Parallel Session

Epidemiology IV

MATHEMATICAL MODELLING OF P. AERUGINOSA TRANSMISSION ROUTES IN INTENSIVE-CARE UNITS

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Keywords: Mathematical disease modelling, Infectious disease dynamics and control, Bayesian methods.

Pseudomonas aeruginosa is an important cause of healthcare-associated infections, particularly in critically ill or immunocompromised patients. Understanding the dynamics of P. aeruginosa transmission within intensive care units (ICUs) is crucial for devising and evaluating successful control strategies.

Pseudomonas infections are caused by strains of bacteria found widely in the environment. Hence, environmental contamination is likely to play an important role within the transmission process. However, there is little quantitative evidence in the scientific literature regarding the contribution of environmental contamination to the transmission of P. aeruginosa within ICUs.

Various mathematical transmission models are used to study the relative importance of transmission routes of P. aeruginosa infections among ICU patients. Other model-based studies investigating the impact of contaminated surfaces to the acquisition of other microorganisms (e. g. [1, 2]) rely on deploying specific values for model parameters derived from the literature. Our aim is to use only longitudinal data and therefore to allow the model to estimate all transmission parameters.

An epidemic model, where patients can be either colonized or susceptible, was used. Once colonized, patients remain colonized. In a first step, two acquisitions routes were considered. The endogenous route is independent of other patients and may be due to antibiotic selection pressure. Cross-transmission, usually occurring via temporarily contaminated hands of HCWs, is proportional to the fraction of colonizations in wards. Subsequently, we considered models additionally including environmental contamination. It is modeled by either one pool of bacterial load linked to contaminated objects in the room or by assuming that only prior bed occupants shedding resistant organisms have a direct impact on the risk of acquisition to subsequent bed occupants. Furthermore, incorporating information about covariates such as age and sex into the transmission models may improve the quality of

estimating the contribution of each route.
Transmission may be reflected in fluctuations of the observed prevalence of colonizations. Predominance of the endogenous route is represented by regression back to the mean. When cross-transmission is important, the acquisition risk for uncolonized patients is high if the prevalence is high and the prevalence is likely to remain high. Fluctuations due to environmental contamination are expected to be in between the two other routes.
Based on a data-augmented MCMC method by [3] the relative importance of the considered acquisition routes are determined using epidemiological data from two ICUs in France. The data was collected within the time period 20/04/1999 - 03/04/2017 and consists of over 8000 patients per ICU. The analysis is performed for both ICUs separately. Information about the admission and discharge day, culture days and results are used as input data for the analysis.
Preliminary results suggest that among cross-transmission and endogenous transmission, the latter one is the prevalent route in both ICUs – with approximately 72% and 84% relative importance respectively. Adding a general pool of bacterial load as environmental contamination to the model did not have a substantial impact on the results. In both ICUs only about 3% of the total transmissions were due to the environment.

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EXPLOITING THE ANTIBIOTIC-INDUCED MORPHOLOGICAL TRANSITION OF *PSEUDOMONAS AERUGINOSA*

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Keywords: Antimicrobial resistance, Pseudomonas aeruginosa, Differential equations.

We present a differential equation model describing the growth dynamics of the pathogenic bacterium *Pseudomonas aeruginosa* in the presence of the β-lactam antibiotic meropenem. Experimental evidence indicates that a subpopulation of the *P. aeruginosa* cells will transition in shape to evade the action of this antibiotic, i.e. form a persistent population. By accounting for this shape transition (and estimating parameters from experimental data) we have developed a model that matches experimental findings. We suggest therapeutic strategies to tackle this persistent population and provide strong theoretical evidence for the potential of using antimicrobial peptides in combination with meropenem.

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A UNIFIED STOCHASTIC MODELLING FRAMEWORK FOR THE SPREAD OF NOSOCOMIAL INFECTIONS

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Keywords: Hospital-acquired or nosocomial infections, Antibiotic resistant bacteria, Infection control, Stochastic model, Reproduction number.

Over the last years, a number of stochastic models have been proposed for analysing the spread of nosocomial infections in hospital settings. These models often account for a number of factors governing the spread dynamics: spontaneous patient colonization, patient-staff contamination/colonization, environmental contamination, patient cohorting, or health-care workers (HCWs) hand-washing compliance levels. For each model, tailor-designed methods are implemented in order to analyse the dynamics of the nosocomial outbreak, usually by means of studying quantities of interest such as the reproduction number of each agent in the hospital ward, which is usually computed by means of stochastic simulations or deterministic approximations. In this work, we propose a highly versatile stochastic modelling framework that can account for all these factors simultaneously, and analyse the reproduction number of each agent at the hospital ward during a nosocomial outbreak, in an exact and analytical way. By means of five representative case studies, we show how this unified modelling framework comprehends, as particular cases, many of the existing models in the literature. We implement various numerical studies via which we: i) highlight the importance of maintaining high hand-hygiene compliance levels by HCWs, ii) support infection control strategies including to improve environmental cleaning during an outbreak, and iii) show the potential of some HCWs to act as super-spreaders during nosocomial outbreaks.

Acknowledgements: This research is funded by the Medical Research Council, through a Skills Development Fellowship (reference number MR/N014855/1)

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USING PREDICTIVE MODELS TO OPTIMISE THE TREATMENT OF BACTERIAL INFECTIONS: COMBINING A NOVEL ANTI-VIRULENCE THERAPY WITH ANTIBIOTICS

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Keywords: Ordinary Differential Equations (ODEs), Microbiology, Pseudomonas aeruginosa, Anti-adhesion, Burn wound.

As the development of new classes of antibiotics slows, bacterial resistance to existing antibiotics is becoming an increasing problem. A potential solution is to develop treatment strategies with an alternative mode of action. In this talk, we consider one such strategy: anti-adhesion therapy. Whereas antibiotics act directly upon bacteria, either killing them or inhibiting their growth, anti-adhesion therapy works by competitively inhibiting the binding of bacteria to host cells. This prevents the bacteria from deploying their arsenal of virulence mechanisms, while simultaneously rendering them more susceptible to natural clearance. Previously, we developed mathematical models to describe the anti-adhesion treatment of a Pseudomonas aeruginosa burn wound infection in the rat. Our models predicted that, when used in isolation, anti-adhesion therapy can at best reduce the bacterial burden, whereas elimination of all bacteria may be possible when combined with regular debridement. In this presentation, we extend our mathematical models to include treatment with antibiotics, using them to predict the optimum treatment regimes for this combination therapy.

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MODELING THE DYNAMICS OF ANTIMICROBIAL RESISTANCE IN A MORBIDOSTAT

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Keywords: Bacterial Resistance, Morbidostat, Antimicrobial Resistance.

The emergence of resistance to antimicrobials (including antibiotics and biocides) is a complex process that is usually modeled based on batch dynamics of microbial growth. Population numbers (biomass), phase of microbial growth and environment, therefore, change during the experiment, being difficult to develop simple mathematical models capturing the relevant dynamics of resistance.

We are currently building a morbidostat: a device build to culture cells maintaining a constant number of cells at the same stage of growth. In this contribution we focus on the *in silico* experiments to study the dynamic behavior of this morbidostat.

The system specifications and operating conditions are defined after the morbidostat setup described in [1]. The injection of a volume of 1 mL of medium with substrate is made periodically into a small lab-scale morbidostat where the culture medium level is kept constant with a dilution rate half of the maximum specific growth rate. When the injection is to be performed, if the biomass increases and is above a given threshold, a medium with the antimicrobial and the substrate is injected. Otherwise, only medium with substrate is injected. The main goal is to record data on the time variation of biomass concentration in the morbidostat.

In this *in silico* study, the formulation of the dynamic model of the morbidostat is made of three ordinary differential equations (ODEs). It takes into consideration the global mass balance to the culture medium, and the partial balances to the biomass and to the substrate. We assume the specific growth rate of the bacteria takes the classical form of Monod law in function of the concentration of substrate.

To model the effect of the antimicrobial we consider two approaches. Firstly, we consider the modeling approach proposed by [2, 3]. Here the growth term in the biomass balance equation is modified to take into account the periodic effect of the antimicrobial injection. We used a similar form to the exponential decaying function proposed by [2] in the context of the mathematical modeling of periodic chemotherapy with drug resistance. Simulation

results are presented to describe the hypothetical bacteria antimicrobial resistance evolution. In the second approach we propose a continuous time model that is included directly in the set of ODEs adding a fourth ODE. This equation is of first oder and it represents the effect of the antimicrobial in function of the concentration of drug in the culture medium inside the morbidostat. It is a time-varying model with two parameters: the time-varying gain or sensitivity to the drug, $K(t)$, and a time constant, τ_1, that is assumed constant. The sensitivity is a decaying exponential function given by $K(t) = \exp(-t/\tau_2)/D_{\text{in}}$, where τ_2 is a time constant and D_{in} is the inlet feed antimicrobial concentration in the morbidostat system. Overall, the proposed continuous time model has two parameters (two time constants) to fit to experimental data. Simulation results are presented to illustrate the application of this conceptual and quite straightforward modeling approach in order to describe the dynamics of the effect of antimicrobial in bacteria.

Acknowledgements: The 1st and 3rd authors acknowledge financial support from the Spanish Government (MINECO) and the European Regional Development Fund (ERDF) through the project "RESISTANCE" (DPI2014-54085-JIN).

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