Disease Dynamics 2008 - Talk Abstracts

Sally Blower, University of California - Los Angeles

Sex & HIV prevention: when is it better to be a man?

Vaginal microbicides, designed to prevent HIV infection in women, are currently considered the most promising biomedical intervention. Large-scale clinical efficacy trials of second-generation microbicides have just begun; if shown to be effective they could be licensed within 5-10 years. Since these microbicides contain antiretrovirals (ARV) it is anticipated they will be highly effective. However there is considerable concern that, if used by HIV-positive women, ARV resistance may evolve. By developing a novel mathematical model we show that planned trial designs could mask resistance risks and therefore enable high-risk microbicides to pass clinical testing. We then parameterize a transmission model using epidemiological, clinical and behavioral data to predict the consequences of wide-scale usage of high-risk microbicides in a heterosexual population. Paradoxically we show reducing an individual's risk of resistance during a trial could lead to unexpectedly high rates of resistance afterwards when microbicides are used in public health interventions. We also find that, surprisingly, although microbicides will be used by women to protect themselves against infection they could be of greater benefit to men. More infections in men, than women, will be prevented if there is a high probability that the drugs are systemically absorbed and/or microbicides are less than 50% effective and/or used on less than ∼60% of days. Men will always benefit more than women in terms of infections prevented per resistant case; but their advantage decreases as the relative fitness of drug-resistant strains increases. Population-level consequences of public health interventions based on ARV-based microbicides could well be surprising.

David Earn, McMaster University

The Great Plague of London

The Great Plague of London, which claimed the lives of one fifth of London's population in 1665, is one of the most famous epidemics of all time. We have recently digitized the mortality records for London during the Great Plague, yielding weekly data for each of the 130 parishes. I will describe the temporal and spatial dynamics of the plague, and discuss our efforts to estimate the transmissibility of the infectious agent. I will also briefly describe other projects in progress inspired by disease-specific mortality records for London over the past 650 years.

Jane Heffernan, York University

HIV Variability and Resistance in Drug Therapy

Viral load and CD4 T-cell counts in patients infected with HIV are commonly used to guide clinical decisions regarding drug therapy or to assess therapeutic outcomes in clinical trials. However, random fluctuations in CD4 T-cell count and viral load, due solely to the stochastic nature of HIV infection, can obscure clinically significant change. We have employed a Monte Carlo simulation to investigate the contributing factors in the expected variability in CD4 T-cell count and viral load. The simulation proceeds at the level of individual cells and HIV virions, thus capturing the inherent stochasticity in viral replication and T-cell infection, something that is ignored in the typical deterministic model of HIV infection. It is evident that the natural variability in HIV infection will have an effect on the emergence of drug resistant mutants. Fluctuations in CD4 T-cell count and viral load influence the number of productively infected T-cells at the current time, which, in turn, affect the probability that drug resistant mutants will be produced. Recently, Smith developed a model of impulsive differential equations that assesses adherence to antiretroviral therapy and the emergence of resistance, determining the mean number of doses that can be missed before resistance emerges. We have extended the Monte Carlo simulation to study the variability in these drug holidays.

Timothy Reluga, Penn State University

Behavior, Immunity, and Bistability in Simple Epidemiology Models

In classical SIR models, asymptotic dynamics can easily be summarized in terms of a single global attractor. However, a number of theoretical studies in the last decade have been shown that epidemic models can have atleast two locally stable solutions for some biologically reasonable ranges of parameters. This bistability may have important repercussions for public

health policy and epidemic preparedness because it may lead to rapid and unexpected changes in state. However, our understanding of the mechanisms creating bistability remains fuzzy. One potential cause of bistability is natural variation in resistance level through behavior or acquired immunity. In this talk, I'll discuss some mathematical models of resistance. These models indicate that behavior changes can easily induce bistability through backward bifurcations, but that acquired immunity can not create backward bifurcations and can only create bistability under extreme conditions.

Fred Brauer, University of British Columbia

Age of Infection Epidemic Models

Age of infection models provide a formulation for epidemic models that includes an arbitrary number of compartments, including selection of some individuals from a compartment for treatment, as well as arbitrary distributions of stay in each compartment. We give a procedure for calculating the reproduction number for such a model and establish a final size relation to give the extent of the epidemic. We show how to extend the results to models with heterogeneous mixing. Part of this work is joint with Christine K. Yang, and another part is joint with James Watmough.

Troy Day, Queen's University

Modeling The Evolutionary Biology of Autoimmune Disease

Autoimmune diseases arises when an individual's adaptive immune response incorrectly targets self-tissue, resulting in a variety of pathologies. One theory for the occurrence of autoimmune disease posits that pathogens who mimic host peptides elicit autoimmune responses when they cause infections. I will present some simple mathematical models for the coevolution of such molecular mimicry and the vertebrate immune system, to better understand the plausibility of this hypothesis.

Eric Arts, Case Western Reserve University

A defined role for mathematical models to test possible causal relationships of ex vivo HIV-1 phenotypic parameters on disease progression and global spread of the epidemic

A primate lentivirus was successfully introduced into the human population from chimpanzees approximately 60 to 80 years. During this time, the major (M) group of HIV-1 has evolved into ten distinct subtypes, undergone countless recombination events, diversified beyond any known pathogen, and established infection in 70 million humans. Although much is known about the molecular evolution and epidemiology in the human population, few studies have explored possible phenotypic differences among or within HIV-1 subtypes and if these differences could impact on virulence and differential spread in the human population. By performing thousands of pairwise competitions between viruses of different HIV-1 subtypes, it is clear that subtype C HIV-1 isolates are less fit than any other group M subtype in human peripheral blood mononuclear cells (termed pathogenic fitness). Coupled with these observations, we and others have described a direct correlation between ex vivo replicative fitness in PBMC with the rate of disease progression.

To test the impact of these ex vivo observations, we have monitored over 250 subtype A, C, or D infected Ugandan and Zimbabwean women, enrolled at the stage of acute infection and then followed for a mean of five years. To summarize years of data collection and analyses on various clinical manifestations, sexual activity, clinical parameters, and opportunistic infections, we have found one striking and highly significant observation. Women infected with subtype C HIV-1 appear to progress more slowly to AIDS (based on CD4 cell decline) than those infected with subtype A and D and much slower than the historical data on subtype B infections (found in the developed world).

Although this observation is supported by the reduced ex vivo fitness of subtype C compared to other subtypes, subtype C has emerged in the past twenty years to dominate the worldwide epidemic (an increase from ¡10% in the early 1990s to ¿50%). The dichotomy between reduced subtype C virulence and rapid spread in the human population could be explained the maintenance of efficient host-to-host transmission. Preliminary experiments suggest similar transmission fitness among different HIV-1 subtypes. Thus, mathematical models are currently in development to access the impact of this reduced virulence, longer asymptomatic disease, and efficient transmission on the global spread of subtype C.

Another model is also being developed explore the underlying mechanism(s) for reduced HIV-1 virulence. This model is based on the dominance of HIV-1 entry into host cells to determine replicative fitness (and possibly virulence).

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Maarten Boerlijst, University of Amsterdam

Spatial Epidemics: Emergent Trade-offs and Evolutionary Cycling

Spread of diseases in human populations can exhibit large scale patterns. An often observed pattern is a so-called "wave of epidemic spread". We demonstrate that in a simple contact network model such epidemic waves can emerge spontaneously. Spatial patterns can have profound effects on selection of disease properties, such as infectiousness and duration of the infectious period. We have recently shown that in this system spatial pattern formation and natural selection can generate an emergent trade-off between infectiousness and infection period, while the system is maximizing outbreak frequency. However, for larger differences in outbreak frequency, the system can display turbulent interface patterns, which can reverse the selection pressure towards maximizing secondary infections. In this way the spatial epidemic system can move into a so-called "evolutionary cycling" regime, where the switch in direction of selection is caused by a phase transition in the system's spatial pattern.

Rustom Antia, Emory University

On the role of the innate immune response in regulating the within-host dynamics of malaria infections

What controls the initial dynamics of malaria infections? Why do some parasite strains reach higher densities than others? In an earlier study we have shown the conditions under which a resource limitation model may be able to explain the dynamics of infection with different parasite strains. In the current study we have developed a mathematical model for the control of acute malaria infections by innate immunity and used this model to ask which factors might allow different parasite strains to reach higher peak densities that others. We end by describing how we might be able to discriminate between the resource limitation and innate immunity models.

Babak Pourbohloul, BC Centre for Disease Control

Time Evolution of Disease Spread on Networks

Two key elements facilitate the understanding and control of communicable disease spread within a social setting. These components are the underlying contact structure among individuals that determines the pattern of disease transmission and the evolution of this pattern over time. Mathematical models of infectious diseases, which are in principle analytically tractable, have taken two general approaches in incorporating these elements. The first approach, generally known as compartmental modeling, addresses the time evolution of disease spread at the expense of simplifying the pattern of transmission. The second approach, which uses networks to incorporate detailed information pertaining to the underlying contact structure among individuals, in its current formalism, disregards the time progression during outbreaks. So far, the only alternative to integrate both aspects of disease spread simultaneously has been to abandon the analytical approach and rely on computer simulations. We offer a new analytical framework, which incorporates both the complexity of contact network structure and time progression of disease spread.

Yang Yang, Fred Hutchinson Cancer Research Center

A Bayesian Framework for Estimating Vaccine Efficacy per Infectious Contact

In vaccine studies for infectious diseases such as human immunodeficiency virus (HIV), the frequency and type of contacts between study participants and infectious sources are among the most informative risk factors, but are often not adequately adjusted for in standard analyses. Such adjustment can improve the assessment of vaccine efficacy as well as other risk factors, and can be attained by modeling transmission per contact with infectious sources. However, information about contacts that rely on self-reporting by study participants are subject to nontrivial measurement error in many studies. We develop a Bayesian hierarchical model fitted using Markov Chain Monte Carlo (MCMC) sampling to estimate the vaccine efficacy controlled for exposure to infection, while adjusting for measurement error in contact-related factors. Our method is used to re-analyze two recent HIV vaccine studies.

Disease Dynamics 2008 - Poster Abstracts

Alexander Lange, McMaster University

How intra host traits are determined by inter host dynamics - an evolutionary approach to the emergence of infectious diseases of multi-strain pathogens

We present a classification with respect to the emergence of infectious diseases of multi-strain pathogens based on an intra- and on an inter host epidemiological model capturing main features of their reproduction and transmission. The contact structure and dynamics of the host population is identified to determine the antigenic variation and intra-host reproduction of possible pathogens on a corresponding evolutionary scale. The potential presence of cross-reactive immunity is shown to be an important factor for the emergence of pathogens of low antigenic variation at high contact rates such as those causing childhood diseases. In contrast, low contact rates are found to favor pathogens of intermediate and high antigenic variation, representing infections ranging from influenza to HIV, with high and low intra-host reproduction, respectively. Our approach, built upon a simplifying but concise and self-contained framework, allows for similar conclus ions as the phylodynamic approach presented by Grenfell et al in 2004 (Science 303, p. 327). This is joint work with Neil Ferguson.

Joel Miller, BC Centre for Disease Control

The impact of clustering on disease spread

Most mathematical models of infectious disease assume homogeneous mixing, and so each individual is equally likely to infect any other individual. However, real populations do not mix homogeneously: Individuals tend to mix in small groups. This has a significant impact on the spread of diseases. We investigate the spread of infectious diseases through clustered networks and find that clustering tends to significantly reduce the rate of spread of a disease, but has relatively little impact on the size or probability of epidemics.

Stewart Chang, University of British Columbia

A model for Mycobacterium tuberculosis infection

Antigen presentation – the process by which antigen-presenting cells (APC) display fragments of pathogens to T cells – is required to initiate cell-mediated immunity and encompasses events occurring at multiple scales in time and length. At small scales genetic polymorphisms lead to changes in molecular-level properties, such as peptide binding to MHC molecules. Events at larger scales, such as MHC expression within the APC (cellular-level) and the frequency with which APCs encounter T cells (tissue-level), also affect whether antigen presentation is successful and an immune response ensues.
Because events at any of these scales may impact the outcome of antigen presentation, a model may need to represent all of them to be fully predictive. To this end we have begun to integrate statistical models of peptide-MHC binding, mathematical models of a single APC and the activation of T cells, and agent-based (cellular automata) models of the lymph node. Pathogens such as Mycobacterium tuberculosis (Mtb) may act at one or more of these scales, and we discuss different ways in which we have represented Mtb infection. We also introduce tools to visualize how genetic polymorphisms may compensate for each other.

Omer Dushek, University of British Columbia

Analysis of serial engagements of T cell receptors in signaling clusters

During stimulation of a T cell by an antigen-presenting-cell (APC) bearing cognate peptide-major-histocompatibility complexes (pMHC), T cell receptors (TCR) have been shown to form stable micrometer-scale clusters in the contact region. pMHC molecules diffusing in the APC membrane may bind and unbind from multiple TCR in a cluster. We use mathematical modeling to characterize the number of clustered TCR bound by a single pMHC. We show that the TCR-pMHC bond kinetics alone do not allow substantial serial engagement of TCR. Mathematical tools: MFP calculations, asymptotic analysis, numerical solutions of PDEs.

Jennifer Hubbarde, University of British Columbia

A Burst-Death Model for Experimental Evolution

Authors: J. E. Hubbarde & L. M. Wahl Estimating the fixation probability of a beneficial mutation has a rich history in theoretical population genetics. However, fixation probabilities are extremely sensitive to assumptions regarding life history. We develop a burst-death life history model which assumes that generation times are exponentially distributed, but the number of offspring per individual is fixed, which may be more appropriate for lytic viruses. Using this model, we estimate the fixation probability for populations of constant size, and for populations which grow exponentially between periodic population bottlenecks. We then predict the optimal time at which to impose bottlenecks, maximizing the probability that beneficial mutations occur and are not ultimately lost. We find that the optimal bottleneck time only weakly depends on the selective advantage but depends strongly on the death rate and burst size. Most importantly, the optimal sampling fraction is a constant with respect to these parameters; sampling about 20% of the population will maximize the rate of adaptation.

Ozge Karanfil, Simon Fraser University

A Mathematical Model of Steady State B Lymphopoiesis in Mouse and Rat Bone Marrow

Unlike the parallel processes of erythrocytopoiesis and granulocytopoiesis, the regulation of the subpopulations of progenitors and non-dividing progeny in bone marrow lymphocytopoiesis is less well quantified. Additionally, studies which attempt to quantify the populations of B cells in mouse (and rat) BM also give variable results due to differences between strains, the use of different markers, variability in experimental conditions, and/or differences in methods.
In this study, we are using a scheme which developed over a number of years by Prof. Osmond and his coworkers. Using immunofluorescence labeling and cell cycle arrest techniques, the Osmond group characterized a B cell differentiation sequence in the mouse BM, which is based on the expression of particular molecules with time: 1) Terminal deoxynucleotidyl transferase (TdT), expressed in the cell nucleus during immunoglobulin heavy (Ig H) chain gene rearrangement 2) B220 cell surface glycoprotein (not exclusively associated with the B lineage) 3) μ chains in cytoplasm (cμ), and 4) μ chains in IgM molecules expressed at cell surface (sμ , sIgM) These four markers define successive stages in B cell development. The earliest defined precursor B cells are called pro-B cells, which is comprised of three populations of proliferating cells before the expression of μ heavy chains. The subsequent B220+ populations comprise cμ+ pre-B cells, which give rise to nondividing B lymphocytes expressing surface IgM. These stages are assumed to form a series of concatenated compartments, the outflow from one compartment being the inflow to the next compartment. 1) Pro-B cells: Early (TdT+ B220-), Intermediate (TdT+B220+), Late pro-B cells (TdT-B220+) 2) Pre-B cells: cμ+ Large μ+ Small 3) B cells: sIgM+
Using this scheme, we were able to make an extensive summary of the existing data on the various B cell precursors and to organize it into a comprehensible framework. We built a mathematical model for the proliferation and differentiation of mammalian B lymphocytes in laboratory mice and rats and estimated all of the parameters to explain the existing steady state data (e.g. the calculated flow from compartment to compartment, the number of mitoses, number of cells per clone). The model is also used to to predict the temporal response to various experimental perturbations that have been reported from the laboratory of Prof. Dr. Dennis Osmond. This is joint work with Michael Mackey

Azamed Gezahagne, East Tennessee State University

Analyzing the Impact of Risk Behavior on ARV drug resistance

Zahid Shareef, University of the West of England

Mathematical Modelling of Non-local Effects in Infectious Diseases

Disease Dynamics 2008 - Poster Abstracts

Abdessamed Tridane, Arizona State University

A Viral Load-Based Cellular Automata Approach to Modeling HIV Dynamics and Drug Treatment

We formulated a novel cellular automata (CA) model for HIV dynamics and drug treatment. The model is built upon realistic biological processes, including the virus replication cycle and mechanisms of drug therapy. Viral load, its effect on infection rate, and the role of latently infected cells in sustaining HIV infection are among the aspects that are explored and incorporated in the model. We assume that the calculation of the number of cells in the neighborhood which influences the center cell's state is based on the viral load. This variable-cell neighborhood enables the simulation of an infection rate that is correlated to the viral load. This approach leads to a new and flexible way of modeling HIV dynamics and allows the simulation of different antiretroviral drug treatments based on their individual and combined effects. The results of the simulation show the three phases of the HIV dynamics (acute, chronic, and AIDS) and the additional drug response phase when drug treatment is added. The dynamics from the model qualitatively match clinical data. Drug treatment combinations with reverse transcriptase inhibitors and protease inhibitors are simulated using various drug efficacies. The results indicate that the model can be very useful in evaluating different drug therapy regimens.

Eunha Shim, Yale University

Antiviral intervention during pandemic influenza: prophylaxis and treatment coverage levels driven by individual and societal interest

Antiviral agents will play a critical role in mitigating the next influenza pandemic. The administration of drugs has epidemiological and evolutionary repercussions that affect both the individual patient and the community. An individual benefits from reduced probability and/or severity of infection but potentially suffers adverse effects related to antiviral drugs. From the community perspective, the positive externality of antiviral intervention is reduced transmission, while the negative externality is selection for drug resistance. We evaluate how the balance among these factors determines the discrepancy between coverage levels driven by self-interest and the community optimum. We find that, at current drug pricing, this discrepancy is larger when antivirals are used for prophylaxis than for treatment.

Samuel Alizon, Queen's University

Transmission-recovery trade-offs to study parasite evolution

Parasite evolution is mainly studied through a trade-off involving host death and transmission. In addition to the lack of evidence, this trade-off largely fails to understand the evolution of sub-lethal parasite effects. Here, I argue that considering host recovery as a main selection pressure faced by the parasite helps to address these problems and opens new perspectives for the study of parasite evolution. This approach also has implications to study within-host dynamics of viral diseases such as HIV or hepatitis C.

Anuj Mubayi, Arizona State University

On the Role of Environmental Context on the Dynamics of Alcohol Use

Celebrations, from weddings to sports events, that do not involve alcohol consumption are rare. Excessive drinking seems to be closely tied in to particular environments and yet there are not useful characterizations of where people drink. In this talk, I will introduce epidemiological type models that look at the role of heterogeneous drinking environments and individual mobility on the distribution of drinking types. College drinking data are used to put in some context to the results of this theoretical study.

Vahid Dabbaghian, Simon Fraser University

A Cellular Automata Model of the Spread of HIV in a Community of Injection Drug Users

Injection drug users (IDUs) who share needles are at high risk for contracting HIV. Social and behavioral dynamics that lead to needle sharing can impact HIV transmission. A cellular automaton was constructed to model an hypothetical IDU community experiencing an HIV epidemic, driven by needle-sharing in the presence of social influences that promote or discourage unsafe injection practices. HIV positive (HIV^+) IDUs who share needles transmit the virus at fixed rates in the model. Social influences are tracked using a social counter associated with each individual. Behavioural change with respect to needle sharing is transmitted once a threshold amount of social influence has been accumulated. Peer influence discouraging needle sharing showed a nonlinear response in exerting a strong impact on needle-sharing behaviour among IDUs. To study the global behaviour of the system, we constructed a phase diagram. Social influence values below the phase transition curve show an effect similar to *herd immunity*, as the epidemic for parameters in this region is eventually driven to extinction. This is joint work with Krisztina Vasarhelyi, Natasha Richardson, Peter Borwein and A.R. Rutherford.

Disease Dynamics 2008 - Discussion Topics

Samuel Alizon, Queen's University

Linking within-host and epidemiological dynamics: is it worth it?

Several studies have developped embedded models that link within-host dynamics to epidemiological dynamics in a variety of ways. One of the specificities of these models is that they simplify both the within-host processes (particularly the immune response) and the epidemiology. One could thus argue if this can give us any insight that classical model could not.

Joel Miller, BC Centre for Disease Control

Vaccinating against mosquitoes to control malaria

It is possible (in principle) to vaccinate people against proteins in the mosquito gut. When a mosquito bites a vaccinated person, it will ingest antibodies which then attack its stomach. This would provide a new tool to help control malaria, dengue, and a number of other mosquito-borne diseases. Very little experimental work has been done on this, and, to my knowledge, no modeling work has been attempted. I would like to discuss some of the options for malaria control through such vaccinations.

Alexander Lange, McMaster University

What are the limitations when describing viral evolution and epidemiology based on mathematical models?

Participants attending this discussion will talk about the amount of biology, medicine, geography, ethics, politics, etc, they need in addition to mathematics to make good scientific statements in this interdisciplinary field of mathematical disease modeling. They will be asked to think about the general or/and not so general boundaries they encounter in their concrete fields of research. Different points of view with respect to these boundaries may stimulate discussion and widen everyone's perspective. It is hoped that united expertise on contentious issues that may come up will lead to new approaches, perhaps concrete projects and new collaboration.

Eunha Shim, Yale University

How to incorporate vaccine efficacy into mathematical models.

Vaccine efficacy and effectiveness are generally estimated using relative risk in the vaccinated group compared to the unvaccinated group, and such data are often obtained from vaccine trials with various settings. To incorporate the effect of vaccination into mathematical modeling, one ideally requires data on the "effective" contacts between people from different epidemiological classes. Typically, we model the impact of vaccination by reducing susceptibility of vaccinated individuals or separating a fraction of susceptible population into vaccinated class. Here we like to discuss how we can improve our parameterization of vaccine efficacy to reflect different effects of vaccination (direct protection, indirect protection, and total average effects on population etc.) using the data from various study designs.
Reference: Halloran ME. Overview of vaccine field studies: types of effects and designs. J Biopharm Stat. 2006;16(4):415-27.

Babak Pourbohloul, BC Centre for Disease Control

Models of epidemics, epidemic of models:
Does every model have direct implications in public health policy design?

I think this is a fundamental issue which is often neglected but has important implications in terms of taking modelers "seriously" in public health decision-making. I would like to raise this issue in modeling forums to get people's opinion/input/reactions.