Bridging the scales of disease dynamics 2006

University of British Columbia, Vancouver
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September 27-29, 2006

Wednesday, September 27

3:00pm Tutorial / Introductory Seminar
Fred Brauer, University of British Columbia

An Introduction to Compartmental Models in Mathematical Epidemiology

Abstract:
This will be a brief description of compartmental models for epidemic and endemic situations starting from the simplest Kermack-McKendrick models and including mention of arbitrary distributions for time in a compartment, recovery with or without immunity, temporary immunity, immigration, patch models, heterogeneity of contacts and contact networks.

4:00pm Tea break

4:30pm Opening remarks

4:35pm Carlos Castillo-Chavez, Arizona State University

Epidemics and Globalization: Challenges and Opportunities

Abstract:
Preparadness is seen by some to be a function of time, resources and planning. Often developed nations have the resources and even a plan to deal with the potential consequences of natural or deliberate "releases" of biological agents. However, our ability to respond in a timely fashion is continuously challenged by globalization. Today, an increasing fraction of the population routinely makes use of air travel, there is an irreversible dependence on immigrant workers (as our populations age) and the generalized use of mass transportation seems inevitable in communities where it has not played a key role. These are but some the factors that continuously reshape the landscape where diseases thrive and evolve. In this talk, I will address some of the challenges and opportunities that we face today. The focus will be on the role of model-driven theory in the presence of technological innovation (vaccines). Can we slow down the negative impact that some of these factors have on disease dynamics and evolution?

7:00pm Dinner, Rich Ocean, 777 W. Broadway.

Thursday, September 28

9:00am Ira Longini, Fred Hutchinson Cancer Research Center and University of Washington

Strategies for Containing or Slowing the Spread of Pandemic Influenza: A Stochastic Simulation Model

Abstract:
The world appears to be on the brink of a deadly influenza pandemic. Recent human deaths due to infection by highly pathogenic avian influenza A (H5N1) virus have raised the specter of a devastating pandemic like that of 1917 - 18, should this avian virus evolve to become readily transmissible among humans. It is optimal to contain a nascent strain of influenza at the source. If this fails, then the best strategy is to slow spread until a well-matched vaccine can be made and distributed. In this talk, I describe a large-scale stochastic simulation model to investigate the spread of a pandemic strain of influenza virus through the United States population of 281 million people. We model the impact that a variety of levels and combinations of influenza antiviral agents, vaccines, and modified social mobility (including school closure and travel restrictions) have on the timing and magnitude of this spread.

9:40am Karl Hadeler, Arizona State University and University of Tübingen

Demographic impact of infectious disease: Case fatality versus differential mortality.

Abstract:
The standard approach to modeling the demographic impact of an infectious disease is to introduce additional (differential) mortality. In this interpretation infected individuals die, while being infected, with some increased RATE. A different approach, going back to Daniel Bernoulli, is based on case fatality: Individuals exit from the infected state with a certain rate, and upon exit they die with a certain PROBABILITY.

For fixed sets of parameters differential mortality models and case fatality models are mathematically equivalent (except in the limiting case of sure death). However, if parameters are varied, the effects of increased differential mortality and of increased case fatality are very different. This shows up already in the basic reproduction number which does depend on differential mortality but not on case fatality.

We perform a qualitative analysis of case fatality models within the framework of homogeneous systems. We explain the results for two extreme scenarios: demographic impact on human populations and pest control by infectious agents.

joint work with Muntaser Safan and Klaus Dietz

10:20am Tea/coffee break

10:50am Rustom Antia, Dept. of Biology, Emory University

Modeling the within-host dynamics of malaria infections

Abstract:
Why is malaria virulent? Despite causing over a million deaths a year the mechanisms by which the malaria parasite causes disease are still poorly understood. A central problem has been to understand what determines the level of virulence during the initial phase of acute primary infections when pathology due to the loss of red blood cells is greatest. There are many hypotheses: the conventional view is that the fastest replicating parasites have the highest virulence; alternatives are that parasites that infect the youngest red blood cells (reticulocytes), or that elicit relatively weak immune responses, are most virulent. Here we present the new hypothesis that virulence is proportional to the fraction of red blood cells that the malaria parasites can infect. We discriminate between this and the earlier hypotheses by developing a mathematical model of acute malaria infections and confronting it with experimental data from the rodent malaria Plasmodium chabaudi. We show that our model can explain the dynamics of single-strain infections. We further test the model by showing that without modification it closely reproduces the dynamics of competing strains in mixed infections. Importantly, our results allow us to explain why the earlier hypotheses fail. Our results suggest that the virulence of acute malaria infections is determined almost exclusively by how wide an age range of red blood cells malaria strains can infect.
Joint work with Andrew Yates and Jaap de Roode.

11:30am Ruy Ribeiro, Los Alamos National Laboratory

Within host dynamics of hepatitis B virus: from infection to treatment

Abstract:
Hepatitis B virus infection affects 200 million people in the world, and more than 1 billion people have been infected at some point in their lives. The within host biology of the virus has a tremendous impact on the epidemiology, with markedly different epidemics in different parts of the world, due to virus sub-type or mode of infection. I will present the life-cycle of HBV, with special emphasis on our work modeling primary infection and treatment. I will attempt to "bridge the scales of disease dynamics" by indicating (or speculating) how some of the within-host dynamic parameters may affect the epidemiology of the virus at the population level.

12:10pm Lunch break

1:30pm Fiona Brinkman, Simon Fraser University

Quantifying genome-wide trends in virulence factors and pathogen-specific genes

Abstract:
Some trends in bacterial virulence, such as an association between virulence genes and horizontal gene transfer, have been previously anecdotally noted but have yet to be confirmed or quantified on a multi-species, comprehensive scale. I present analyses performed by our group that attempt to quantify, using diverse, multi-genome datasets (up to 267 different bacterial strains analyzed), selected trends in pathogenicity, including trends not previously observed. We show, in support of previous anecdotal statements, that genomic islands (bacterial genomic regions thought to have horizontal origins) do disproportionately contain more virulence factors and pathogen-specific genes than the rest of a given pathogen genome. Ominously, these genomic island regions also contain more novel genes, and based on our work and those of others it appears that there is a large gene pool that bacteria have access to that encode a wealth of pathogen adaptations. We also provide evidence that pathogen-specific virulence factors are disproportionately toxins or are involved in type 3 and type 4 secretion. We further report that even though disproportionately more pathogen than non-pathogen genomes have been sequenced to date, pathogen-specific genes are markedly understudied or unclassified by common gene function classification systems suggesting a need to improve the classification and analysis of pathogen genes. We propose that more sophisticated analyses of trends in bacterial virulence is possible if we develop, and utilize, a Virulence Gene Experiment Database that incorporates contextual information for a given virulence gene experiment. Our work in general provides the first large scale, quantitative data describing selected trends in bacterial virulence and provides insights regarding pathogen evolution and pathogen-specific traits that are likely of primary importance in a pathogenic lifestyle.

2:10pm John Kelly, University of Kansas

Linking dynamical and population genetic models of persistent viral infection

Abstract:
A large body of mathematical theory has been developed to characterize persistent viral infections within vertebrate hosts. Most of the theory can be classified as either dynamical models that predict the population dynamic interaction between virus and host cells or population genetic models that predict gene sequence evolution of the pathogen. These two bodies of theory can be linked by considering the demography of the viral population. Gene sequence evolution is usually modeled as a mutation-limited process in which the rate of evolution is proportional to the mutation rate per replication cycle and the number of replication cycles (pathogen generations) per unit time. The latter is clearly dependent on dynamical parameters such as the clearance rate of free virus or the death rate of infected cells. Here, I review analytical methods that explicitly link dynamical and population genetic theories. These methods are extended to consider the evolutionary consequences of internal host structure, the tendency for a virus to infect multiple different compartments (e.g. tissue types). Infection of multiple compartments, coupled with virus migration, may establish sources and sinks of viral production within the host. Paradoxically, the existence of reproductive sinks can simultaneously reduce the number of viruses within a host and accelerate the genetic evolution of the viral population.

2:50pm Tea/coffee break

3:10pm Troy Day, Queen's University

A theoretical framework for disease life history evolution

Abstract:
I will present some theoretical results that link within-host dynamics of pathogen replication to between host epidemiological and evolutionary dynamics. One of the main novelties of the approach I will present lies in its ability to make short-term evolutionary predictions and to account for populations that are not at evolutionary or epidemiological equilibrium. The core ingredients of the approach are genetic covariance functions for epidemiological parameters over the course of an infection. I will illustrate the approach with an example taken from research on malaria.

3:50pm Carl Bergstrom, University of Washington

How do immune systems protect against pathogens while avoiding subversion and autoimmunity?

Abstract:
Immune systems face the challenging problem of protecting the organism from pathogens while minimizing energetic costs and resource use. In addition, immune systems (1) must avoid generating or perpetuating autoimmune responses and (2) must be robust against internal sabotage and subterfuge by rapidly evolving pathogens. Unfortunately, these two additional requirements can be in direct conflict with one another; mechanisms which shut down autoimmune reactions can be exploited by pathogens to shut down legitimate immune responses. Using examples from vertebrate adaptive immunity and RNA interference, we explore the ways in which immune systems address these competing requirements and deploy strategically robust immune defenses.

4:30pm Poster Session

Olga Krakovska, University of Western Ontario

Can patients benefit from HIV therapy when adherence to the prescribed regimen is low?

Abstract:
Current HIV therapy, although highly effective, is also associated with high toxicity and therefore causes severe side effects. Thus, patients often do not adhere well to the prescribed drug regimen. We have previously established a model that optimizes HIV therapy by weighing toxicity against CD4+ T-cell counts, and incorporates the probability that drug resistance will emerge. We use this model to investigate the influence of adherence on therapy benefit. For a drug with a given half-life, we compare the effect of varying the dose amount and dose timing for different rates of adherence. We find that the overall therapy benefit attainable at a given adherence level depends on the pharmacokinetic parameters of the underlying drug. When adherence is poor, we find that the benefit of therapy can still be relatively high, as long as the dose timing and dose amount are varied accordingly.

Thomas Riggs, University of Michigan

In silico imaging of the dynamics of antigen presentation and cellular activation in a lymph node

Abstract:
To study individual interactions of cell types within a lymph node (LN), we developed a computational model that describes the dynamics of antigen presentation during an immune response. We designate cells as agents that interact with each other within a LN environment according to known rules governing their behavior; our model describes the spatial and temporal patterns of antigen presentation that occur during an immune response to a single, specific antigen. The physical structure of the LN plays a significant role in the ability of CD4+ T cells to locate antigen-loaded dendritic cells and become effector cells. Computer simulations were analyzed using Latin Hypercube sampling and partial rank correlation coefficients to determine the key associations between input parameters and the number of activated and effector cells produced in the LN. This methodology allows analysis and stratification of which processes are most important in regulating the immune response within the LN. Our analyses suggest that among the factors enhancing proliferation and differentiation of CD4+ T effector cells, the probability that a dendritic cell activates a naive CD4+ T cell is more important that their probability of binding. The lifetimes of mature or licensed dendritic cells are also crucial. Within a biologic range, the number of divisions of activated cells is strongly related to output of effector cells. We also evaluated cell motility by contrasting our simulation results vs. data from in vivo 2-photon microscopy experiments and vs. data generated from a completely random walk to illustrate the differences in cell displacement vs. time.
Joint work with Nicolas Perry, Adrienne Waltsa, Mark J. Miller and Denise E. Kirschner.

Emi Shudo, Los Alamos National Laboratory

Robustness of the signal transduction system of the mammalian JAK/STAT pathway and dimerization steps.

Abstract:
Interferons activate the JAK/STAT pathway, where multiple separate steps of dimerization of STAT are required prior to the expression of genes coding antiviral molecules (defense response). In this paper, we examine the role of these dimerization steps by analyzing the dynamical behavior of several modified models. In the original model, based on experimental results, only dimers of phosphorylated STAT1 that translocate to the nucleus activate the defense response or gene expression. In the alternative models, monomers can be translocated to the nucleus and/or activate the defense response. We study the robustness of the system against the noise included in the input and that inherent in its own reaction, analyzing the Hill constant of the signal-response curve, delay of the response triggered by low IFN gamma, and the parameter sensitivity in a situation of low IFN gamma. We found that the structure of the JAK/STAT1 pathway observed in the immune system of mice makes the system behave robustly against noise. That is, (1) the system reacts to noise included in the input with low sensitivity and slowly, and (2) the concentration of antiviral molecules at the steady state does not change substantially when kinetic parameters fluctuate. We evaluated relative contribution of different dimerization steps to the robustness.

Sarah Cobey, University of Michigan

Episodic selection and influenza virus diversity

Abstract:
One of the strongest selection pressures that pathogens face is host immunity. The genetic and antigenic diversity of pathogens thus results from the evolutionary accessibility of different phenotypes and their competition through cross-immunity. Recently, it was shown that influenza A (H3N2) viruses fall into distinct antigenic clusters, with a single cluster dominating at any one time, and clusters replacing one another every few years. A new model posits that during the period of a single cluster's dominance, sequences explore neutral genotype space. Discovery of a new antigenic cluster causes a selective sweep in which the genetic diversity of the previous cluster is extinguished through strain competition. This model presupposes that there is strong selection between clusters and weak or no selection within clusters. Here we find evidence of episodic selection on the major antibody-binding protein of influenza viruses, hemagglutinin, in support of this model. We hypothesize that the weak positive selection found within clusters may be important for influenza's survival by accelerating diffusion and enabling phenotypic change. Quantifying the spectrum of selection pressures on influenza will shed light on the complicated feedbacks between phenotype and genotype diversity, with implications for managing the evolution and epidemiology of the virus in different host populations.

Joel Miller, Los Alamos National Laboratory

The effect of local network structure on R_0

Abstract:
The spread of disease is governed in part by the properties of the disease, but more significantly by the structure of social interactions in the population through which it spreads. Much modeling of disease spread has used the assumption of a uniformly mixed population, but it is well-established that the dynamics of epidemics spreading on social networks differ from those of epidemics on uniformly mixed populations. In this poster we study how small-scale structure in a social network affects the global dynamics of disease, with particular emphasis on how R_0 is affected by local structures. We derive an expression for R_0 and compare it with simulations based on a social network provided by the EpiSimS model of Portland, OR.

Stewart Chang, University of Michigan

A model for Mycobacterium tuberculosis infection and the effect of host genetic polymorphisms at multiple spatial scales

Abstract:
Antigen presentation is a key process during immune recognition that encompasses events occurring at a number of spatial scales. During antigen presentation, receptors known as MHC molecules bind peptides derived from pathogens, and the stable complexes are displayed on the cell surface for recognition by T cells. Small spatial scales are relevant because genetic polymorphisms lead to single-residue changes in MHC molecules as well as other proteins. Likewise, larger spatial scales are also relevant. Peptide-MHC complexes aggregate on the cell surface, and their non-uniform distribution may affect the engagement of T cell receptors. On the scale of cell populations, T cells may compete for binding to antigen-presenting cells, and on a still larger scale, these cell-cell interactions occur within a complex milieu of other cell types and cytokines. Because events at any of these spatial scales may impact the outcome of antigen presentation, a model that includes these events may be necessary to accurately represent what is happening in vivo. To this end, we have begun to integrate statistical models of peptide-MHC binding with mathematical models of single antigen-presenting cells and their ultimate effects on T cells. We have developed analytical tools to depict how some parameters may compensate for others at the same or different scales. For example, polymorphisms have been identified in the genes for IFN-g as well as for MHC and may complement each other. Pathogens such as Mycobacterium tuberculosis may affect events at one or more spatial scales, and we also discuss different ways in which we have simulated infection at each scale.

Eunha Shim, Arizona State University

Mathematical modeling of rotavirus infection with vaccination and maternal antibodies

Abstract:
The impact of rotavirus, the most prevalent diarrheal pathogen in young children worldwide, may be reduced by recently approved vaccines. An age-structured model that describes the rotavirus transmission dynamics of infections is introduced. Conditions that guarantee the local and global stability analysis of the disease-free steady state distribution as well as the existence of an endemic steady state distribution are established. The impact of maternal antibodies on the implementation of vac- cine is evaluated. Model results are used to identify optimal age-dependent vaccination strategies. The implmentation of numerical scheme is carried out using discretization. Also the seasonlity of rotavirus infection is studied using a simple mathematical model that includes the impact of breast feeding, seasonality and the possibility of control via vaccination. Data from Australia are fitted to a model that incorporates the effect of seasonality in the transmission process. The impact of temporary and partially effective vaccines is explored.

Lin Wang, University of British Columbia

Impact of Travel Between Patches for Spatial Spread of Disease

Abstract:
A multi-patch model is proposed to study the impact of travel on the spatial spread of disease between patches with different level of disease prevalence. The basic reproduction number for the i-th patch in isolation is obtained along with the basic reproduction number of the system of patches R_0. Inequalities describing the relationship between these numbers are also given. For a two-patch model with one high prevalence patch and one low prevalence patch, results pertaining to the dependence of R_0 on the travel rates between the two patches are obtained. For parameter values relevant for influenza, these results show that, while banning travel of infectives from the low to the high prevalence patch always contributes to disease control, banning travel of symptomatic travelers only from the high to the low prevalence patch could adversely affect the containment of the outbreak under certain ranges of parameter values. Moreover, banning all travel of infected individuals from the high to the low prevalence patch could result in the low prevalence patch becoming disease-free, while the high prevalence patch becomes even more disease-prevalent, with the resulting number of infectives in this patch alone exceeding the combined number of infectives in both patches without border control. Under the set of parameter values used, our results demonstrate that if border control is properly implemented, then it could contribute to stopping the spatial spread of disease between patches.

Rafael Meza, University of Washington

Reservoir Interactions and Emerging Infectious Diseases

Abstract:
Animal populations act as reservoirs for emerging diseases , including H5N1 influenza , SARS, and West Nile fever. In order for transmission to be self-sustaining, a pathogen must have a basic reproductive number $R_0 > 1$. Following a founding transmission event from an animal reservoir into humans, a pathogen is not yet adapted to its new environment, and is likely to have an $R_0 < 1$. However, subsequent evolution may rescue the pathogen from extinction in its new host. Recent applications of branching process theory investigate how the emergence of a disease agent is influenced by the number and rates of these evolutionary steps. In addition to direct evolution, ongoing contacts between human and reservoir populations may also contribute to pathogen evolution. In this work we extend a stepping-stone model of pathogen evolution to include reservoir interaction. Here, we demonstrate that the probability of a founding event culminating in a newly emerged disease can be significantly influenced by ongoing reservoir interactions.
Joint work with T. Reluga, D.B. Walton, H. Qian and A. Galvan

Raibatak Das, University of British Columbia

Plasma membrane recruitment of signaling proteins in B lymphocytes

Abstract:
We use multi color confocal fluorescence microscopy to visualize the stimulated translocation of a fluorescently labelled adaptor protein, Gab1, and its domain-deleted mutants, in live B lymphocytes. Using image processing algorithms we quantify the real time recruitment of this cytosolic protein to the plasma membrane, and its colocalization with crosslinked B cell receptor. Our data show an antigen dose-dependent kinetics for the recruitment. We are currently modeling our experimental observations with a combination of stochastic and deterministic tools to estimate relevant biophysical parameters that determine the recruitment and colocalization kinetics.

Omer Dushek and James Bailey, University of British Columbia

Aspects of thymic development of T cells

Abstract:
TBA

Friday, September 29

9:00am John Mittler, University of Washington

Optimal timing for induction-maintenance therapy: Effects of viral fitness and dynamics on the suppression of drug resistant virus.

Abstract:
Current attempts to optimize combination therapies for patients infected with drug resistant virus often fail to completely suppress viral replication. Here we use mathematical models to study how viral fitness, the number of drug resistant viruses in the body, and target-cell/immune-system dynamics influence the probability that antiretroviral therapy will be successful. In cases where drug resistance imposes a fitness cost, these models show that the trajectory of viral load change at the time therapy is initiated can be an important predictor of whether therapy will be successful: initiating treatment when viral load is decreasing can often reduce the risk of selecting for drug resistant mutants relative to treatments initiated when viral load is stable or increasing. These findings suggest new strategies for optimizing therapy regimens in salvage therapy patients and other patients with limited therapy options. In particular, these models suggest that there is a critical window of time during the first 90 days of therapy when brief periods of super-intense therapy may help prevent the evolution of drug resistance. The optimal time to initiate this brief period of super-intense therapy may be several days or weeks after the initiation of standard (maintainable) therapy. Using results from a stochastic version of the model, we summarize predictions concerning the kinds of drugs that would be most effective for these induction-maintenance therapies, the length of the induction period, and the percentage of patients that would benefit from these strategies.

9:40am Lindi Wahl, University of Western Ontario

The emergence of drug resistance: estimating rates of emergence and improving drug regimens

Abstract:
The spread of drug-resistant pathogens is an important epidemiological concern, but the initial emergence of drug resistance must be understood at the in-host level. In this talk, I will discuss the estimation of fixation probabilities, the chance that drug-resistant microbes will emerge de novo in an infected host or hosts. We tackle this through the solution of a partial differential equation describing the appropriate probability generating function. The second section of the talk deals with the design of more effective dose regimens for antimicrobial therapy. Using HIV as an example, we use a well-established dynamical system to numerically predict drug regimens which control the viral population and reduce side effects, without increasing the risk of drug-resistance. The optimal regimens we predict incorporate drug holidays and reduce the overall dose by as much as 50%, without unduly increasing the risk of resistance.

10:20am Tea/coffee break

10:50am Glenn Webb, Vanderbilt University

Mathematical Models of Prion Proliferation

Abstract:
Abnormal prions are hypothesized to be the causative agent of neurodegenerative diseases such as mad cow disease. Mathematical models of the dynamics of normal and abnormal prion proliferation are analyzed. The models consist of an ordinary differential equation for the normal prion monomer forms coupled to a partial differential equation for the fibril density of abnormal prion polymer forms. Model simulations are compared to experimental data for prion proliferation.

11:30am Junling Ma, University of Victoria

Influenza seasonality caused by antigenic drift?

Abstract:
A key characteristic of Influenza epidemics is that they occur in winter. Traditionally, this seasonality is thought to arise from seasonal changes in transmission rates. However, fitting a seasonally forced transmission model to influenza mortality time series reveals that the periodic introduction of new flu variants may also play a fundamental role. In fact, we can fit the mortality curve very well with no seasonal variation in transmission rates. In this talk, we will see that flu-like cyclic dynamics can emerge from the coupling of the epidemic process (described by a deterministic compartmental model) and the viral mutation process (described by a nonhomogeneous Poisson process). While not required to generate periodicity, seasonal forcing ensures that the average period between epidemics is exactly one year.

12:10pm Lunch break

1:30pm Michael Gilchrist, University of Tennessee at Knoxville

Using nested models to better understand the conflict and resolution of selection at the between and within-host scales.

Abstract:
Natural selection acts on virus populations at two distinct but interrelated levels: within individual hosts and between them. Studies of the evolution of virulence typically focus on selection acting at the epidemiological or between-host level and demonstrate the importance of trade-offs between disease transmission and virulence rates. Within-host studies reach similar conclusions regarding trade-offs between transmission and virulence at the level of individual cells. Studies which examine selection at both scales assume that between- and within-host selection are necessarily in conflict. We explicitly examine these ideas and assumptions using a model of within-host viral dynamics nested within a model of between-host disease dynamics. Our approach allows us to evaluate the direction of selection at the within- and between-host levels and identify situations leading to conflict and accord between the two levels of selection. In addition, we are now expanding this framework to examine how, in the instance of two competing strains, these conflicts between selection at different levels is resolved.

2:10pm Aaron King, University of Michigan

Between-host consequences of within-host dynamics: the case of the Bordetellae

Abstract:
The neolithic revolution of 10,000 years ago is associated with many rapid changes. Among the most dramatic were intense changes in the characteristics of many human pathogens. We examine the case of the bacteria of genus Bordetella, which infect the respiratory tracts of mammals. The ancestral species are believed to have shared many characteristics with B. bronchiseptica, a generalist which produces a persistent infection in a broad range of mammals. The recently-evolved B. pertussis, by contrast, specializes in the lower respiratory tract of humans and produces the extremely acute symptoms of whooping cough. Immunological studies of the two pathogens have revealed differential expression of specific virulence factors. We take up the question of whether these factors, which modify within-host pathogen dynamics, can account for the emergence of a new niche in burgeoning human populations.
Joint work with Sourya Shrestha.

2:50pm Tea/coffee break

3:10pm Discussion,

Can the scales of disease dynamics be bridged?

Abstract:
Given the diversity of pathogens and the range of spatial and temporal scales over which interesting dynamics occur, is it reasonable to seek general theories for disease dynamics across the scales? To what extent can detailed models at various scales inform modeling at the other scales? Which diseases are ripe for mathematical modeling? How can modern experimental techniques and detailed bioinformatic-style data aid us? These questions and others will be discussed in the light of the presentations at this meeting.

4:00pm End of meeting