10.4 Use of mathematical models to inform control of an emerging epidemic

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When confronted with a new disease and the risk of an emerging epidemic, mathematics is not perhaps the first science called upon by policy makers and pathologists. Yet, if we are to predict the future course of disease and to compare the effectiveness of different control strategies, an epidemiological model informed by biological and economic insights is an essential tool in the armoury (Gilligan 2008). Finding an appropriate model is an exercise in compromise between what we think we ought to know, what is measurable or can be reasonably estimated, and what is necessary to predict the future dynamics of epidemics, with and without control (Gilligan 2008). Here we draw upon recent work by ourselves and our collaborators in analysing the regional spread of rhizomania disease in the UK, sudden oak death in California, cassava mosaic disease in Africa and especially citrus canker disease in urban populations in Florida (Gilligan & van den Bosch 2008). Our intention is to show that a relatively simple epidemic model can allow policy makers and pathologists to examine a range of 'what if scenarios'.
By simple epidemic model we mean a model with as few parameters and variables as possible. We begin by considering the variables: the plant, i.e. the tree, is the unit of interest. We consider initially just three classes:

- Susceptible trees (S): a tree starts off as healthy but susceptible to infection;
- Infectious trees (*I*): are both infected and capable of infecting other trees;
- Removed trees (*R*): comprise trees that die or are removed.

Other classes can be added, of which the most important is cryptically infected trees, in which the tree is both infected and infectious but may not be showing visible or detectable symptoms. Failure to allow for this can seriously under-estimate the spread of infection and disease, and undermine control efforts. An example is shown in Fig. 1 for Rhizomania disease of sugar beet spreading in the UK. Other refinements allow for changes in infectivity with host age.
There are three basic processes that control epidemics. These are:

- dispersal (how far can inoculum disperse?); it is characterised by a dispersal kernel with one or more dispersal parameters (α);
- transmission (what is the chance of infection when inoculum contacts a susceptible host?); it is characterised by transmission rates which may distinguish primary transmission (ε) for inoculum introduced from outside a region of interest and secondary transmission (β) for tree to tree spread within a region of interest;
- duration of infectiousness (when does the host stop transmitting infection?); it is characterised by an infectious period which may be natural or control-induced ($1/\mu$).

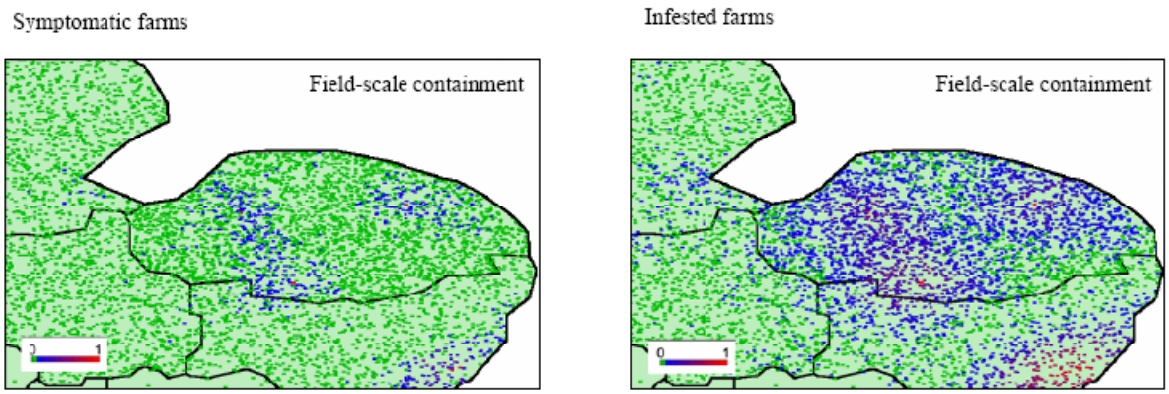


Fig. 1 Rhizomania disease of sugar-beet in the UK was believed to be localised in three sites in Eastern England. A stochastic (i.e. probabilistic) model, which allowed for cryptic infection (Gilligan et al. 2007), clearly showed that many more farms were infested (compare right with left panels) than had previously been assumed in devising field-scale control strategies. Within the model, individual fields rather than individual plants were classified as susceptible, infested/symptomatic and infested/asymptomatic (i.e. cryptically infested). The intensity of blue–red shading indicates the chance of a site being in a particular state ranging from blue (negligible) to red (highly likely).

Deriving estimates for the epidemiological parameters is one of the most challenging aspects of disease prediction. Recent work on the spread of citrus canker in urban Miami using data from Gottwald et al. (2002) has shown how Bayesian statistical methods can be used to estimate epidemiological parameters from spatio-temporal maps for the spread of disease (Cook et al. 2008; Gilligan et al. 2009). The method essentially furnishes 'best guesses' for the values of the epidemiological parameters. These are presented in the form of posterior probability distributions (Fig. 2) that formalise the degree of belief for parameters taking a particular value. An example is given in Fig 2 for one site in Broward county in which parameters are estimated, first with just the first three approximately monthly maps of infected and healthy trees, and then for successively more trees. We considered three parameters, the dispersal kernel (α, under an assumption of exponential spread, although others were considered), the rate of secondary (tree-to-tree) transmission (β) and the rate of primary transmission (ε) from external sources of inoculum. Trees were considered to remain infectious for long periods during the course of the observations.

Several important results emerge. Early predictions of the parameter values, especially of α and β, are imprecise with very wide posterior distributions. Basing a control strategy on these estimates could lead to a lot of uncertainty. Waiting a little longer, albeit at the risk of the pathogen spreading further, provides more precise estimates for the parameters upon which to base control strategies. We note too that while α and ε are more or less constant after the first few observation times, β varies with time, becoming smaller with time. It is probable that this relates to changes in environmental conditions and the onset of a long period of dry conditions (Gottwald et al. 2002).

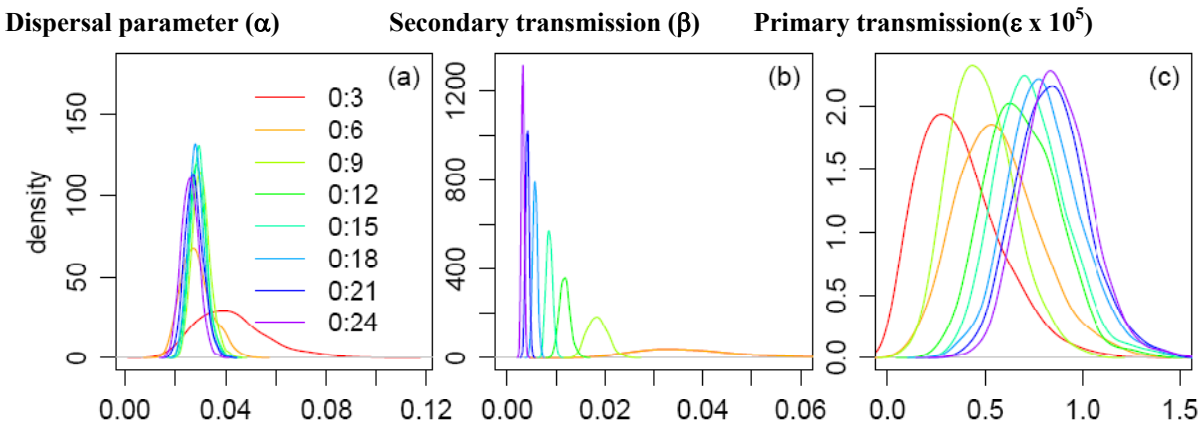
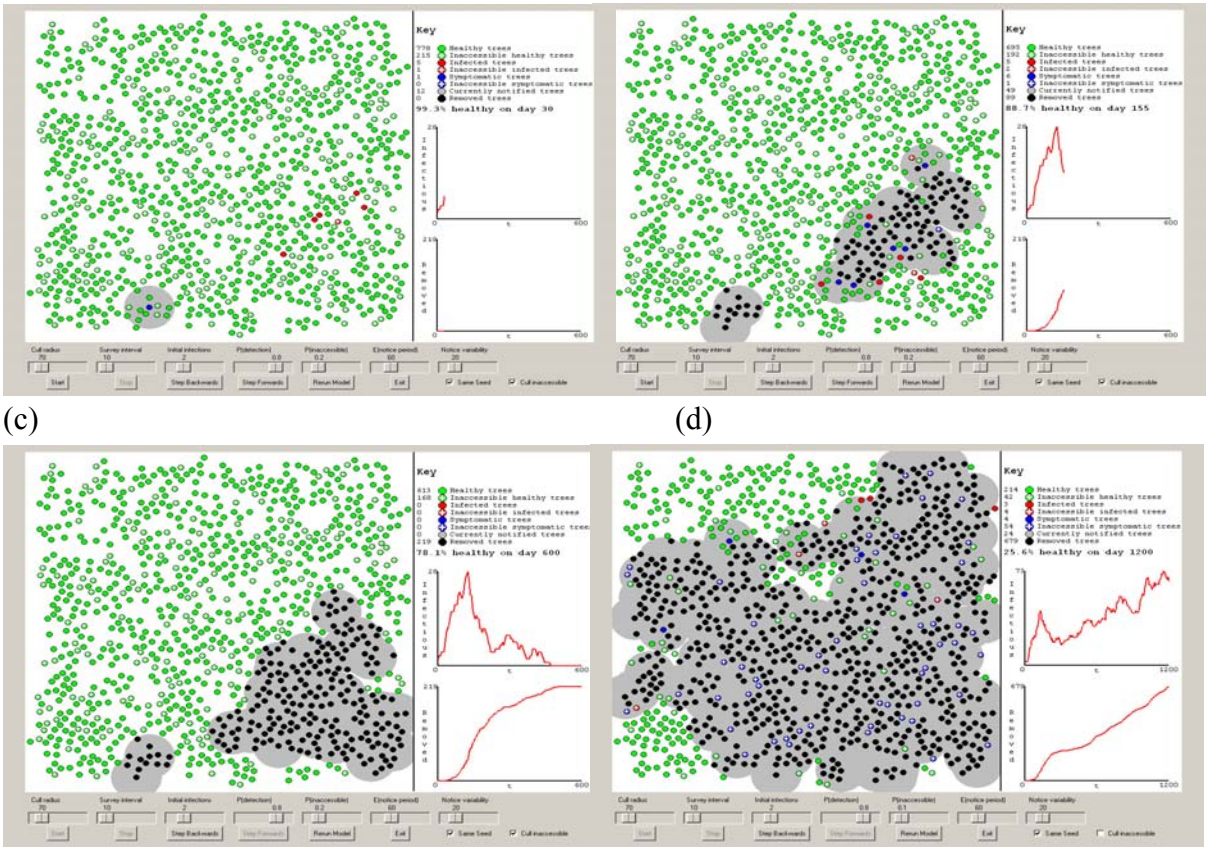


Fig. 2 Best guesses in the form of posterior probability distributions for (a) an exponential dispersal parameter (α); (b) the secondary transmission rate (β) and (c) the rate of primary external transmission (ε x 10^5) for the spread of citrus canker on trees in Broward County based upon cumulative windows taking account of successively more observations over time (Gilligan et al. 2009).

How can these parameter estimates be used to analyse control strategies? We consider an epidemic, such as for citrus canker, in which control is effected by removal of all trees around a symptomatic tree. Extending the zone of removal around an infected tree seeks to cull cryptically-infected trees that are not yet showing symptoms but which are capable of spreading infection. The challenge is to remove as few trees as possible while bringing the epidemic under control as swiftly as possible. In epidemiological terms this involves matching the scales of control with the inherent spatial and temporal scales of the epidemic (Dybiec et al. 2004). Two control variables may be changed, the radius of removal and the frequency with which sites are revisited to check for infected trees that were missed during previous visits. Individual epidemics are simulated for disease spreading on known densities of susceptible hosts and the effects of different strategies for removal radius and frequency of revisit can be compared. Two approaches are followed in the choice of parameters: either the median (most likely) parameters are chosen or the simulations are repeated many times, each time sampling parameter values from the entire posterior distributions to allow for uncertainty in what the true parameters might be. Chance variation is also incorporated into the models to reflect natural variation in the probability of transmission.

A simple example of a simulation is given in Fig 3 in which the sequence of control centred on notification of trees for removal around a symptomatic tree is illustrated with continuing spread of infection and disease from infected but undetected trees. As removal of trees proceeds, the spatial and temporal scale of control just manages to match the inherent temporal and spatial scales of the epidemic and eventually the epidemic is brought under control (Fig 3c). Strikingly, however, a small proportion of infected trees that escape removal could, in this simulated example negate the control strategy (Fig. 3d). Note too that while the underlying epidemic is captured by a relatively simple model, numerous additional practical considerations can be introduced. These include a variable detection rate, denoted by P(detection), whereby inspectors miss symptomatic trees, and allowance proportion of trees that are inaccessible, to detect, P(inaccessible) or to remove.

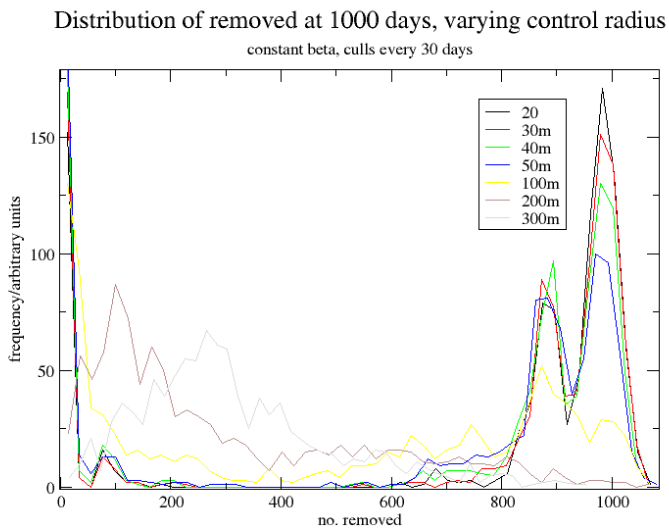
(b)



(c) (d)

Fig. 3 Example of output from single replications of a stochastic model for spread of infection through a population of susceptible trees in an urban environment subjected to a specified culling radius and survey (revisit). The data are used for for illustration and control parameters are in arbitrary units. The model is easily adjusted for plantations. (a) Early stage epidemic. Trees are notified for removal (grey culling radius) following detection of a single symptomatic (blue) tree. Other infected trees (red) remain undetected to the north west of the detected site. (b) The epidemic continues to spread and more trees are notified for culling (grey circles). Note that there are still some infected (red) tress outside the notified zones for culling. Within the culling zones, trees are removed after a variable notice period to allow for logistical and legal delays between notification and removal. (c) Eventually by matching the scales of the control strategy with the epidemic scales, the epidemic is eradicated. (d) A small proportion infected trees escaping culling can have devastating effects upon the eradication scheme with the epidemic still spreading after 1200d.

Of course, a single simulation, although illustrative, is not sufficient to determine the selection of a single control strategy amongst competing alternatives. It is of much more importance to consider the probability distributions for the outcomes for control strategies based upon large numbers of simulated epidemics. An example for the distribution of the numbers of trees removed from an urban site is given for different culling radii and a fixed survey interval in Fig. 4. Whereas increasing the culling radius predictably shifts the distribution, it is striking to note that some treatments (cf 100m) are associated with remarkably wide distributions of outcomes. It follows that although, on average, a treatment may be successful in containing an epidemic with



relatively small numbers of trees, a stochastic model allows us also to assess the risks and likely costs of failure as well as success. Deciding how to identify an optimal strategy, often requires weighting of several variables, typically the total costs of control but also the duration of the epidemic. This is an area of current research and some approaches will be discussed in the presentation.

Fig. 4 An example of the distribution of the numbers of trees removed from an urban site for different culling radii and a fixed survey interval. Note that these data were simulated to analyse simple treatments for which the model assumed instant removal of notified trees.

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Selected references

Cook AR, Gibson GJ, Gottwald TR, Gilligan CA. 2008 Constructing the effect of alternative intervention strategies on historic epidemics. *Journal of the Royal Statistical Society Interface* **5**, 1203-1213.

Dybiec B, Kleczkowski A, Gilligan CA. 2004 Controlling disease spread on networks with incomplete knowledge. *Physical Reviews Series E* **70**, 066145.

Gilligan CA. 2008 Sustainable agriculture and plant diseases: an epidemiological perspective. *Philosophical Transactions of the Royal Society Series B- Biological Sciences* **363**, 741-759.

Gilligan CA, Cook AR, Jamieson LE, Gibson GJ, Gottwald TR. 2009 Bayesian analysis of an emerging epidemic: citrus canker in urban Miami. (in draft).

Gilligan CA, Truscott JE, Stacey AJ. 2007 Impact of scale on the effectiveness of disease control strategies for epidemics with cryptic infection in a dynamical landscape: an example for a crop disease. *Journal of the Royal Society Interface* **16**, 925-934.

Gilligan CA, van den Bosch F. 2008 Epidemiological models for invasion and persistence of pathogens. *Annual Review of Phytopathology* **46**, 385-418.

Gottwald TR, Sun X, Riley T, Graham JH, Ferrandino F, Taylor EL. 2002 Geo-referenced spatiotemporal analysis of the urban citrus canker epidemic in Florida. *Phytopathology* **92**, 361-377.