Institution: The University of Edinburgh/Heriot-Watt University (Maxwell Institute)

Unit of Assessment: B10, Mathematical Sciences

Title of case study: Statistical methods are helping to control of the spread of epidemics

1. Summary of the impact

In a series of papers from 2003, Gibson (Maxwell Institute) and collaborators developed Bayesian computational methods for fitting stochastic models for epidemic dynamics. These were subsequently applied to the design of control programmes for pathogens of humans and plants. A first application concerns the bacterial infection *Clostridium difficile* in hospital wards. A stochastic model was developed which was instrumental in designing control measures, rolled out in 2008 across NHS Lothian region, and subsequently adopted across NHS Scotland. Incidence in Lothian reduced by around 65%, saving an estimated £3.5M per annum in treatment and other costs, reducing mortality and improving patient outcomes, with similar impacts elsewhere in Scotland. A second application concerns the spread of epidemics of plant disease in agricultural, horticultural and natural environments. Models developed in collaboration with plant scientists from Cambridge have been exploited by the Department for Environment, Food and Rural Affairs (Defra) and the Forestry Commission under a £25M scheme, initiated in 2009, to control sudden oak death in the UK, and by the United States Department of Agriculture to control sudden oak death in the USA.

2. Underpinning research

Statistical methods for parameter estimation. Research carried out by Gibson (Maxwell Institute) and collaborators formulated and tested Bayesian methods for estimating parameters in stochastic epidemics models that could take account of the incomplete nature of observations typically available in real-world settings. The methods drew extensively on modern computational approaches including data augmentation and Markov chain Monte Carlo and were subsequently applied in interdisciplinary studies on a) hospital acquired infections and b) the spatio-temporal spread of plant pathogens.

Hospital-acquired infections. Gibson in collaboration with Renshaw (Strathclyde), PhD student Campbell (Strathclyde), and Starr (NHS) formulated models for the dynamics of *C. difficile* in hospital wards. Model development was informed by data from two medicine-for-the-elderly wards, collected over a 17-month period under an earlier project (PIs: Gibson, Starr and Poxton (University of Edinburgh), 1998-2001), which recorded the infection status of individuals and incidence of clinical cases of *C. difficile*. Analysis of these data highlighted the potential importance of, for example, the use of certain antibiotics, as risk factors [1]. The main analysis of the data, published in final form in [3] presented a stochastic compartment model for *C. difficile* dynamics which allowed for potentially differing transmission rates between patients in the same and different rooms within wards, various resistant and susceptible states and the possible transitions between them, and the random nature of *C. difficile* infection. As the data had been collected in the course of day-to-day running of the wards, they did not constitute an exhaustive census of the population. The Bayesian data-augmentation and computational techniques used in [3] were therefore instrumental in allowing the stochastic models to be parameterised in a statistically sound fashion, and to be used to predict outcomes and inform the control strategies. The model was applied to predict the potential reduction in disease incidence that might be achieved by controlling several factors associated with *C. difficile* infection. These results, together with the earlier risk analysis [1], provided quantitative evidence that reducing the rate of transition of patients to the susceptible compartment could be highly effective. They supported the implementation of a control strategy for *C. difficile* based on antibiotic control across Lothian. The Bayesian data-augmentation techniques were also refined and applied by Gibson (2003-2006) in collaboration with Pettitt and Forester (Queensland University of Technology) to characterise the dynamics of meticillin-resistant *Staphylococcus aureusis* (MRSA) in intensive care units [2].

Spatio-temporal spread of plant pathogens. Gibson and Cook (Maxwell Institute) and Gilligan and colleagues (Plant Sciences, Cambridge) tailored the Bayesian data-augmentation approach to fitting spatio-temporal models of plant pathogens, for which data typically record only snapshots of the infected population at sparse sampling times. Algorithms were initially developed using data from epidemics in laboratory microcosms on the fungal pathogen *Rhizoctonia solani* [4, 5] before being applied to the larger-scale Miami citrus canker epidemic [6]. The methods enabled estimation of key parameters controlling the spatial and temporal dynamics of dispersal of pathogens, the prediction of pathogen spread, and assessment of the likely efficacy of putative control measures. Cook (Maxwell Institute) worked with the epidemiology group, Plant Sciences, Cambridge, during 2007-8 on host-pathogen systems for which spatio-temporal models were required, and subsequently applied the methods developed in [4-6] to data on sudden oak death. This work has had a direct bearing on policy for controlling the spread of this disease. Further collaborative studies involving Gibson have employed the methods to estimate dispersal characteristics of citrus canker and citrus greening.

Attribution. G.J. Gibson has been Professor of Statistics at the Maxwell Institute since 2000. His collaborators were from the University of Strathclyde (A. Campbell, E. Renshaw), NHS Lothian (J. M. Starr), University of Edinburgh (I. Poxton, H. Martin, J. McCoubrey), University of Cambridge (C. A. Gilligan, W. Otten) and Queensland University of Technology (M. L. Forrester, A. N. Pettitt). A. Cook was a PhD student in the Maxwell Institute (2002-6) and an RA in the Maxwell Institute on BB/C007263/1 (2005-8).

3. References to the research

References marked (*) best indicate the quality of the research.

[1] Starr, J.M., Martin, H., McCoubrey, J., Gibson, G. and Poxton, I. R., Risk factors for *Clostridium difficile* colonisation and toxin production, *Age and Ageing*, **32**, 657-660 (2003). http://dx.doi.org/10.1093/ageing/afg112

[2]* Forrester, M.L., Pettitt, A.N. and Gibson, G.J., Bayesian inference of hospital-acquired infectious diseases and control measures given imperfect surveillance data, *Biostatistics*, **8**, 383-401 (2007). http://dx.doi.org/10.1093/biostatistics/kxl017

[3]* Starr, J.M., Campbell, A., Renshaw, E., Poxton, I.R. and Gibson, G.J., Spatio-temporal stochastic modelling of *Clostridium difficile*. *Journal of Hospital Infections*, **71**, 49-56 (2009). http://dx.doi.org/10.1016/j.jhin.2008.09.013

[4] Gibson, G.J., Otten, W, Filipe, J.N.F., Cook, A.R., Marion, G. and Gilligan, C.A., Bayesian estimation for percolation models of disease spread in plant communities, *Statistics & Computing* **16**, 391-402 (2006). http://dx.doi.org/10.1007/s11222-006-0019-z

[5]* Cook, A.R., Otten, W., Marion, G., Gibson, G.J. and Gilligan, C. A., Estimation of multiple transmission rates for epidemics in heterogeneous populations, *Proc. Nat. Acad. Sciences*, **104**, 20392-20397 (2007). http://dx.doi.org/10.1073/pnas.0706461104

[6]* Cook, A.R., Gibson, G.J., Gottwald, T.R. and Gilligan, C.A., Constructing the effect of alternative intervention strategies on historic epidemics. *J. Roy. Soc. Interface* **5**: 1203-1213

(2008). http://dx.doi.org/10.1098/rsif.2008.0030

Funding

Research Grants: BB/C007263/1. Experimental design for stochastic dynamical models in the life sciences, Gibson (PI), C. A. Gilligan (Co-I), 2005-9 (£183k).

4. Details of the impact

Control of *C. difficile*. The immediate impact of the research was to inform changes to healthcare practices in **NHS Lothian** medicine-for-the-elderly wards which served to reduce the incidence of *C. difficile*, with consequent improvements in patient outcomes. A control strategy, based on control of broad-spectrum antibiotic prescribing and informed by the mathematical models, was identified and implemented in a 12-month pilot study from November 2007 across seven medicine-for-the-elderly wards in Edinburgh hospitals. During the pilot study there were a total of 60 cases of *C. difficile* infection in the wards, compared to 120 during the previous 12 months. Following this initial success, and other pilot studies, a tool-kit of measures was rolled out across all acute wards in Lothian (the 2nd largest NHS region in Scotland) in September 2008. The NHS Lothian consultant who led the pilot study has indicated that 'the mathematical and statistical models were key to providing the quantitative evidence necessary to justify the approach taken in the pilot studies' [7].

Following the introduction of the toolkit of measures, the incidence of *C. difficile* declined considerably. Monthly median incidence in Lothian during the 15 months from Jan 2007 – March 2008, was 106 cases per month. During the 24 months from April 2008 – March 2010, the monthly median incidence was 61 cases per month [9,10]. A more recent estimate of the impact of the control measures can be found in the summary document NHS Lothian at a Glance HEAT 2011-12 Target Performance [11] which notes the 'significant progress in reducing the rate of *C. difficile* infections' and that 'Year-end rates for new cases represented a reduction of 74% compared to 2007-8'.

As well as the beneficial changes to clinical practices, disease prevention, and patient health outcome, reduction in mortality and morbidity, the research has contributed to substantial economic benefits. The management of each clinical case of *C. difficile* infection was estimated to cost £4k in 2000. Thus, a 74% reduction from monthly median levels of the order of 100 cases per month represents – not accounting for cost inflation – a reduction of monthly costs of the order of £300k translating to annual reductions of around £3.5M. Moreover, there is the 'opportunity-cost' benefit that increased infection-control resources can now be targeted at other pathogens, such as norovirus, or other healthcare issues. The impact been extended from Lothian to the whole of Scotland with the adoption of measures to control antimicrobial prescribing by NHS Scotland [8] and a proportionate reduction in *C. difficile* infection levels has been seen.

Control of arboreal pathogens. The spatio-temporal parameter-estimation techniques [4-6] were adopted by the epidemiology group at Cambridge in a major initiative to develop a spatio-temporal modelling toolbox that could be applied to a wide variety of plant diseases [12]. This group was approached by **Defra** and **US Department of Agriculture** (USDA) to apply the toolbox to a range of emerging plant pathogens, including sudden oak death, a devastating disease that is threatening woodlands in California and woodlands and heathlands in the UK, and whose host range includes more than 100 economically and ecologically important woody hosts. In the Californian context, models parameterised using the methods [4-6] were employed to demonstrate the value of early action in detecting and controlling disease, to determine the regions of the state at greatest risk up to 2030, and to demonstrate that creating barriers by removing large areas of vegetation is unlikely to work. More widely, they have been used to inform US policy advisers and policy makers about the risks of spread of sudden oak death in Eastern states of the US [13].

In the UK, **The Forestry Commission** and **Defra** are using the models to inform, adjust and implement sampling and disease control policies for sudden oak death throughout England and Wales as part of a £25M eradication and control scheme launched in 2010 [14]. Specifically the models formulated by the Cambridge group since 2008 allow comparison of different 'what-if' scenarios about the likelihood of disease spread and are providing policy makers with information about the likely efficacy of different culling distances and sampling frequencies, and to guide aerial and ground surveys for the disease, using 'hazard maps' predicted by the parameterised models. The insights on sudden oak dynamics from the US setting – such as the structure of appropriate models for pathogen dispersal and the parameter ranges – obtained using the parameter estimation method of [4-6], were utilised directly in the initial modelling studies of the UK sudden oak death epidemic, and helped to underpin the subsequent advice to policy makers [14].

5. Sources to corroborate the impact

Control of *C. difficile*

[7] Through their position as Consultant at NHS Lothian: for corroboration of the importance of the inference and predictive modelling in designing the control strategy.

[8] Senior Manager, NHS Lothian: for corroboration of the effectiveness of controlling antimicrobial prescribing on levels of *C. difficile* in NHS Lothian and of the wider impact across NHS Scotland.

[9] Guthrie *et al.*, Reduction of *Clostridium difficile* in NHS Lothian using a toolkit approach, Poster, NHS Scotland Event – Sharing the learning, 2010. http://www.knowledge.scot.nhs.uk/media/CLT/ResourceUploads/21710/CE21.pdf

[10] Media articles citing effectiveness of control measures for *C. difficile* in NHS Lothian region include: http://news.stv.tv/east-central/85809-decrease-in-levels-of-cdiff-in-lothian/

[11] NHS Lothian at a Glance, HEAT 2011-12, Target Performance. http://www.nhslothian.scot.nhs.uk/OurOrganisation/KeyDocuments/AnnualReviews/NHS%20Lothian%202012%20Performance%20Handout.pdf

Control of arboreal pathogens

[12] Senior Academic, Department of Plant Sciences, Cambridge University: for corroboration of the role of the inferential techniques for parameterisation of models within the toolkit.

[13] Senior Scientist, US Department of Agriculture, Florida: to provide evidence of impact of models in practical disease control for tree diseases in the US.

[14] Senior Scientist, Forestry Commission: for evidence of the use of the models to inform Forestry Commission Policy on practical control decisions about where and how to control sudden oak death on Forestry Commission land.

Note: should links to web pages be broken, please use the website http://www.maths.ed.ac.uk/~mthdat25 to access pdf versions of the pages