Institution: Maxwell Institute of Mathematical Sciences

Unit of Assessment: UoA 10 – Mathematical Sciences

Title of case study: New statistical methods for integrating epidemic and genetic data within spatio-temporal models help to control the spread of *Mycoplasma bovis* in New Zealand.

Period when the underpinning research was undertaken: 2010-2015

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Gavin Gibson	Professor of Statistics, Acting Head of School (2014-16)	September 2000 - present
George Streftaris	Professor of Statistics	March 2001 - present

Period when the claimed impact occurred: July 2018 – December 2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact

Methods for the simultaneous estimation of epidemic dynamics and pathogen evolution developed by researchers at Heriot Watt University were incorporated into a user-friendly computer package BORIS by scientists from the University of Melbourne. From July 2018, the BORIS package has been used as an analytic tool within the New Zealand Ministry of Primary Industries (MPI) eradication programme for *Mycoplasma Bovis*, a bacterial disease that affects dairy and beef cattle, estimated to cost a total of NZD886,000,000. Specifically, BORIS has been used to identify potential times and sources for observed infections so that risk factors for transmission, or potential failures in biosecurity can be identified. The eradication programme has been highly effective with only 4 premises out of more than 20,000 having active disease in July 2020 and infection having been successfully cleared from 246 premises by that time.

2. Underpinning research

The research leading to the impacts described concerns methods of inference for individual-based spatio-temporal models of epidemics and, in particular, methods that enable the estimation of unobserved transmission graphs (who infected whom) and times of infection events. Such insights can be key to understanding the factors underlying disease transmission when controlling emerging epidemics.

Building on their earlier work on fitting and testing spatio-temporal models for partially observed epidemics [3.1] Gibson, Streftaris and Marion (Biomathematics and Statistics Scotland), with PhD student Lau, tackled the problem of simultaneously inferring pathogen evolution and spatio-temporal epidemic transmission in settings where genetic sequence data on pathogens are available in addition to case data - a major current challenge in epidemic modelling. Motivated by pathogens such as foot and mouth disease (FMD), they extended the spatio-temporal Susceptible-Exposed-Infective-Removed (SEIR) model for epidemic transmission with a 2-parameter Kimura model for pathogen evolution and introduced a novel Bayesian method for fitting the extended model to partial observations of an emerging epidemic [3.2]. By explicitly representing sequences transmitted during infection events as latent variables, and imputing sequences transmitted to unsequenced infections, they were able to dispense with the requirement that pathogen sequences be available for all infected

host units - where a unit in the context of diseases such as FMD is typically a farm – making them applicable in real-world settings. Moreover, the methods can accommodate multiple introductions of an epidemic into a population, allowing imputation of a general infection graph rather than the infection tree implied by a single introduction. These enhancements were achieved using data-augmentation methods coupled with Markov chain sampling approaches. An important innovation in the method was the formulation of efficient proposal distributions for jointly updating unobserved times of, or sources for, infection events and the genetic sequence transmitted during the corresponding event. A key finding of [3.2] was that the methods were capable of identifying infection sources with high accuracy when epidemic data were complemented by even modest amounts of genomic data on pathogens.

The methods of [3.2] were assessed in comparison with the main competing approaches in an independent study by a team led from the Division of Veterinary and Agricultural Sciences at the University of Melbourne and were found to be the most robust for reconstructing transmission trees from partial observations of disease incidence and pathogen genomics [5.1, 5.2]. The Melbourne-led team (with input from Lau) subsequently incorporated the algorithm presented in [3.2] – enhanced with the capacity to include contact data and farm-level covariates - into a user-friendly computer package [5.3] facilitating its use by groups working on the control of ongoing epidemics. Of particular relevance to this case study is the application of the methods to *Mycoplasma bovis* in New Zealand.

3. References to the research

[3.1] Lau, M. S. Y., Marion, G. & Streftaris, G., Gibson, G. J. (2014) New model diagnostics for patio-temporal systems in epidemiology and ecology, J. R. Soc. Interface.11: 20131093. http://doi.org/10.1098/rsif.2013.1093

[3.2] Lau, M. S. Y., Marion, G. & Streftaris, G., Gibson, G. J. (2015) A Systematic Bayesian Integration of Epidemiological and Genetic Data, PLOS Computational Biology 11, 11, 27 p., e1004633L. https://doi.org/10.1371/journal.pcbi.1004633

4. Details of the impact

Mycoplasma bovid is a bacterial disease that affects dairy and beef cattle, causing severe illness with major impact on production. It is a disease of major significance to the New Zealand farming industry, which represents the second largest export market for the country. The New Zealand epidemic was first detected in 2017, following which a major eradication programme was announced in May 2018 [5.4]. The total cost of the programme was estimated to be NZD886,000,000 (05-2018) [around GBP470,000,000], including NZD16,000,000 in lost production and NZD870,000,000 of response costs needed to fight the cattle disease over a 10-year period [5.4]. According to [5.4], had the epidemic been allowed to proceed unchecked the cost would have been approximately NZD1,300,000,000 (05-2018) [around GBP689,000,000] over 10 years, with ongoing productivity losses across the New Zealand farming sector.

As part of a wider programme of epidemiological work that included support (approximately AUD70,000) from New Zealand's Ministry of Primary Industries (MPI), Firestone and colleagues developed a computer package BORIS (Bayesian Outbreak Reconstruction Inference and Simulation) [5.2, 5.3] which incorporated the methods of [3.2] with the additional capacity to accommodate contact data and farm-level covariates. According to the team who developed BORIS, *"The main benefits provided by your algorithm derive from its capacity to fit epidemic dynamics and pathogen phylodynamics within an integrated framework, to represent multiple introductions, and to cope with partial sampling scenarios – essentially allowing the state of unobserved nodes in a network to be inferred"* [5.5].

The BORIS package, code for which is now freely available from GitHub [5.3], has subsequently been applied within the *M bovis* eradication programme since July 2018 [5.2,

5.6] as one of a suite of analytic tools, to analyse epidemiological and genomic data in order to inform the government of the timing of likely introduction of *M bovis* into New Zealand, whether there were multiple introductions, and the extent to which the case network could be determined. Specifically, BORIS is used to infer timing of infections, infectious periods for farms, and to identify likely transmission routes (who-infected-whom) for the ongoing epidemic. Such insights serve to identify possible infector-infectee links, and corresponding time periods, that should be scrutinised in order to understand the potential risk factors, or failures in biosecurity, that may lead to transmission of the disease. Unlike competing genomic methods, BORIS has the capacity to impute chains of infection that include farms for which genetic data on the pathogen may not be available. Results of these analyses are key to providing confidence to MPI of their understanding of the outbreak [5.5, 5.6]. Since the eradication programme was initiated, the epidemic has been successfully controlled to the extent where, as of July 2020 (resp. November 2020), there were only 4 (resp. 6) properties (out of more than 20,000 dairy and beef farms) [5.5] in New Zealand where the disease was known to be active, having been successfully cleared from 246 premises by that time. BORIS continues to be used as a decision-support tool for guiding surveillance teams within the programme as it moves towards eradication of the disease [5.6].

More widely, the techniques of [3.2] have been promoted through a training programme delivered by Firestone on the use of the BORIS package to Australian government veterinarians at the Department of Agriculture, Water and the Environment (Canberra, November 2019). To date 20 scientists have received training in its use [5.2]. BORIS has also helped improve the understanding of spread of foot-and-mouth disease in Japan [5.7], for example demonstrating the high transmissibility of the disease from farms holding predominantly pigs.

5. Sources to corroborate the impact

[5.1] Firestone, S. M., Hayama, Y., Bradhurst, R. *et al.* Reconstructing foot-and-mouth disease outbreaks: a methods comparison of transmission network models. *Sci Rep* 9, 4809 (2019). https://doi.org/10.1038/s41598-019-41103-6 Provides a critical assessment of methods of [3.2] in comparison to competing methods.

[5.2] Letter of support from Senior Lecturer, Faculty of Veterinary and Agricultural Sciences, University of Melbourne. Corroborates details relating to the implementation of the techniques of [3.2] within the BORIS package, the benefits they bring, how they have been applied to *M bovis* and FMD, and training given in the use of the methods.

[5.3] Firestone S. M., Lau M. S. Y., Kodikara S., Demirhan H., Hayama Y., Yamamoto T., et *al.* (2019) BORIS: R package for Bayesian Outbreak Reconstruction Inference and Simulation. GitHub repository, https://github.com/sfires/BORIS

[5.4] Press release, New Zealand Government, 28/5/2018, “Plan to eradicate Mycoplasma bovis”, https://www.beehive.govt.nz/release/plan-eradicate-mycoplasma-bovis
Announcement of *M bovis* eradication plan including estimated costs and scale given in Section 4.

[5.5] Press release, New Zealand Government, 22/7/2020, “*M. bovis* eradication makes gains three years on from detection”, https://www.beehive.govt.nz/release/mbovis-eradication-makes-gains-three-years-detection.
Provides details of status of epidemic in July 2020 including number of properties where *M bovis* was active.

[5.6] Letter of support from Chief Departmental Science Advisor, Ministry for Primary Industries (MPI), New Zealand. Corroborates use of BORIS within the ongoing *M Bovis* eradication programme and effectiveness of the programme.

[5.7] Firestone SM, Hayama Y, Lau MSY, Yamamoto T, Nishi T, Bradhurst RA, et al. (2020) Transmission network reconstruction for foot-and mouth disease outbreaks incorporating farm-level covariates. PLoS ONE 15(7): e0235660. https://doi.org/10.1371/journal.pone.0235660
Describes use of BORIS package for the analysis for reconstructing transmission networks for foot and mouth disease in Japan.