MINISYMPOSIUM

HOW TO DESIGN EVOLUTION-PROOF PUBLIC HEALTH INTERVENTIONS?

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In his Nobel prize lecture on December 11, 1945 Alexander Fleming warned against the risk of 'making' microbes resistant to penicillin. Unfortunately, it was only recently that the World Health Organisation recognized this risk and even eventually admitted that the use of any anti-microbial agent will eventually select for resistance (Read *et al.* 2011, *PNAS*). Although they appear as more robust to parasite evolution, vaccination campaigns also act as major selective pressures on parasites (Day & Gandon 2008, *Vaccine*). The case of Marek Disease Virus in poultry shows that failure to anticipate such evolution can have dramatic consequences (Read *et al.* 2015, *PLoS Biol*).

Mathematical biology has a pivotal role to play in reconciling microbiology and epidemiology with evolutionary biology (Alizon & Méthot, *in press PLoS Biol*). At the within-host level, kinetics models can help us determine optimal treatment protocoles to maximise the time before drug resistance evolve. At the between-host level, epidemiological models can include resistance both for prophylactic and therapeutic interventions. A key challenge consists in combining both these scales in a nested perspective (Mideo *et al.* 2008, *TREE*).

These call for a variety of mathematical and simulation models. For instance, early stages of an infection or of an outbreak typically require to account for stochastic dynamics. Conversely, large scale epidemics or full blown infections allow for the use of analytical models, which open perspectives for more thorough analyses.

From a more technical standpoint, the search for optimal strategies has led to the application of optimal control theory, either at the epidemiological level (Hansen & Day 2012 *Proc B*) or at the within-host level Pena-Miller *et al.* 2012, *J R Soc Interface*.

In terms of data, these models have classically relied on incidence time series but with the advent of next generation sequencing, genetic data is not become more and more valuable, as illustrated by the field of phylodynamics (Volz *et al.* 2013, *PLoS Comput Biol*).

The speakers of this minisymposium will present recent modelling approaches developed both at the within-host and between-host level in order to understand how public health policies and treatments protocoles impact microbial evolution. The ambition of the mini-symposium is to determine whether it is possible to realistically devise intervention strategies that are robust to microbial evolution.

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MATHEMATICAL PERSPECTIVES ON HOST IMMUNITY AND ANTIBIOTIC TREATMENT

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Keywords: Antibiotics, Immunity, Within-host dynamics, Resistance, Treatment.

Antimicrobial resistance of infectious agents is a growing problem worldwide. To prevent the continuing selection and spread of drug resistance, rational design of antibiotic treatment is needed, and the question of aggressive vs. moderate therapies is currently heatedly debated. Host immunity is an important, but often-overlooked factor in the clearance of drug-resistant infections. In this work, we compare aggressive and moderate antibiotic treatment, accounting for host immunity effects. We use mathematical modelling of within-host infection dynamics to study the interplay between pathogen-dependent host immune responses and antibiotic treatment. We compare classical (fixed dose and duration) and adaptive (coupled to pathogen load) treatment regimes, exploring systematically infection outcomes such as time to clearance, immunopathology, host immunization, and selection of resistant bacteria. Our analysis and simulations uncover effective treatment strategies that promote synergy between the host immune system and the antimicrobial drug in clearing infection. Both in classical and adaptive treatment, we quantify how treatment timing and the strength of the immune response determine the success of moderate therapies. We explain key parameters and dimensions, where an adaptive regime differs from classical treatment, bringing new insight into the ongoing debate of resistance management. Emphasizing the sensitivity of treatment outcomes to the balance between external antibiotic intervention and endogenous natural defenses, our study calls for more empirical attention to host immunity processes.

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WHY DOES DRUG RESISTANCE READILY EVOLVE BUT VACCINE RESISTANCE DOES NOT?

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Keywords: Vaccination, Chemotherapy, Evolution, Resistance, Epidemiology.

Why is drug resistance common and vaccine resistance rare? Drugs and vaccines both impose substantial pressure on pathogen populations to evolve resistance and indeed, drug resistance typically emerges soon after the introduction of a drug. But vaccine resistance has only rarely emerged. Using well-established principles of population genetics and evolutionary ecology, we argue that two key differences between vaccines and drugs explain why vaccines have so far proved more robust against evolution than drugs. First, vaccines tend to work prophylactically while drugs tend to work therapeutically. Second, vaccines tend to induce immune responses against multiple targets on a pathogen while drugs tend to target very few. Consequently, pathogen populations generate less variation for vaccine resistance than they do for drug resistance, and selection has fewer opportunities to act on that variation. When vaccine resistance has evolved, these generalities have been violated. With careful forethought, it may be possible to identify vaccines at risk of failure even before they are introduced.

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MULTIPLE INFECTIONS ON NETWORKS

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Keywords: Networks, Multiple infections, Individual-based models, Vaccination.

Network models have played a pivotal role in highlighting the impact of contact heterogeneity on epidemic outcome. For many pathogens (e.g. HPV), infections with multiple strains within a host impose important ecological constraints (e.g. immunity, host cell competition) for transmission. To investigate the interplay of contact heterogeneity and intra-host competition, we develop an individual-based network model of multiple infections for both transient and persistent epidemics. Depending on strain interaction patterns and network topologies, we evaluate ecological diversity and infection barcodes. Finally, we discuss applications to vaccine-induced strain replacement.

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TOWARDS SIMULATION OF INTER-HOSPITAL SPREAD OF MULTIDRUG-RESISTANT ENTEROBACTERIACEAE BASED ON REAL HEALTHCARE SYSTEM DATA

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Keywords: Multidrug-resistant Enterobacteriaceae, Hospital network model, Healthcare data analysis, Patient transfers.

Recently multidrug-resistant Enterobacteriaceae (MDR-E) have become a major public health threat in many European countries. While traditional infection control strategies primarily target the containment of intra-hospital transmission, there is growing evidence highlighting the importance of inter-hospital patient traffic for the spread of MDR-E within healthcare systems.

We propose a network model, which reflects a patient traffic in healthcare system and thus provide the framework to systematic study of transmission dynamics of MDR-E and the effectiveness of infection control strategies to contain their spread within healthcare systems. However, to do that first it is necessary to analyse real patients' hospitalization data. They serve as a base for the network model reflecting the complexity of the real hospital network connections and dynamics of patient transfers between healthcare facilities.

In healthcare systems there is a strong emphasis on the privacy of patients thus, hospitalization records available for researchers are limited. We would like to present some examples and to demonstrate what are the problems and limitations with derivation of a patient transmission network from these data and how to overcome them. Examples of such networks will be presented. Also we would like to examine possible extensions of considered model taking into account additional effects like indirect transfers of patients staying in society for a certain period of time between dismisses and next admissions.

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