Opening Workshop of the SAMSI Program Genomes to Global Health: Computational Biology of Infectious Disease
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Abstracts

Martin Blaser
New York University
School of Medicine
Martin.blaser@med.nyu.edu

"Use of Repetitive DNA in Helicobacter Pylori for Persistence in Human Hosts"

Rob De Boer
Utrecht University
Department of Ost – Pathogen
r.j.deboer@bio.uu.nl

"MHC Polymorphism and Peptide Diversity"

The genes encoding the major histocompatibility (MHC) molecules are among the most polymorphic genes known in vertebrates. Since MHC molecules play an important role in the induction of immune responses, this polymorphism is probably due to selection for increased protection of hosts against pathogens. In contrast to the large population diversity of MHC molecules, each individual expresses only
a limited number of different MHC molecules. This is widely believed to represent a trade-off between maximizing the detection of foreign antigens, and minimizing the loss of T cell clones during self tolerance induction in the thymus. Here we review three theoretical models that we have developed to study the diversity of MHC molecules, both at the individual and at the population level. We have found that thymic selection does not limit the individual MHC diversity. Expression of extra MHC types decreases the number of clones surviving negative selection, but increases the number of positively selected clones. The net effect is that the number of clones in the functional T cell repertoire would increase if the MHC diversity within an individual were to exceed its normal value.

It has been proposed that the large population diversity of the MHC is due to selection favouring MHC heterozygosity. Since MHC heterozygous individuals can present more peptides to the immune system, they are better protected against infections than MHC homozygous individuals. Using a population genetics model, we found however that this heterozygote advantage is insufficient to explain the large degree of MHC polymorphism found in nature. Only if all MHC alleles in the population were to confer unrealistically similar fitness contributions to their hosts,

could heterozygote advantage account for an MHC polymorphism of more than ten alleles. Thus, additional selection pressures seem to be involved. Using a computer simulation model we found that frequency-dependent selection by host--pathogen coevolution provides such an additional selection pressure that can account for realistic polymorphisms of the MHC. The polymorphism of the MHC thus seems a result of host--pathogen coevolution, giving rise to a large population diversity despite the limited degree of MHC diversity within individuals.

Finally we studied whether the peptides of nine amino acids (9-mers) that are typically used in MHC class I antigen presentation are sufficiently unique for self:non-self discrimination. The human proteome contains 28783 proteins comprising a total of 10^7 distinct 9-mers, most of which (76%) occur only once in the human proteome. Enumerating all distinct 9-mers for a variety of viral and bacterial proteomes we found that the average overlap, i.e., the percentage of foreign 9-mers that are also a human self peptide, is about 0.2%.

Victor DeGruttola*, Andrea Foulkes**, David Loecke*
*Department of Biostatistics, Harvard School of Public Health **Department of Biostatistics, University of Pennsylvania
victor@sdac.harvard.edu

"Markov Models for Characterizing the Development of HIV Resistance Mutations"

Development of resistance of Human Immunodeficiency Virus Type 1 to antiretroviral therapies is a serious medical and public health concern. A wide variety of mutations have been identified that either singly or in combination reduce the susceptibility of the virus to available therapies. This presentation will describe methods for characterizing the genetic pathways that lead to high level drug resistance under selective drug pressure, as well as for estimating the rate which viral populations progress along these pathways. These methods can be used to determine whether the presence of certain mutations among drug-sensitive viruses predispose a patient under a particular treatment to develop patterns of mutation that confer high-level drug resistance. Our approach assumes that viral genotypes can be characterized as belonging to discrete states, defined by patterns of viral mutations; we considers two approaches to modeling the rates of transition between these states. The first approach treats the state at a given time point as known while the second treats this as a latent variable. We also consider incorporation of covariates, such as genetic diversity among clones of virus from a single patient, which may impact on the type of mutations that develop, as well as on the speed and the order of their occurrence. We apply our methods to genetic sequences of virus cloned from plasma of 170 patients who participated in three phase II clinical studies of efavirenz combination therapy (DMP 266-003, DMP 266-004 and DMP 266-005). Multiple viral clones are available from each plasma sample at each time of measurement, allowing for consideration of the effect of minority species on the evolution of the viral populations infecting patients; the availability of such information motivates the second analytic approach. The sequences can be found in the Stanford HIV Resistance Website.

Walter Fitch and Geoffrey Graham
University of California – Irvine
Department of Eco-Evo
wfitch@uci.edu

"Predicting the Future Evolution of B-Type Human Influenza Virus"

In 1999, [Bush et al., Science 286, 1921-1925 (1999)] we culminated a study in which we determined eighteen residues in the A-type influenza hemagglutinin that were under positive selection to change their amino acid. We also reconstructed a putative evolutionary tree which had the usual single long lineage (trunk) that shows all but one branch dying out in the course of four or five years. Assuming that the positively selected positions were changing under selection pressure to evade, or at least mitigate the effects of, the human immunological counterattack, we asked whether we might use t changes in these amino acid positions to predict from which group of influenza viruses that currently cause influenza, future epidemics will arise. We predicted these groups for eleven consecutive years. Our predictions were correct in nine of the cases. This work now examines the B-type influenza to see if we get similar results. This could be important for helping to choose strain for inclusion in the vaccines against influenza.

Joanna Fueyo
IBM
Information Based Medicine
jfueyo@us.ibm.com

"Bioinformatic Methods for Virulence Gene Prediction in Microbial Pathogens"

Byron Goldstein
Los Alamos National Laboratory
Theoretical Biology & Biophysics
bxg@lanl.gov

"Monoclonal Antibodies in the Treatment of Disease: Modeling How They Couple Target Cells to Killer"

One emerging strategy in drug development is to take advantage of immune effector mechanisms to destroy cancer cells or over-reactive immune cells. The drug, usually a monoclonal antibody, is designed to couple the target cells to cells of the immune system that express Fc receptors on their surface and mediate cell killing. As an example we look at in vitro experiments that study how a drug (Alefacept) used in the treatment of psoriasis and psoriatic arthritis mediates the elimination of a subset of T cells that drive the autoimmune disease. We develop a model to predict the concentration range of the drug over which it couples T cells to killer cells and we use the model to analyze the experiments. The model reveals what properties of the drug, target cell and killer cell determine the lowest concentration of drug that will be effective.

M. Elizabeth Halloran
Emory University
Department of Biostatistics
mehallo@sph.emory.edu

"Stochastic Models and Analytic Issues for Interventions against Pandemic Influenza"

We present an overview of topics related to stochastic modeling of and evaluation of interventions for pandemic influenza.

Can Kesmir
Utrecht University
Department of Biology
c.kesmir@bio.uu.nl

"A Bioinformatics Approach to the Antigen Presentation and Processing Pathways"

In the recent years we have been developing a number of tools to predict the specificity of several steps involved in the antigen presentation and processing pathways. I will start my talk by giving an overview of the the tools developed by us and the others. While developing these tools, we learned a lot about the biology of these pathways. For example, we now can show that the specificity of the enzymes/molecules involved in the pathways have co-evolved to optimize the antigen presentation.

In the second part of my talk, I will use HIV as a model pathogen to demonstrate how we study the interactions between hosts and pathogens using these bioinformatics tools.

Aoyade Oduola
World Health Organization
Basic & Strategic Research
oduolaa@who.int

"New Paradigm for Management of Tropical Diseases"

Jorge Velasco-Hernandez
Instituto Mexicano del Petróleo
Department: Matemáticas Aplicadas y Computación
velascoj@imp.mx

"A Mathematical Model for Nutrient Depletion and Detachment in a Heterogeneous Biofilm"

Hulin Wu
University of Rochester
Biostatistics and Computational Biology
hwu@bst.rochester.edu

"Modeling Long-Term HIV Dynamics and Antiviral Treatment with Consideration of Pharmacokinetics, Adherence and Drug Susceptibility"