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SMHD 2019

Stochastic modelling in Health & Disease

School of Mathematics, University of Leeds

11-13 September 2019

SMHD 2019 is a 3-day meeting bringing together researchers working on the modelling of Biological systems related to infection and immunity, at the cellular, within-host and population levels, with special focus on stochastic and probabilistic approaches. Talks will cover topics including: developing mathematical and computational models for infection, immunity and disease spread, statistical approaches for informing models from experimental and clinical data, or the development of new methodologies for analysing these systems, including new techniques for the analysis of stochastic processes. The meeting consists of a number of talks delivered by keynote speakers, as well as contributed talks.

Schedule (Wednesday 11^{th} - Friday 13^{th} September 2019)
13 Keynote talks -40min- (*35+5*), 14 Contributed talks -25min- (*20+5*)

	Wednesday	Thursday	Friday
09:00 – 09:40	Registration	Catherine Noakes	Kieran Sharkey
09:40 – 10:20	Konstantin Blyuss	Lulla Opatowski	Grant Lythe
10:20 – 10:45	Jake Carson	David Sirl	Jonty Carruthers
10:45 – 11:15	Coffee Break	Coffee Break	Coffee Break
11:15 – 11:40	Francesco Di Lauro	Marco-Felipe King	Malwina Luczak
11:40 – 12:20	István Kiss	Theodore Kypraios	Farzad Fatehi*
12:20 – 12:45	Jean-Charles Croix	Yi Ming Lai	Alice Corbella*
12:45 – 13:45	Lunch	Lunch	Lunch & END*
13:45 – 14:10	Joe Hilton	Clement Twumasi	
14:10 – 14:50	Thomas House	Kit Yates	
14:50 – 15:30	Joshua Ross	Carmen Molina-París	
15:30 – 16:00	Coffee Break	Coffee Break	
16:00 – 16:40	Ada Yan	Gabriela Gomes	
16:40 – 17:05	Simon Spencer	Renata Retkute	
17:05 – 18:30	Wine Reception		

*11:40-12:05, 12:05-12:30. Lunch & end: 12:30-13:30

The meeting is taking place at the School of Mathematics, University of Leeds. Registration will take place 9:00-9:35 at the main entrance of the School of Mathematics. Information on how to reach the School can be found at `https://physicalsciences.leeds.ac.uk/info/6/school_of_mathematics/99/contact_us`. The talks will take place at:

- Wednesday 11th: **Roger Stevens LT01** (note that Roger Stevens is a building located next to the School of Maths. From the School of Maths Level 9, go upstairs into Dolche Vita Cafe at Level 10, turn right and cross the bridge. You are now at Roger Stevens).
- Thursday 12th - Friday 13th: **School of Mathematics MALLs** (School of Maths, Level 8)

More information about this meeting can be found at `https://matml.github.io/smhd2019.html`

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List of Abstracts

Wednesday, 11th September. 9:00-09:40, Registration at School of Mathematics, main entrance, Level 9

Wednesday, 11th September. 9:40-10:45, Roger Stevens LT01. Chair: Martín López-García

Stochastic effects in autoimmune dynamics

Konstantin B. Blyuss[1], Farzad Fatehi[2], Yuliya N. Kyrychko[1]

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Among various causes of autoimmunity, a particularly important role is played by infections that can lead to a breakdown of immune tolerance. In this talk, I will discuss a model of immune response to a viral infection, and subsequent onset of autoimmunity, with particular account for cytokines and different types of T cells. Of particular biological relevance is the analysis of stochastic oscillations around deterministically stable states, as well as the effects of stochasticity on dynamics of the system in a bi-stable regime. I will show how variance of stochastic fluctuations and their coherence depend on system parameters. To make the model more realistic, it is important to also consider the effects of time delays associated with various processes involved in the development of immune response. I will discuss a method for deriving stochastic delayed differential equations and a corresponding numerical simulation algorithm, and will show how it can be used to simulate stochastic dynamics in a time-delayed model of autoimmunity.

Bayesian model selection for individual level infectious disease models

Jake Carson[1], Simon Spencer[1]

[1]*Department of Statistics, University of Warwick, UK*

The validity of insights gained from infectious disease models depend on the appropriateness of the model assumptions. At a minimum, public health professionals need access to statistical tools that are able to compare the appropriateness of competing models in the light of real-world data. Infectious disease models typically contain few model parameters, but inference is made challenging due to the fact that information such as the infection and recovery times of individuals is not directly observed. When the conditional distribution of the hidden infection process given the available data is tractable, effective approaches exist for estimating the model evidence to a high precision, allowing for the comparison of competing models through the use of Bayes factors. For discrete-time infectious disease models the full conditional distribution can be sampled from using the forward filtering backward sampling (FFBS) algorithm. However, for individual level models the computational cost of the FFBS algorithm grows exponentially with the population size, and so can only be utilised when modelling small populations. Recently proposed variants of the FFBS algorithm reduce the computational complexity of imputing the hidden infection process, but do not directly sample from the full conditional distribution. We demonstrate how these developments can be used to form effective proposal distributions for estimation of the model evidence when studying larger populations.

Wednesday, 11th September. 10:45-11:15, Coffee break. Waterside Café, Roger Stevens Level 6

Wednesday, 11th September. 11:15-12:45, Roger Stevens LT01. Chair: Konstantin Blyuss

Inference of disease and network parameters based on mean-field models

F. Di Lauro[1], R. Inkpen[1], I.Z. Kiss[1]

[1]*Department of Mathematics, University of Sussex, Falmer, Brighton BN1 9QH, UK*

Epidemic propagation on networks is a well studied process. In many cases, the exact nature of the network on which such dynamics unfolds is unknown, and so is the infection rate, with more information being available about the recovery rate. This has motivated a lot of work on network and epidemic parameters inference from observation of incidence data. Many of the research in this direction is concerned with explicitly inferring the links of the network when node-level temporal data are available. In this work, we tackle the problem of inferring both network and epidemic parameters when only population-level data are observed, but when the network is given by a parametric model. The likelihood of observed data is written down using mean-field-model-like approximations and thus we overcome the complexity of the problem. We show that, when the infection rate is known, we correctly recover the parameters of the network for both Erdős-Rényi and Regular networks. However, as expected, the infection rate and average degree cannot be readily disentangled. To overcome this issue, we explore the possibility of augmenting the likelihood with information about the growth rate or final epidemic size that provides a further relation between rate of infection and average degree.

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Network inference from population-level observation of epidemics

F. Di Lauro[1], J.-C. Croix[1], M. Dashti[1], L. Berthouze[2], I.Z. Kiss[1]

[1]*Department of Mathematics, University of Sussex, Falmer, Brighton BN1 9QH, UK*
[2]*Centre for Computational Neuroscience and Robotics, University of Sussex, Falmer BN1 9QH, UK*

The network paradigm is widely accepted as the gold standard in modelling complex systems such as epidemics or neuronal activity in the brain; however, in most cases, the exact nature of the network on which such dynamics unfold is unknown. This has motivated a significant amount of work on network inference. Whilst a large body of work is concerned with inferring network structure based on detailed node-level temporal data, in this work we tackle the more challenging scenario of inferring the family of the underlying network when only population-level temporal incidence data are available. A key obstacle is the forbiddingly high dimensionality of the resulting stochastic epidemic model. To tackle this, we approximate the susceptible-infected-susceptible (SIS) model on networks by a birth-and-death process, whose rates encode the structure of the underlying network and disease dynamics. Using systematic simulations, we propose a parsimonious (three-parameter) model of these rates and show that different well-known network families map onto distinct regions of the parameter space of this model. This result provides an a priori characterisation of different network families. Then, given population-level temporal epidemic data, we employ a Bayesian classifier to derive posterior distributions over different network families. We show that the proposed methodology yields excellent results when tested on synthetic and real-world networks. Our framework extends readily to many network families and spreading processes and it could provide a new benchmark in network inference from population-level data.

Keywords: Epidemics, Networks, Inference, Bayesian.

Non-parametric Bayesian inference for discretely observed diffusions: Applications to epidemics.

Jean-Charles Croix[1], Masoumeh Dashti[1], István Z. Kiss[1]

[1]*School of Mathematical and Physical Sciences, University of Sussex, UK*

The susceptible-infected-susceptible (SIS) epidemic dynamics on networks is approximated by a scalar Itô process representing the proportion of infectious nodes, whose drift and diffusion coefficients are encoding the underlying contact structure. Doing so, the usual master equation is replaced by the Fokker-Planck equation, providing a tractable likelihood for inference based on observations of a single epidemic at discrete times. However, the likelihood is not available in explicit form and thus must be carefully analysed. In this work, we study the well-posedness of this Bayesian inverse problem, consisting in the estimation of both drift and diffusion coefficients from discrete observations of the infected counts. In the case of a real epidemic, where the network of contacts may only be partially or not known, our approach makes it possible to recover some information about the properties of the underlying network simply from the discrete temporal observation of the number of infected individuals/nodes.

Wednesday, 11th September. 12:45-13:45, Lunch. Waterside Café, Roger Stevens Level 6

Wednesday, 11th September. 13:45-15:30, Roger Stevens LT01. Chair: István Kiss

A household-structured approach to endemic infections

Joe Hilton[1], Matt Keeling[1]

[1]*University of Warwick*

This work introduces a mathematically tractable approach for modelling endemic infections in a complex demographic setting, with implications for both disease dynamics and control strategies. Age- and household- structured transmission are central to the dynamics of childhood infections such as measles and mumps. In unvaccinated populations these infections are often endemic, circulating over long timescales which allow individuals to age out of risk groups and move between households. The resulting changes in household-level immunity and susceptibility make it difficult to predict the impact of public health interventions such as vaccination, suggesting the need for infectious disease models with underlying transmission structures which evolve dynamically. Our approach combines a demographic model describing the life cycle of a family unit with an age- and household-structured model of infectious disease dynamics. Using data from demographic studies and contact surveys, we model UK-like and Kenya-like populations in order to understand the impact of demography on infectious disease dynamics. The underlying household structure of our model allows us to compare interventions which distribute vaccine uniformly and by household. We find that structured contacts have the most impact when person-to-person transmission is comparatively weak, in which case age and household structure act in tandem to concentrate infection within households containing school-age children and their younger siblings. In this setting uniform vaccination performs better than household-based vaccination, which allows infection to concentrate in unvaccinated households. This improvement is less substantial if transmission is intensified, weakening the impact of contact structure.

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Modelling infections in closely connected sub-populations: Scabies in residential care homes

Thomas House[1,2]

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[2]*IBM Research, Sci-Tech Daresbury, WA4 4AD.*

In the context of an ageing population, understanding the transmission of infectious diseases such as scabies through well-connected sub-units of the population, such as residential care homes, is particularly important for the design of efficient interventions to mitigate against the effects of those diseases. Here, we present a modelling methodology based on the efficient solution of a large-scale system of linear differential equations that allows statistical calibration of individual-based random models to real data on scabies in residential care homes. In particular, we review and benchmark different numerical methods for the integration of the differential equation system, and then select the most appropriate of these methods to perform inference using Markov chain Monte Carlo. We test the goodness-of-fit of this model using posterior predictive intervals and propagate forward the resulting parameter uncertainty in a Bayesian framework to consider the economic cost of delayed interventions against scabies, quantifying the benefits of prompt action in the event of detection. We also revisit the previous methodology used to assess the safety of treatments in small population sub-units – in this context ivermectin – and demonstrate that even a very slight relaxation of the implicit assumption of homogeneous death rates significantly increases the plausibility of the hypothesis that ivermectin does not cause excess mortality based upon the data of Barkwell and Shields.

Reference: T. M. Kinyanjui, J. Middleton, S. Güttel, J. A. Cassell, J. V. Ross and T. House, "Scabies in residential care homes: Modelling, inference and interventions for well-connected population sub-units," PLOS Computational Biology **14**:3 (2018) e1006046.

Epidemic fadeout

Peter Ballard[1], Nigel Bean[1,2], Alun Lloyd[3,4] and Joshua V. Ross[1,2]

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[3]*Department of Mathematics, North Carolina State University, USA*
[4]*Biomathematics Graduate Program, North Carolina State University, USA*

Outbreaks of infectious diseases can give rise to a large first wave of cases, followed by a period with a low level of cases, before seeing subsequent waves with dissipating amplitude leading to disease endemicity. In other outbreaks we see only the first wave of infection. Epidemic fadeout refers to this latter scenario, in which infection is eliminated in the trough following the first wave of an outbreak. I will discuss work that has led to a greater understanding of the probability of epidemic fadeout and use of interventions to maximise this probability. This includes results for directly-transmitted and vector-borne disease dynamics.

Wednesday, 11th September. 15:30-16:00, Coffee break. Waterside Café, Roger Stevens Level 6

Wednesday, 11th September. 16:00-17:05, Roger Stevens LT01. Chair: Thomas House

How can we use the probability of infection upon exposure to better characterise an ongoing immune response within the host?

Ada Yan[1], Pengxing Cao[2], Sophie Zaloumis[3], Julie Simpson[3], Steven Riley[1], Karen Laurie[4], James McCaw[2,3,5,6]

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[2]*School of Mathematics and Statistics, The University of Melbourne, Australia*
[3]*Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Australia*
[4]*WHO Collaborating Centre for Reference and Research on Influenza, Victorian Infectious Diseases Reference Laboratory, Peter Doherty Institute for Infection and Immunity, Australia; now at Sequirus*
[5]*Murdoch Children's Research Institute, The Royal Children's Hospital, Australia*
[6]*Victorian Infectious Diseases Reference Laboratory Epidemiology Unit, Peter Doherty Institute for Infection and Immunity, Australia*

An immune response from an ongoing or past infection can prevent an individual from becoming infected when exposed to the same or a different pathogen. We sought to understand this protection by conducting experiments using the ferret model of human influenza, measuring the viral load across primary and challenge infections while varying the time between exposures.

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Some animals became infected with the challenge virus while others did not, with the proportion infected varying systematically with the time between exposures. These data suggest that a stochastic within-host model is required to capture this behaviour.

First, I will present a method to calculate the probability of being infected given an exposure event, accounting for an ongoing immune response which is changing over time. This involves modelling the start of the challenge infection as a branching process with time-dependent parameters. Then, I will discuss how, if the main stochastic behaviour of interest is whether an infection is successful, a semi-deterministic model can be used to approximate the full stochastic infection model of infection. Each realisation of this model chooses between two deterministic trajectories, representing the viral load conditional on infection, and the viral load conditional on extinction. This choice is based on the probability of being infected given an exposure event, which can be calculated using the previously discussed method. This simplification enables one to write down the model likelihood and infer parameter values. Last, I will present preliminary results from fitting such a semi-deterministic model to data from the aforementioned ferret challenge experiments.

Bayesian inference for multi-strain epidemics with application to *Escherichia coli* O157:H7 in feedlot cattle

Panayiota Touloupou[1], Barbel Finkenstadt Rand[1], Thomas E. Besser[2], Nigel P. French[3], Simon E. F. Spencer[1]

[1]*Department of Statistics, University of Warwick*
[2]*Department Veterinary Microbiology and Pathology, Washington State University, Pullman, WA 99164, USA*
[3]*The New Zealand Food Safety Science and Research Centre, School of Veterinary Science, Massey University, Palmerston North, New Zealand*

For most pathogens testing procedures can be used to distinguish between different strains with which individuals are infected. Due to the growing availability of such data, multi-strain models have increased in popularity over the past few years. Quantifying the interactions between different strains of a pathogen is crucial in order to obtain a more complete understanding of the transmission process, but statistical methods for this type of problem are still in the early stages of development. Motivated by this demand, we construct a stochastic epidemic model that incorporates additional strain information and propose a statistical algorithm for efficient inference. The model improves upon existing methods in the sense that it allows for both imperfect diagnostic test sensitivities and strain misclassification. Extensive simulation studies were conducted in order to assess the performance of our method, while the utility of the developed methodology is demonstrated on data obtained from a longitudinal study of *Escherichia coli* O157:H7 strains in feedlot cattle.

Wednesday, 11th September. 17:05-18:30, Wine Reception. Waterside Café, Roger Stevens Level 6

Thursday, 12th September. 09:00-10:45, School of Mathematics, Level 8, MALLs. Chair: Joshua Ross

Modelling the influence of airflow on transmission of airborne infection in indoor environments

Catherine Noakes[1]

[1]*School of Civil Engineering, University of Leeds*

Airborne transmission is an infection route for many diseases including communicable infections such as TB and influenza, as well as opportunist pathogens in hospitals; in hospital environments it is of particular concern for immune compromised individuals. Quantifying risks are necessary to determine appropriate control strategies, both in terms of engineering approaches such as ventilation and management strategies such as treating, locating and scheduling patients. However airborne transmission is complex to evaluate as it requires understanding of the buidling airflows alongside the infection dynamics and human-environment interactions.

This presentation considers the relationships between airflow and infection transmission and the approaches that can be used to model airflows and engineering control strategies, and couple these with epidemic risk models. Examples are given from a number of projects to show how the airflow effects are more significant close to the source patient, and how models can be applied at ward level to explore the design and cost-effectiveness of engineering interventions. The paper also discusses how measurement of airflow during outbreaks is critical to being able to quantify the generation rate of airborne pathogens and hence develop effective infection dynamics models.

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Assessing the transmission of antibiotic resistant bacteria on human contact networks

Lulla Opatowski[1]

[1]University of Versailles Saint Quentin en Yvelines (UVSQ), Institut Pasteur, Inserm, Paris, France

Healthcare-associated infections with Multidrug resistant bacteria (MDR) represent a huge public health issue worldwide. Implementation of effective control measures is crucial for hospitals but can generate non-negligible disorganisation and costs. Designing efficient control measures is complex, due to the strong stochasticity of events in hospitals and our still limited understanding transmission routes of these pathogens. In this context, hypothesis driven mathematical models are particularly useful. They can help analyse MRB epidemics, estimate unknown parameters and simulate counterfactual scenarios to help implementing optimized control measure. In this talk I will present a series of studies in which we developed specific stochastic individual based models of MRB spread in hospitals to investigate the role of between-human contacts within and between wards on pathogen transmission. The first study focuses on the analysis of the between-ward dissemination of vancomycin-resistant *Enterococci* (VRE) in hospitals. Based on specific data extracted from a real outbreak in a French hospital and Bayesian inference, a spatially explicit model was built and used to assess the economic and human costs associated with a series of hypothetical scenarios of control measure implementation. The second study focuses on the analysis of methicillin-resistant *Staphylococcus aureus* (MRSA) transmission over a network of patients and health-care workers. Based on detailed contact-data collected using RFID log-censors in a French rehabilitation hospital, an agent-based model explicitly formalizing inter-individual contacts was built and used to analyse how contact-based control measures can help reducing the spread of MRB in hospitals.

A network epidemic model with preventive rewiring

David Sirl[1]

[1]*University of Nottingham, UK*

Network epidemic models have developed enormously in the last 20 years or so in response to some of the unrealistic assumptions of homogeneity in most simple epidemic models. A significant feature of most epidemic-on-a-network models is that the epidemic evolves on a static network. We consider an SIR (Susceptible→Infectious→Removed) epidemic spreading on a configuration-model network (a random network with specified degree distribution), with the addition of some simple network dynamics. The addition is to allow susceptible individuals to 'drop' connections to infectious neighbours. A further extension permits such susceptible individuals to then 'rewire' to connect instead with someone else in the population. Stochastic epidemic models very often exhibit threshold behaviour where epidemics starting with few infective individuals either die out rapidly or take off and infect a large fraction of the population, and these models are no exception! The focus here is mainly on further analysis of the supercritical case where the epidemic can/does 'take off'.

For the model with dropping only (i.e. with no rewiring), we present some limit theorems (in the limit of large population size) for the temporal evolution and for the final size of the epidemic (the number of initially susceptible individuals that are ultimately recovered). For the model with rewiring included too, we show that whilst the preventive behaviour of rewiring is always rational at the individual level, it may have negative consequences at the population level.
This work is joint with Frank Ball (Nottingham), Tom Britton (Stockholm) and KaYin Leung (Stockholm).

Thursday, 12th September. 10:45-11:15, Coffee break. School of Mathematics, Reading Room, Level 9

Thursday, 12th September. 11:15-12:45, School of Mathematics, Level 8, MALLs. Chair: Lulla Opatowski

The role of surfaces in the transmission of bioaerosols from source to patient in hospital rooms

Marco-Felipe King[1], P. Andrew Sleigh[1], Catherine J. Noakes[1]

[1]*School of Civil Engineering, University of Leeds*

Aerial dispersion of bioaerosols and subsequent contamination of surfaces is recognised as a potential transmission route for health-care acquired infections. Pathogens accrue on health-care workers (HCW) hands as they touch surfaces and can subsequently be transmitted to other patients.

Steady state computational fluid dynamic (CFD) simulations were used to predict bioaerosol deposition onto surfaces from a patient coughing regularly a) single and b) multi-bed hospital rooms. The prediction was validated using experimental data of *Staphylococcus aureus* bioaersol desposition in a climatically controlled chamber. A discrete-time Markov chain was fitted to observational data of 400 episodes of patient care and used to predict HCW surface contacts in a) and b). A mechanistic model of pathogen accretion on HCW hands was developed considering the physical parameters of transfer from surface-to-hands and vice-versa. A Monte-Carlo simulatoin was used to assess the effect of CFD deposition patterns in conjunction with the contact sequence patterns to predict the contamination levels of bacteria on HCWs hands as they perform patient care in the two rooms.

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Hand colonisation was found to depend sigifnicantly on patient care type, room layout and in particular on the spatial distribution of pathogens between surfaces, which is influenced by ventilation. During care within multi-bed rooms colonisation levels increase due to the spatial spread of microorganisms contaminating multiple patient surfaces caused by the ventilation strategy.

Modelling, Bayesian inference and model assessment for nosocomial pathogens using whole-genome-sequence data

R. Cassidy[1], T. Kypraios[1], P.D. O'Neill[1]

[1]*School of Mathematical Sciences, University of Nottingham*

Whole genome sequencing of pathogens in outbreaks of infectious disease provides the poten- tial to reconstruct transmission pathways and enhance the information contained in traditional epidemiological data. In recent years there have been numerous new methods and models developed to exploit such high-resolution genetic data. However, corresponding methods for model assessment have been largely overlooked. In this paper we develop both new modelling methods and new model assessment methods, specifically by building on the work of Worby et al. (2016). Although the methods are generic in nature, we focus specifically on nosocomial pathogens, and analyse a data set collected during an outbreak of MRSA in a hospital setting.

Complex contagions: a dynamical systems approach

Yi Ming Lai[1]

[1]*School of Mathematical Sciences, University of Nottingham*

Complex contagions refer to phenomena where multiple exposures to a spreading process are needed to activate or infect a node in a network. One popular model for these types of processes is the Watts threshold model, where each actor in the network switches from an inactive to an active state if a threshold fraction of its neighbours is active. We revisit this classical model using dynamical systems: each node on the network is governed by a differential equation driven by the state of its neighbours. Considering extremely fast dynamics, approximated by each node moving to its steady-state in a single 'step', recovers the Watts threshold model.

For more general time scales, we can use this new approach to gain additional insight into the temporal structure of these spreading processes or cascades. For example, this model has the additional property that higher numbers of active neighbours increase the rate of infection. On Newman–Watts small-world networks, we present an expression for the proportion of active nodes against time that is of logistic form, matching the "S-shaped" curves found widely in the literature. We find that on these networks, increasing the number of connections can reduce the mean path length and in turn speed up cascades. Conversely, on networks with already short mean path lengths (e.g. Erdős–Rényi $G(n, p)$ networks with $p \gg n^{-1}$), adding more connections can slow down a cascade.

This work is joint with Mason Porter (UCLA).

Thursday, 12th September. 12:45-13:45, Lunch. School of Mathematics, Reading Room, Level 9

Thursday, 12th September. 13:45-15:30, School of Mathematics, Level 8, MALLs. Chair: Marco-Felipe King

Comparative modelling of parasite population dynamics of two *Gyrodactylus* species

Clement Twumasi[1], Owen Jones[1], Joanne Cable[2]

[1]*School of Mathematics, Cardiff University*
[2]*School of Biosciences, Cardiff University*

Understanding fully host-parasite systems is challenging if employing just experimental approaches, whereas mathematical models can help uncover in-depth knowledge of the infection dynamics. The current study compares the infection dynamics of two parasite species (*Gyrodactylus turnbulli* and *Gyrodactylus bullatarudis*) across three host populations (ornamental, Lower Aripo and Upper Aripo fish), by developing a Continuous-time Markov Chain (CTMC) model. The model simulates the movement of parasites for two age groups over the external surfaces (eight body regions) of a fish over a 17-day infection period with population carrying capacity (dependant on host size and area of body regions). The model was parameterised by the birth, death and movement rates of young and older parasites, in the presence or absence of host's immune response. Host death was assumed to occur at a rate proportional to the total number of parasites on the fish. The CTMC simulation model was fitted using a novel Weighted-iterative Approximate Bayesian Computation (ABC). The findings from this study would help policy makers and biologists to better understand the *Gyrodactylus*-fish system using mathematical models and inform management decisions for the control of gyrodactylid infections.

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Hybrid frameworks for modelling stochastic biological processes

Kit Yates[1]

[1]*Department of Mathematical Sciences, University of Bath*

Spatial reaction-diffusion models have been employed to describe many emergent phenomena in biological systems. The modelling technique for reaction-diffusion systems that has predominated due to its analytical tractability and ease of simulation has been the use of partial differential equations (PDEs). However, due to recent advances in computational power, the simulation, and therefore postulation, of computationally intensive individual-based models has become a popular way to investigate the effects of noise in reaction-diffusion systems.

In a wide variety of biological situations, computationally-intensive, high-resolution models are relevant only in particular regions of the spatial domain. In other regions, coarser representations may suffice to capture the important dynamics. Such conditions necessitate the development of hybrid models in which some areas of the domain are modelled using a coarse-grained representation and others using a more fine-grained representation.

In this talk I will discuss recent work from my group on connecting coarse and fine representations of reaction-diffusion phenomena. The models to be coupled will include both on and off-lattice individual-based representations of diffusion with and without volume exclusion as well as macroscopic partial differential equations. In each scenario we will demonstrate good agreement between our hybrid models and the full individual-based representation whilst achieving significant computational savings.

IL-7 in naive T cell homeostasis: modelling at the molecular, cellular and population scales

Carmen Molina-París[1]

[1]*Department of Applied Mathematics, School of Mathematics, University of Leeds*

In this talk I will introduce a mathematical model of naive T cell homeostasis. The number of naive T cells in the peripheral pool is regulated by IL-7 signalling, and T cell receptor diversity is regulated by peptide-MHC signalling. The development of a mathematical model requires understanding the key molecular, cellular and population processes involved in peripheral naive T cell homeostasis. In order to do so, we make use of state-of-the-art experimental evidence to develop a model of IL-7 binding to its IL-7 receptor (IL-7R), internalisation, recycling, degradation, and synthesis. At the cellular level, we introduce the idea of survival and proliferation thresholds for naive T cells in the presence of IL-7. These elements allow us to define a population model of resting and cycling naive T cells, that includes the dynamics of extra-cellular IL-7. The model is then used to parameterise recent experiments by Hogan et al. (2013). We compare theoretical predictions with experimental ones.

Thursday, 12th September. 15:30-16:00, Coffee break. School of Mathematics, Reading Room, Level 9

Thursday, 12th September. 16:00-17:05, School of Mathematics, Level 8, MALLs. Chair: Kit Yates

The effects of individual non-heritable variation on fitness estimation and coexistence

Gabriela Gomes[1]

[1]*Liverpool School of Tropical Medicine*

Demographic theory and data have emphasized that non-heritable variation in individual frailty enables selection within cohorts, affecting the dynamics of a population while being invisible to its evolution. Here we include the component of individual variation in longevity or viability which is non-heritable in simple bacterial growth models and explore its ecological and evolutionary impacts. First, we find that this variation produces consistent trends in longevity differences between bacterial genotypes when measured across stress gradients. Given that direct measurements of longevity are inevitably biased due to the presence of this variation and ongoing selection, we propose the use of the trend itself for obtaining more exact inferences of genotypic fitness. Second, we show how species or strain coexistence can be enabled by non-heritable variation in longevity or viability. These general conclusions are likely to extend beyond bacterial systems.

Supported by MRC Medical Research Council Project MR/N014855/1 UNIVERSITY OF LEEDS

Approximate Bayesian Computation for infectious disease modelling: application to the 2004 measles outbreak in Malawi

Renata Retkute[1], Amanda Minter[2]

[1]*The Zeeman Institute for Systems Biology and Infectious Disease Epidemiology Research, University of Warwick, UK*
[2]*Centre for the Mathematical Modelling of Infectious Diseases, London School of Hygiene and Tropical Medicine, London, UK*

Approximate Bayesian Computation (ABC) techniques are a suite of model fitting methods which can be implemented when a likelihood function is intractable or not known. We compared the performance of the ABC rejection and ABC sequential Monte Carlo algorithms using stochastic model with age structure and the 2010 measles outbreak in Malawi data, consisting of weekly cases and percentage of cases in three age groups. We found that there is a trade-off between number of model runs, acceptance rate and effective sample size when choosing a number of runs per proposed parameter set and number of nearest neighbours for covariance matrix of the perturbation kernel. Our analysis indicates that having more then one model run increases computation burden and decreases the effective sample size, which can not be out-weighted by improvement in the overall acceptance rate.

Friday, 13th September. 09:00-10:45, School of Mathematics, Level 8, MALLs. Chair: Ada Yan

Capturing the quasi-stationary distribution within a deterministic framework for stochastic SIS dynamics

Kieran Sharkey[1], Christopher Overton[1], Robert Wilkinson[2]

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The stochastic SIS model represents an important class of epidemic dynamics, and is thought to accurately represent various processes, such as the spread of sexually transmitted diseases and computer viruses. A feature of this model is the existence of a single absorbing state, corresponding to the disease free state, to which the system will always converge for finite population sizes and disease transmission parameters. There has been a long history of deterministic representations of the SIS model. Relating these models to the stochastic dynamics frequently makes use of mean-field assumptions, which are derived from the infinite population limit. These models provide useful theoretical insight but do not feature the absorbing state, and therefore it is hard to link the insights back to the stochastic model.

In this work we develop novel methods to account for the absorbing state of the stochastic SIS model within a deterministic framework. We do this by deriving a deterministic approximation to the quasi-stationary distribution (QSD) of the model; i.e. the long-term steady state behaviour conditional on not having reached the absorbing state. In particular, we build a system of population-level equations, which when solved provide an accurate and efficient approximate to the QSD of the Markovian network-based SIS model for a large range of networks and parameter sets.

How many TCR clonotypes does a body maintain?

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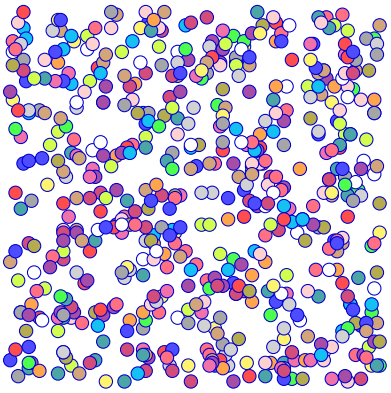
There are approximately 400000000000 naive CD4+ T cells in your body, about the same as the number of stars in our galaxy. The number of cells of one T-cell receptor (TCR) clonotype is an integer that increases or decreases by one cell at a time, as cells divide or die. New clonotypes are released from the thymus and compete with other clonotypes in the periphery for specific and non-specific resources.

Stochastic models of immune system dynamics, describing millions of cells that interact with each other and with their environment, are more realistic than deterministic ones. Estimates of distributions of times to clonal extinction are a way to estimate clonal sizes, and hence diversity, in adult mice and humans. For example, with the estimate that the ratio of thymic production to peripheral division is four percent, the model predicts that the number of distinct T-cell clonotypes in the human body is nine percent of the total number of T cells. Most clonotypes in a mouse may consist of just one or two T cells.

Supported by Project MR/N014855/1

How can realistic computational models of the T-cell repertoire be constructed? Which attributes of a cell are immutable, which can change reversibly and which only change in one direction? What are the lineages and spatial organisation of memory subsets? How are IL-2 and IL-7 resources shared out in homeostasis?



A novel stochastic multi-scale model of *Francisella tularensis* infection to predict risk of infection in a laboratory

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Francisella tularensis is a highly infectious gram-negative bacterium capable of causing a debilitating disease with as few as 10 organisms, and has been classified as a category A bioterrorism agent by the Centers for Disease Control and Prevention. Previous efforts to quantify the risk to a population associated with such biological agents have used classical dose response models that focus on the probability of response but make little reference to the underlying biological mechanisms or the time until response. I will present a multi-scale stochastic model for the within-phagocyte, within-host and population level infection dynamics of *Francisella tularensis*. The within-phagocyte model explicitly accounts for the experimentally observed distribution of rupture times for infected phagocytes, whilst linking within-phagocyte and within-host dynamics by means of a probability mass function for the number of bacteria released in rupture events. The within-host model is used to obtain the probability of response and mean response time of an infected individual as a function of initial infection dose. A Bayesian approach is applied to parametrise both the within-phagocyte and within-host models using infection data. Finally, it is shown how these dose response probabilities at the individual level can be used for estimating the airborne propagation of *Francisella tularensis* in a laboratory setting at the population level, by means of a deterministic zonal ventilation model.

Friday, 13th September. 10:45-11:15, Coffee break. School of Mathematics, Reading Room, Level 9

Friday, 13th September. 11:15-12:30, School of Mathematics, Level 8, MALLs. Chair: Martín López-García

Near-criticality in mathematical models of epidemics

Malwina Luczak[1]

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In an epidemic model, the basic reproduction number R_0 is a function of the parameters (such as infection rate) measuring disease infectivity. In a large population, if $R_0 > 1$, then the disease can spread and infect much of the population (supercritical epidemic); if $R_0 < 1$, then the disease will die out quickly (subcritical epidemic), with only few individuals infected.

For many epidemics, the dynamics are such that R_0 can cross the threshold from supercritical to subcritical (for instance, due to control measures such as vaccination) or from subcritical to supercritical (for instance, due to a virus mutation making it easier for it to infect hosts). Therefore, near-criticality can be thought of as a paradigm for disease emergence and eradication, and understanding near-critical phenomena is a key epidemiological challenge.

In this talk, we explore near-criticality in the context of some simple models of SIS (susceptible-infective-susceptible) epidemics in large homogeneous populations.

Supported by Project MR/N014855/1

Comparative analysis of different treatment options in the context of a stochastic intracellular model of a hepatitis B viral infection

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Hepatitis B virus is a major cause of liver cancer worldwide, making the development of anti-viral strategies against this virus a priority worldwide. I will present a new stochastic agent based model for the intracellular dynamics of a hepatitis B virus (HBV) infection that includes details on all essential steps of a viral life cycle, from viral entry to secretion of empty and complete virions, and subviral particles. In particular, my model includes unprecedented details of the virion assembly step based on our insights on the roles of packaging signals (PS) motifs in the pregenomic RNA (pgRNA), as well as on the formation of subviral particles. Using this set-up, I present a comparative analysis of different treatment options, including Geldanamycin, Nucleos(t)ide analogues, and Interferon-α. I will contrast these results with a recently developed strategy targeting the PSs, demonstrating the therapeutic potential of these novel virus assembly inhibitors.

Joint inference of severity and transmission of influenza from multiple dependent data sources

Alice Corbella[1], Anne Presanis[2], Paul J. Birrell[2,3] and Daniela De Angelis[2,3]

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Pandemic and seasonal outbreaks of influenza strongly threaten population health worldwide. Public Health England collects data on the daily/weekly counts of influenza cases at different levels of severity. These data streams jointly provide a noisy signal of the underlying transmission and severity process. Yet, counts from different data streams might be affected by unknown dependencies, generated by individuals detected multiple times at different levels of severity.

We propose a model to synthesize information from multiple data, and available prior information, to gain knowledge on the transmission and the severity of seasonal influenza. The model comprises a deterministic transmission model and a stochastic severity and detection model. The likelihood of multiple dependent data is not available in closed form; hence, we propose an algorithm to draw inference when data are dependent. We show via simulation that alternative methods that ignore the dependence across data streams, while accelerating computations, provide over-precise estimates of the parameters.

This joint model is fit to four datasets from the 2017/18 influenza season leading to a comprehensive description of the magnitude of the underlying epidemic, and of the burden on health facilities.

The model proposed is original in that it preserves a deterministic transmission model, that describes well seasonal influenza epidemics on large populations, while including a stochastic severity model. The model is equipped with a corresponding inferential method for exact inference. The analysis of real data proves the value of the methods proposed, providing estimates of indexes useful for policy planning and intervention.

Friday, 13th September. 12:30-13:30, Lunch & End. School of Mathematics, Reading Room, Level 9