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Minisymposium “**Immuno-epidemiological models**”

Program and abstract

Thursday, June 19, 2014

9.00-9.30 Christiaan H. van Dorp

Modelling HIV virulence evolution in the context of immune escape

9.30-10.00 Roland R. Regoes

Disentangling human tolerance and resistance against HIV

10.30-11.00 Akira Sasaki

The coevolution of human antiviral protein APOBEC3G and HIV protein Vif: A theoretical study

11.00-11.30 Zhilan Feng

Backward bifurcations in a model coupling within-host and between-host dynamics

11.40-12.00 Fabio Luciani

Immunology and epidemiology of hepatitis C virus: plenty of data for a nested model approach

12.00-12.20 Giorgio Guzzetta

Identifying host immune factors that drive epidemic dynamics in a multi-scale model of tuberculosis

12.20-12.40 Wilfred de Graaf,

Combining a within host model for immune response and waning immunity with a population level transmission model

12.40-13.00 Andrea Pugliese

An immuno-epidemiological model coupling within-host dynamics and between-hosts transmission

Organizers: Odo Diekmann and Andrea Pugliese

ABSTRACTS

Modelling HIV virulence evolution in the context of immune escape

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A pathogen like HIV evolves rapidly under multiple levels of selection, and has to cope with a heterogeneous host population. Although these aspects have been studied before, the true nature of host-heterogeneity has not been addressed to our satisfaction. During (untreated) infection, HIV evades cellular immune responses and because of the massive polymorphism of the Human Leukocyte Antigen, the targets of these responses (epitopes) differ strongly between hosts.

Supported by data, it has been suggested that HIV has evolved virulence levels that are optimal for transmission. Some models indeed predict this, but others caution that this mode of adaptation is not self-evident, mostly due to the short-sightedness of evolution during the infection of an individual host. Several theories have been proposed to better explain the evolution of virulence, and we aim to contribute to these attempts.

We are developing a model of HIV's evolutionary dynamics that is highly detailed and realistic, and captures the interesting features of host-heterogeneity, immune escape and compensatory mutations, and selection on multiple levels. We hypothesise that these properties might be sufficient to explain HIV's observed virulence distribution.

Disentangling human tolerance and resistance against HIV

Roland R. Regoes, Paul J. McLaren, Manuel Battegay, Enos Bernasconi, Alexandra Calmy, Huldrych F. Günthard, Matthias Hoffmann, Andri Rauch, Amalio Telenti, Jacques Fellay and the Swiss HIV Cohort Study

In evolutionary ecology, "tolerance" is defined as an evolutionary response of a host population against pathogen pressure, which is characterized by the lack of pathogenesis despite high pathogen loads. To-date tolerance has not been quantified and disentangled from host resistance in any clinically relevant infection of humans. Using data from the Swiss HIV Cohort Study, we studied if there is variation in tolerance to HIV in humans. We found that tolerance differs significantly across Human Leukocyte Antigen B (HLA-B) genotypes, while classical protective HLA-B alleles are associated with resistance but not with tolerance. Furthermore, we found increased tolerance against HIV in HLA-B heterozygotes and young individuals. Thus, tolerance is a feature of infection with HIV, and the identification of the mechanisms involved may pave the way to new treatment approaches.

The coevolution of human antiviral protein APOBEC3G and HIV protein Vif: A theoretical study

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Apolipoprotein B mRNA-editing, catalytic polypeptide-like 3 G (A3G) is a key protein in human innate immune defense against human immune deficiency virus-1 (HIV-1). It induces G-to-A hypermutation in HIV cDNA to stop the viral replication in the infected cell. A viral infectivity factor (Vif) of HIV-1 is a countermeasure against A3G by binding A3G, thereby rolling the viral mutation rate back to below the error threshold. A simple mathematical model for the coevolution of A3G and Vif expression levels predicts coevolutionary cycles that are made up of a phase of the co-escalation of A3G and Vif expression levels and a phase of their co-deceleration. In the co-escalation phase, the hosts try to push up the viral mutation rate towards the error catastrophe by increasing A3G expression level, and viruses try to mitigate it by increasing Vif expression level. In the co-deceleration phase, the hosts try to pull down viral mutation rate to slow down the speed of the antigenic escape from immune response, and viruses try to enhance its mutability by decreasing Vif expression levels. We discuss the other coevolutionary outcomes and the condition for their occurrences in the parameter space. A more microscopic model for Vif expression regulation through the modification of multiple splicing rate is also discussed.

Backward bifurcations in a model coupling within-host and between-host dynamics

Zhilan Feng, Purdue University

Analysis of a mathematical model that couples explicitly the within-host and between-host dynamics in an environmentally-driven infectious disease will be presented. The within-host sub-system is linked to a contaminated environment (E) via an inoculation rate $g(E)$ for the hosts. The within-host parasite load $V(E)$ can affect the environment contamination, which directly contributes to the infection rate of hosts for the between-host sub-system. When the two sub-systems are considered in isolation (i.e., $g(E)=0$), the dynamics are standard and simple. That is, either the infection-free equilibrium is stable or a unique positive equilibrium is stable depending on the relevant reproduction number being less or greater than 1. However, when the two sub-systems are explicitly coupled (i.e., $g(E)>0$), the full system exhibits more complex dynamics including backward bifurcations; that is, multiple positive equilibria can exist with one of which being stable even when the relevant reproduction number is less than 1. Analytic results are obtained which help determine the conditions for various bifurcations as well as global dynamics of the sub-systems. The analysis is carried out by separating the fast and slow variables based on the fact that the immunological and epidemiological processes occur on very different time scales, which provides the possibility to use tools from singular perturbation theory. Numerical simulations of the full system confirm the analytic results.

Immunology and epidemiology of hepatitis C virus: plenty of data for a nested model approach.

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Introductions

Hepatitis C virus (HCV) evolves rapidly to escape host selective pressures. It is known that innate immune responses mediated by NK cells, HCV-specific neutralizing antibodies (NAbs), as well as T cell responses are critical determinants of the outcome of infection. HCV can be naturally cleared in 30% of the infected people, thus offering the unique opportunity to study the mechanisms with which the host immune response successfully drive viral clearance, or unsuccessfully lead to chronic infections and hence to the larger spread of the disease. Recent data showed that both host and viral genetic factors strongly affect the outcome of the infection. For instance, viral genome mutations have been discovered to drive immune escape, while host genetic polymorphisms in the Interferon Lambda $\lambda 3$ region predicts viral clearance. Furthermore, the highly polymorphic HLA genes also drive the probability of viral recognition and consequently the probability of T cell response specific against evolving variants.

Results

Here I argue that the vast data set generated during the last decade, and the dichotomous outcome of this infection offer an ideal model to study how within host immunological and genetic factors affect the success of a viral infection, and ultimately its spread at the epidemiological level. These arguments can then be expanded to other rapidly mutating pathogens that cause chronic infection in humans. Here I will also review some experimental and theoretical work pointing towards this goal. I will present some phylogenetics analyses on viral sequences showing that viral genomes carry heritable traits, which affect disease outcome. Also, I will review recent experimental data convincingly showing the strong role played by host genetic factors in driving the success of the host immune response.

Conclusions

The lack of a vaccine for rapidly mutating viruses causing chronic infections (e.g. HIV, HCV) or their limited efficacy (Influenza) rely on the extreme and rapid adaptation dynamics of these viruses at both within and between host levels. Therefore, mathematical modeling that nest within-host into epidemiological models with the vast data available can now be developed to understand and eventually predict outcome of diseases.

Identifying host immune factors that drive epidemic dynamics in a multi-scale model of tuberculosis

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When a pathogen is transmitted from an infected individual to a susceptible host, many complex factors influence the outcome of transmission: whether the pathogen will cause disease, what are the lengths of latent and infectious periods, if protective immunity will arise and how long will immunity last (memory). Transmission models of disease are numerous and capture many epidemiological aspects. However, broad individual variability exists, that in classical compartmental models is captured by assuming Poisson processes for transitions between epidemiological states (e.g. infectious to removed). Using multi-scale models that explicitly account for the dynamics of host-specific immune responses operating in the population scale can allow a finer-grained description of outcomes of infection and ultimately a better understanding of transmission dynamics. In this study, we propose a multi-scale model for Mycobacterium Tuberculosis (Mtb), the bacterium that causes tuberculosis (TB). The multi-scale model bridges together two existing models: a socio-demographic, individual based model for TB transmission dynamics, and a mechanistic, validated ODE model for host Mtb immune response, expressly adapted for multi-scale integration. Changes to individual epidemiological status are driven by state variables of host immune response (such as bacterial load), whose value over time is determined in an ODE model by two classes of factors: i) characteristics of the infection episode and ii) host immune specific characteristics. The multi-scale model is calibrated against epidemiological data on TB incidence (both over time and by age) in a low burden demographic setting and the predicted age-specific frequency and timing of infection outcomes is compared with currently used estimates in epidemiological models. Relations between host immune factors, their distribution in the population and relevant aspects of TB epidemic dynamics are identified by multivariate sensitivity analysis. Finally, we discuss possible applications of the model for improved understanding of TB epidemiology and disease control.

Combining a within host model for immune response and waning immunity with a population level transmission model

Wilfred de Graaf, Utrecht University

We present a simple phenomenological within-host model describing both the interaction between a pathogen and the immune system and the waning of immunity after clearing of the pathogen. We implement the model into a Bayesian hierarchical framework to estimate its parameters for pertussis using Markov chain Monte Carlo methods. We identify a threshold antibody level that separates a large increase in antibody level upon infection from a small increase and accordingly might be interpreted as a threshold separating clinical from subclinical infections. To study the effects of immune structure on population level prevalence we implement the within-host model at the individual level as a building block into a population level transmission model. For the case of very short infections and a constant force of infection this leads to a relatively simple linear first order partial differential equation. Using a generation expansion we compute the age-dependent ratio of the probability of observing a symptomatic infection in the individual host in a next infection event to the probability of observing an asymptomatic infection.

An immuno-epidemiological model coupling within-host dynamics and between-hosts transmission

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Several recent papers have introduced explicit modelling of hosts' immune response in epidemic dynamics, giving rise to "nested epidemic models" especially in order to discuss the evolution of hosts and pathogens [1,2]. If, as assumed in [1], pathogen load at infection is fixed, the model can reduce to an age-of-infection structure, and its qualitative behaviour follows the usual properties of epidemic models, although host heterogeneity in within-host parameters can give rise to relevant evolutionary consequences [3].

On the other hand, if initial infection load depends on the pathogen load of the individual from whom the infection is acquired, the models become much more complex; we present a mathematical framework to handle this case, although some open problems remain.

We have also performed several numerical simulations for the case of a single epidemic wave in a closed population, with different values of the parameters concerning pathogen transmission and isolation of the diseased individuals. Our aims have been, on the one hand, to understand the effects of these parameters on macroscopic features such as R_0 , final size or mean duration of the epidemics; on the other hand, to compare the model results with those of simpler SIR or SEIR models, matched as for the values of R_0 , mean length of infectious or latent periods, as could be estimated from the simulations.

A clear difference between models is that the present model yields an epidemic curve to which several smaller waves are in contrast with classical unimodal curve of epidemic models.

Extending the model to endemic infections poses the problem of an effective way to model reinfections, without arriving at an intractable model. Some possible ways of simplifying the problems will be suggested.

REFERENCES

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