicide-resistant strains relative to resident, avirulent and fungicide-sensitive strains. McDonald & Linde (2002) recently reviewed the durability of resistance for a large number of fungal and oomycete pathogens and proposed that the risk of failure of genetical control depended not on the nature of the resistance genes but on the evolutionary potential of the pathogen. They identified three factors, population size, rate of gene and genome flow (migration) and the reproduction or mating system (i.e. asexual or sexual), from which to produce a risk factor for loss of resistance. García-Arenal & McDonald (2003) subsequently extended the analysis to viral diseases, noting that resistance to viruses was generally more durable than resistance to fungal and fungal-like pathogens.

Traditionally, analyses of virulence dynamics and fungicide dynamics tended to focus only on the relative frequencies of genotypes in the pathogen population. More insight into the likelihood of invasion and persistence of novel strains is gained by combining population genetics and epidemiological dynamics (Gubbins & Gilligan 1999; van den Bosch & Gilligan 2003; Gudelj *et al.* 2004; Hall *et al.* 2004; Parnell *et al.* 2005). Combining the approaches takes account of the influence of a dynamically changing supply of susceptible tissue on the outcome of competition between pathogen strains (Gubbins & Gilligan 1999). It allows for the influences of spatial structuring of the host population (Parnell *et al.* 2005, 2006) and for local stochastic elimination of strains (Gubbins & Gilligan 1999) on the invasion and persistence of novel strains. It also allows greater insight into the definition of durable control. Johnson (1979, 1981, 1984) originally proposed that durability of a resistance gene should be empirically assessed in terms of area, time-span, degree of exposure to the target pathogen. Subsequent analyses have sought to define and quantify the mechanistic bases for durable resistance. A population genetics approach leads naturally to a convention for measurement of the durability of resistance as the time-span from introduction of the resistant cultivar to the time when the frequency of the virulence gene reaches a preset threshold, above which the resistance is considered to have broken down. This definition fails to take account of the area receiving the treatment within the landscape (Johnson 1984; van den Bosch & Gilligan 2003). Consider a resistant crop. The conventional approach to preserve the durability of newly released resistance genes is to introduce resistant cultivars at low cropping ratios (Pink & Puddephat 1999). But analysis of durability in this way fails to take account of the yield benefit from sowing the resistant crop over a greater area. The conventional definition for durability also assumes that breakdown is inevitable and that the virulence matching the resistant genotype is already present in the population, which, of course, may not be the case. Durability is enhanced, if it is not already present, by the delay for the virulent genotype to enter the system, through mutation or immigration, and to establish a population. These considerations lead to two new measures of durability (van den Bosch & Gilligan 2003). One is the expected time until invasion of the virulent genotype, by mutation or immigration, and expected establishment of a population. The other is the additional yield measured by the expected number of uninfected host growth days. Each was compared with the conventional measure for a range of cropping ratios for a newly released resistant variety (figure 6). The results challenge the universality of the buffering effect of low cropping ratios by showing that the expected time to invasion can be delayed by *high* as well as low cropping ratios. Surprisingly, too, yield gain through cultivation of the resistant variety is only slightly influenced by

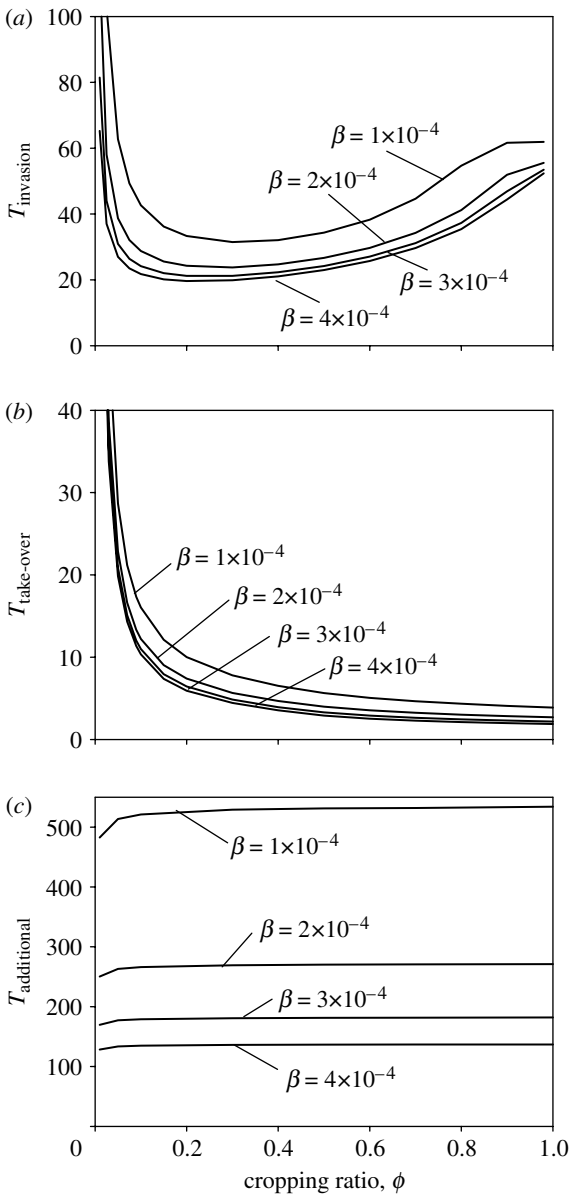

Figure 6. Measures for durability of resistance. Effects of cropping ratio (ϕ) of a newly released resistant variety and different transmission rates (β) for infection on: (*a*) the expected time until the virulent pathogen invades ($T_{invasion}$), (*b*) the time until the virulent genotype comprises a critical proportion (arbitrarily set to 90%) of the pathogen population ($T_{take\text{-}over}$), (*c*) the total number of additional uninfected crop growth days due to the release and deployment of the resistant variety ($T_{additional}$). Further details are given in van den Bosch & Gilligan (2003).

cropping ratio (figure 6*c*). There are cases in which resistant cultivars have been widely grown without breakdown of resistance: Steffenson (1992), for example, describes how the gene Rpg1 successfully conferred resistance to *Puccinia graminis* f. sp. *tritici* on barley for more than 40 years in the northern great plains of the US and Canada. Arguably, however, intentional widescale routine testing of the advantages of high cropping ratios for the release of resistant cultivars may be premature. One possible alternative would be to use a high cropping ratio in a restricted part of the crop's area and none in the rest of the area in a manner similar to refugia for pest resistance (Tabashnik *et al.* 2005). I anticipate that this will be an area of intense research, not only for the deployment of resistant varieties but also for the release and use of new forms of chemical control.

(c) *Invasion and persistence of virulent and fungicide-'resistant' strains*

Epidemiological models for the invasion and persistence of chemical control are similar to those for genetical control. Until quite recently, most models ignored stochasticity and density dependence imposed by the dynamical changes in the availability of untreated tissue. Moreover, by invoking exponential growth of the pathogen, invasion of fungicide-resistant forms is inevitable, and attention focuses not on whether or not a resistant strain can invade but the time to reach a critical level. This is unrealistic. By allowing for competition for susceptible (untreated) sites, it is possible to show that there is a threshold below which resistance cannot develop within the host population (Gubbins & Gilligan 1999). The threshold depends upon the relative fitness of the resistant and sensitive strains and the effectiveness of control. The latter may influence one or more of the following: reduction in the transmission of infection, the duration of infectiousness and the conversion of host to infectious pathogen tissue (Hall *et al.* 2007). The relative fitness of the resistant strain is given by the ratio R_{0r}/R_{0s}, where R_{0s} and R_{0r} are the basic reproductive numbers for the sensitive and resistant strains, respectively. Even crude estimates for the efficiency of control and the basic reproductive numbers can provide a simple rule of thumb for whether or not invasion may be expected.

Fungicides differ from many forms of genetical control in being subject to decay over time, requiring repeated application. By including parameters for the amount of fungicide applied, longevity and application frequency of the chemical, it is possible to predict the outcome of invasion of the resistant strain, even when there is a time-varying selection pressure on the pathogen population (Gubbins & Gilligan 1999; Hall *et al.* 2004). Notably, these models share a common generic structure with antiviral drug resistance and antibiotic resistance (Hall *et al.* 2004).

The durability of genetical and chemical control depends not only on the ability of a virulent or fungicide-sensitive strain to invade an existing pathogen population but also whether the wild type is completely replaced or can coexist. Complete exclusion of the resident (controllable) pathogen strain by the invading strain means that the gene or fungicide cannot be used again as a sole method of control. Empirical evidence shows both scenarios with coexistence (Chin *et al.* 2001; Bierman *et al.* 2002) and competitive exclusion (Baroffio *et al.* 2003). To develop effective resistance management strategies, it is imperative to understand the processes that influence which of these outcomes is likely to occur. Initially, it was thought that models could be of little assistance because coexistence was predicted to occur only under exceptional circumstances with restrictive assumptions about the magnitudes of the parameter values (Gubbins & Gilligan 1999). The obvious way to account for a spectrum from competitive exclusion to

coexistence is to allow for spatial heterogeneity in the selection pressures. This is conveniently done using a metapopulation framework. Thus, when Parnell *et al.* (2005, 2006) allowed for differential selection pressures due to incomplete coverage of plants by fungicide either within or between crops, three scenarios were possible, ranging from failure to invade, through coexistence, to competitive exclusion of the resident strain. The outcome within fields depends upon the balance between incomplete spray coverage and a cost to resistance, with healthy host density maximized when there is coexistence. Recent work by Salathé *et al.* (2005) suggests that coexistence is possible within stochastic systems without invoking costs of resistance.

At the regional scale, invasion of resistant strains is determined by a trade-off between the fraction of fields that are sprayed and the intrinsic reproductive ability R_0 of the target pathogen (Parnell *et al.* 2006). If the between-field movement of the pathogen is high (high R_0), the resistant strain dominates all treated fields but the sensitive strain dominates all untreated fields. This occurs because, in the long term, resistant strains are competitively superior in treated fields and sensitive strains are competitively superior in untreated fields. If R_0 is very high, mixing is complete and all treated fields become infested with the resistant strain and all untreated fields become infested with the sensitive strain. If, however, R_0 is low, strains cannot move between fields to the extent that allows them to capitalize on their within-field competitive advantage and may therefore be excluded. The outcome is then dependent on the fraction of fields sprayed (Parnell *et al.* 2006). Once again the analogy with refugia is apparent.

Further work on the invasion and persistence of virulent and fungicide-resistant pathogen strains will increasingly focus on the integration of genetical and epidemiological mechanisms. Foremost among these will be empirical evidence or otherwise for fitness costs (Vera Cruz *et al.* 2000; Brown 2003) as well as research on the evolution of fitness modifiers and evolutionary trade-offs among epidemiological parameters. Clearly, there is also a need to identify control strategies that balance the conflicting aims of resistance management (to reduce the risk of failure) and yield enhancement by application of genetical, chemical and other control methods to suppress disease. Some initial models that integrate crop yield have been explored by Hall *et al.* (2007). Most strategies depend upon host diversification within the landscape. We do not, however, know how introducing host diversity into the landscape affects evolutionary divergence towards specialist or generalist pathogens, or even if it might lead to a switch in pathogenicity from one host to another. This can be investigated by analysing the evolutionary trade-offs that occur over successive generations of a pathogen exposed to two or more hosts. Preliminary results show that evolutionary outcomes strongly depend on the shape of the trade-off curve between pathogen transmission on sympatric hosts (Gudelj *et al.* 2004). Using methods based upon adaptive dynamics, it has been possible to determine criteria under which evolutionary branching occurs from a monomorphic into a dimorphic population, as well as the conditions that lead to the evolution of specialist (single host range) or generalist (multiple host range) pathogen populations (Gudelj *et al.* 2004). Since some pathogen species can undergo 20–30 generations in a growing season, the consequences of this form of evolution may become apparent within decades.

4. OPTIMIZATION OF DISEASE CONTROL USING AN EPIDEMIOLOGICAL FRAMEWORK

The control of disease epidemics often requires expensive resources. These include investment costs for breeding programmes, the development, testing and registration of new chemicals or biological control agents. There are also variable costs for the application of control methods. There may be economic, environmental or ecological restrictions on the use of different methods associated with the accumulation of toxic chemicals in the environment, or the risk of failure through premature build-up of virulence to resistance genes or insensitivity to pesticides in pathogen populations that could render the control and investment ineffective. This creates two problems for the implementation of control. The first is a strategic issue about the long-term effectiveness and the corresponding risks of failure associated with different control strategies. We discuss briefly how the risks can be ameliorated by buffered implementation of novel control. The second is how to optimize the deployment of control when resources are limited or there are other restrictions on use (such as the risk of failure through over-use).

(a) *Buffered implementation of genetic and chemical control*

Following some spectacular failures, increasing attention is being given to the buffered implementation of genetical and chemical control methods through time and space. This is variously done by the cultivation of refugia of non-resistant or untreated crops, by alternating pesticides through time and space to impose different selection pressures, and by diversifying the genetic bases for control. Each demands an understanding of the 'dynamical landscape' in order to match the scale of control with the scale of the epidemic. This is most well advanced for a pest problem involving the deployment of *Bt*-resistance for insect pests on maize and cotton in the US and elsewhere, where there are mandatory requirements for refugia (Rausher 2001; Cerda & Wright 2004). By permitting multiplication and persistence of the sensitive form of the pest population on susceptible crops within refugia, the build-up of mutant pests that can feed and reproduce on the *Bt*-resistant crops is delayed. Arguably though, with this and other schemes most attention has focused on relatively local scales, yet there may be broader issues for larger scales. For example, should a new pesticide or resistant variety be released at a continental scale? Would heterogeneity at a local scale be sufficient to prevent problems of invasion of pesticide-resistant or virulent strains at a much larger scale? We do not yet know. Recent examples for the apparent widescale occurrence and spread throughout Western Europe of fungicide resistance forms in the eyespot and mildew pathogens of wheat suggests that large-scale dynamics must be considered. These pathogens differ in dispersal

mode, with eyespot predominantly spread by short-distance rainsplash whereas mildew can spread over longer distances by wind. A combination of the analyses of Aylor (2003) for continental spread with those of network (Dybiec *et al.* 2004) and landscape (Keymer *et al.* 2000) models may help to answer these questions.

(b) *Economic considerations in the optimization of disease control*

All too often, optimization of epidemiological models occurs without any formal consideration of economic or social constraints. Meanwhile, economists and social scientists frequently address problems that influence policy for the implementation and deployment of disease control strategies, but many of the underpinning models are biologically naive, lacking, in particular, insights into stochastic and spatial dynamics of disease propagation. The two need to be integrated. Two promising approaches can be adapted from economic theory. The first concerns decisions about the implementation or release of new methods for control under uncertainty. The method is based on options approaches, originally derived for financial markets (Dixit & Pindyck 1994) and has been applied by Morel *et al.* (2003) and Wesseler (2003) to the release of *Bt* resistant maize. Essentially, the problem suggests that a government or other organization obtains the right to deploy a genetically resistant crop within a given time frame. Conventional analysis would look at a simple cost–benefit analysis, so that a new variety is released immediately if the net benefits (calculated as the difference between variable benefits (e.g. increased yield and revenues) and variable costs (e.g. decreased pesticide costs)) are greater than for the conventional crop. Otherwise the variety is shelved. But this ignores uncertainty in year-to-year variation in pest damage and yield due to epidemiological and environmental factors, as well as variability in price and other variables such as input costs. Conventional cost–benefit analysis also ignores irreversible benefits and irreversible costs that may accompany the release of a new variety. Foremost among the irreversible costs is the risk of the pest overcoming resistance. Reduction in pesticide residues in groundwater or a decreased risk of pesticide resistance occurring in the pathogen population are examples of irreversible benefits. It follows that there are now three decisions: to release immediately; to release at some time in the future when there is more information to assess whether the benefits exceed the costs; or not to release at all (Morel *et al.* 2003; Wesseler 2003). The time (if at all) for release is obtained by optimization of a function that incorporates benefits and costs under uncertainty with a discount rate on the investment (Morel *et al.* 2003; Wesseler 2003). These exploratory analyses show that the critical value that must accrue for release of a transgenic crop is amplified in the presence of uncertainty. Some counter-intuitive results emerge for analysis of *Bt* maize, whereby mandatory refuge areas and tax incentives that might be expected to delay release actually promote earlier release (Wesseler 2003). Conversely, in illustrating the application of real options analysis to the release of *Bt* maize, Morel *et al.* (2003) argue that while a simple cost–benefit analysis would favour release, preliminary allowance for uncertainty did not. The analyses are based upon assumptions that breakdown of resistance is inevitable, instantaneous and ubiquitous when it occurs, and hence that mean field models capture a spatially heterogeneous system adequately. The consequences of these assumptions for the release of transgenic crops and pest resistance are discussed from an epidemiological perspective by Gilligan (2003). It will be increasingly important in devising strategies for sustainable disease control to enhance the cross-disciplinarity between economists and epidemiologists.

A further area of current interest in linking epidemiological with economic modelling arises when resources for treatment are scarce or when there are other constraints over the amount of control (usually chemical or cultural, but sometimes genetical or biological) that can be applied. Finding the optimal control strategy subject to constraint requires estimates for the cost of treatment and the cost of infection. It also requires knowledge of the effectiveness of control and the way that this affects the dynamics of disease, which, in turn affects the way that control maps onto an epidemiological model. A simple example for chemical control is given in figure 2 for an eradicant. Application of the chemical renders infected plants no longer infectious, if the scale of interest is the field. A similar model applies at the regional scale in which the application of chemical stops an infected field exporting inoculum. Finding an optimal strategy depends not only on the instantaneous cost of treatment and cost of infection but also on the way these change during the course of an epidemic. Suppose that a treatment has a long-lasting effect either from a single application or by repeated applications. Treating too early may be costly in unnecessary use of chemical. Leaving it till the epidemic is advanced may be too late to prevent significant disease losses. It might also mean that there are more fields to treat, making treatment more expensive. Finding an optimal solution is challenging for systems with nonlinear dynamics, even without allowing for uncertainty and the inherent stochasticity of the system. Progress can be made using methods from control theory (Pinch 1993). This requires the definition of an objective function that incorporates the costs of treatment and infection. The potential lies in being able to determine whether or not to spray and if so, when and for how long. Surprisingly, however, for many simple epidemiological models, the optimal solution involves a so-called 'bang bang' solution in which all infecteds are treated and then treatment is stopped at a particular level of infection or vice versa. Abrupt changes in turning on or off a control method are surprising and do not fit comfortably with current agricultural practice. The introduction of nonlinearities into the epidemiological model, however, can lead to 'interior solutions' in which there is variable treatment of some but not all infected sites, depending upon the prevalence of infection. Following early theoretical work (Gupta & Rink 1973; Sethi 1974, 1978; Greenhalgh 1987) directed at medical applications, there has been renewed interest in these methods, particularly for antibiotic resistance and for susceptible–infected–

susceptible (SIS) models (Goldman & Lightwood 2002; Rowthorn & Brown 2003) and more recently to the control of botanical epidemics (Forster & Gilligan 2007). Since they provide a rigorous yet parsimonious means of analysing the effectiveness of strategies for control under budget constraints, they are an important future tool for the analysis of botanical systems.

5. CONCLUDING REMARKS

Although much national and international attention is currently focused on animal and human disease, research on the epidemiology of plant pathogens and the development of sustainable strategies for the management and control of plant disease has perhaps never been so pressing. Supported by the potential of molecular biology to identify new sources for genetical, chemical and biological controls, the implementation within globally and locally changing agricultural environments demands new approaches to durable control. This, in turn, requires fusion of population genetics and epidemiology at a range of scales from the field to the landscape and even to continental deployment of control measures. It also requires an understanding of economic and social constraints that influence the deployment of control. This will involve a switch in focus from within-field to regional control of epidemics. I have argued here that this will be supported by stochastic, spatio-temporal models that also describe the changing crop mosaic through which disease spreads.

The support of a professorial fellowship from the Biotechnology and Biological Sciences Research Council is gratefully acknowledged. I am also grateful to current and former members of the Epidemiology and Modelling Research Group at Cambridge, notably Dr Adam Kleczkowski, Dr Wilfred Otten, Dr Simon Gubbins, Dr Richard Hall, Dr Bartek Dybiec and Dr Doug Bailey and to numerous collaborators, especially Dr Frank van den Bosch, Dr Stephen Parnell and Dr Ivana Gudelj at Rothamsted Research, and Dr Gavin Gibson at Heriot Watt University for their permission to cite joint work.

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