Research at the interface of mathematics and biology has the potential to advance our basic understanding of pathogenic mechanisms and lead to new therapeutic strategies. Mathematical studies, when used in conjunction with data, can suggest potential (or unforeseen) biological mechanisms, determine biologically important rate parameters, and evaluate pathogenic mechanisms that are difficult to test experimentally. My research combines experimental and theoretical techniques to investigate mechanisms in immunology, virology, and epidemiology. Currently I am examining why the immune system fails to control HIV-1 infection. I use mathematical models of HIV-1 dynamics with experimental data from HIV-1 vaccine studies to elucidate the mechanisms of viral escape from immune control. The results of such work may uncover fundamental mechanisms of immunology as well as have important implications for HIV-1 vaccine development.

CURRENT RESEARCH PROGRAM

HIV-1 continues to be a serious problem with over 16,000 new infections each day and nearly 40 million individuals infected worldwide. Safe, effective, and economical therapies remain out of reach for the vast majority of the infected population. Development of a vaccine represents the best hope for control of the epidemic. While several vaccine candidates have proceeded to clinical trials, none has proved efficacious. HIV-1 vaccine development is a challenge in part because the virus mutates and escapes from the cellular immune response (particularly cytotoxic T lymphocytes, or CTLs). Viral escape depends on 1) the fitness of the mutant, and 2) the pressure exerted by CTLs. The timescale over which escape occurs, as well as the amount of antiviral pressure exerted by CTLs, however, are not known. Details of fitness constraints are also unknown at this time.

I use stochastic models to estimate the kinetic parameters involved in HIV-1 escape. In my work with Dr. Otto Yang (UCLA, Medicine), an experimental immunologist, and biostatistician Dr. William Cumberland (UCLA, Biostatistics), I construct Markov chain models describing the system, and I fit the model simulations to *in vivo* data. Using the frequencies of HIV-1 strains under CTL pressure in patients, estimates of the biological parameters of interest (including the timing of viral escape and the rates of escape) are derived. These estimates are then used to assess fitness costs and the amount of antiviral pressure exerted by the CTLs in both acute infection and chronic infection. The results are then used to assess immunological mechanisms. Further studies may delineate the components of CTL pressure, such as target cell specificity, binding, and antiviral function (i.e. efficiency of killing).

This approach represents an advance over earlier efforts that utilize deterministic models. Deterministic models are appropriate to describe systems of large, well-mixed populations. Stochastic models are much better suited to deal with rare

events and emergent populations, and therefore they are more likely to accurately depict the emergence of new viral species in the host. Thus these methods have the potential to yield realistic estimates of the kinetic parameters involved in viral escape.

Evaluation of the forces driving viral escape and determination of the extent to which CTLs exert selective pressure on the virus could help delineate the components of antiviral pressure and elucidate the mechanisms of viral escape from immune control. These studies will potentially advance our basic understanding of the cellular immune response in both acute infection and chronic infection and could provide insight into fundamental mechanisms in immunology and HIV-1 virology. Furthermore, there is an urgent clinical need to better understand the determinants of HIV-1 escape *in vivo*. The ability to predict the patterns of escape would allow vaccine development against the correct targets.

I recently submitted a foundation grant proposal to support this work. Additionally, I am currently preparing a grant proposal to request an R21 grant from the NIH to further support this research.

LONG-TERM RESEARCH GOALS

My research plan is guided by the belief that theoretical studies are best optimized when closely tied to experimental research. My future work will aim to bridge the gap between theoretical and experimental studies by focusing on

- providing quantitative estimates of biologically important rate parameters,
- generation of hypotheses of pathogenic processes that cannot be easily determined by experiments, and
- experimental evaluation and validation of theoretical predictions.

I look forward to research investigating mechanisms in immunology, virology, infectious diseases, and epidemiology. My research favors models that use relevant experimental data wherever possible. I avoid overly complicated models that are not biologically relevant. Finally, my research aims to be directed towards targeted, biologically important questions.

RESEARCH HIGHLIGHTS AND BACKGROUND

In order to develop the best skills for research at the interface of experimental and mathematical biology, I obtained interdisciplinary training including a Ph.D. in experimental cellular and molecular biology, an undergraduate degree in

mathematics, and postdoctoral training in mathematical biology and biostatistics. This training was motivated by a desire for a thorough understanding of the biological context and a clear knowledge of theoretical techniques that would enable a focused, directed approach towards answering difficult research questions.

Selected highlights of my research thus far are as follows:

- As a postdoctoral fellow at UCLA, I investigated the potential impact of prophylactic and therapeutic vaccines on the HSV-2 epidemic, with Dr. Sally Blower (UCLA Biomathematics). Utilizing models of HSV-2 population dynamics and rigorous methods of uncertainty and sensitivity analyses using Latin Hypercube Sampling, we found that prophylactic vaccines could reduce new infections by nearly 20%. We calculated that even imperfect vaccines could prevent over 1 million infections in the US within a decade after introduction. These studies can be used to guide vaccine development and implementation.

- As part of my thesis work in Dr. Paul Klotman's lab (Mount Sinai Medical Center), I conducted experimental studies that showed that HIV-1 caused cell proliferation and a faster progression through the cell cycle in renal epithelial cells, due to loss of contact inhibition. I also examined cell cycle gene expression using microarray analysis to determine the potential molecular mechanisms by which HIV-1 induced cell cycle aberrations. Our research illuminated key findings in the pathogenesis of renal disease in HIV-infected individuals.

- At Los Alamos National Laboratories, I analyzed a model of HIV-1 infection with suboptimal therapy with Dr. Alan Perelson (Los Alamos) and Dr. Avidan Neumann (Bar-Ilan University). This led to experimental studies in which we evaluated a mechanism of viral escape from therapy that was suggested by the model. We showed that viral production could be limited by the availability of target cells when drug therapy was suboptimal *in vitro*. This finding helps explain the viral breakthrough seen in patients on therapy.

- By fitting viral load data after the initiation of antiretroviral therapy to a mathematical model of HIV-1 dynamics, I provided the first quantitative estimates of viral kinetic parameters in HIV-infected patients with end stage renal disease. I served as Principal Investigator of this IRB-approved clinical study.

- I constructed an epidemiological model of HIV-infected individuals with end stage renal disease that assesses the potential effect of antiviral therapy on the development of the disease and provides estimates of

future disease prevalence. We estimated that antiretroviral therapy has reduced the development of end stage renal disease among AIDS patients by 38%. The model also predicted that the prevalence of disease will continue to increase, even with therapy, due to the increase in those living with AIDS. This model can be used to assess the effect of therapy for other diseases as well.

Currently I am coordinating the statistical analyses of clinical HIV vaccine trial TBC-3B conducted by Otto Yang, Dr. Beth Jamieson (UCLA Hematology/Oncology), and Dr. Peter Anton (UCLA Digestive Diseases). This study measures cellular immune responses (to HIV-1 genes gag, pol, and env) in both blood and mucosa and aims to determine whether vaccination in the shoulder or the groin gives better immune responses. Two vaccines (Vaccinia and Canarypox) are being tested, and immune responses are measured by antibody production, specific CTL responses, and activated cell phenotypes. I am also developing stochastic models of HIV escape from immune control, incorporating experimental data with model analyses, as described in detail above.

TEACHING EXPERIENCE AND INTERESTS

Teaching is a richly gratifying experience for me. I truly enjoy the challenge of explaining concepts and ideas to a wide range of students. Throughout my academic career, I have always taken every opportunity to teach. Although it was not required, I chose to teach during my graduate studies because of my satisfaction in increasing students' understanding, the excitement of sparking their curiosity, and the fulfillment of contributing to the learning process.

Teaching Experience

In January 2006, as Visiting Assistant Professor in the Department of Mathematics, I am co-teaching Mathematical Biology at Harvey Mudd College with Dr. Lisette de Pillis. This is the core advanced course for undergraduate majors in mathematical biology and is taken by students in related disciplines as well. Last spring, I served as guest lecturer for this class. Being invited to co-teach in January 2006 is a testimony to the positive reception to my teaching. My lectures focus on mathematical models in immunology, virology, and epidemiology. We cover model construction, mathematical analysis, simulation, and interpretation of results for models of viral dynamics, infectious disease epidemics, and tumorigenesis. The models can be used to evaluate mechanisms that are difficult to test directly by experiment, to estimate otherwise unknown parameters, to suggest potentially unforeseen mechanisms, and to directly investigate biological questions. Furthermore the models can extend beyond theoretical interest and make an impact on biological questions relevant to experimental biologists. My goal is to impart to the students an understanding of where, why, and (most importantly) how mathematical modeling can be used

to investigate mechanisms of pathogenesis. Students have the opportunity to incorporate experimental data with the models in individual research projects.

In graduate school, I taught Immunology to medical students for 4 years. The advanced introductory course was geared toward students with and without prior exposure to immunology, and it required that concepts be fully explained in consideration of the students' differing backgrounds. I consistently received positive feedback on my teaching, and my evaluations mentioned the clarity of my explanations as well as my helpfulness outside of the classroom.

Training

I have taken several courses and workshops in teaching, including a course on the Fundamentals of University Teaching at the City University of New York and a course at UCLA specializing on teaching science at the college and university level. These classes, which aimed to prepare future faculty for academic careers, covered topics including instruction, course design, student assessment, learning theories, and stages of intellectual development. Through these classes, coupled with my own teaching experience, I have developed my teaching philosophy.

Mentoring

While a graduate student, I mentored an undergraduate summer student, Michael Dwyer (Oberlin College, '97). I guided his research efforts in his analysis and simulation of a mathematical model of *in vitro* HIV-1 infection that investigated the role of cell-to-cell viral transmission.

Teaching Interests

Besides teaching mathematical biology, I would welcome the opportunity to teach computational biology, bioinformatics, systems biology and networks, biocomplexity, immunology (introductory and advanced), microbiology, virology, and infectious disease epidemiology. My courses on mathematical biology and modeling would involve linear algebra and differential equations. They would incorporate a substantial level of computational and numerical methods, and they would be supplemented with opportunities for individual and/or group research projects. My role as teacher is to transmit my enthusiasm to my students in a way that helps them transform their questions into tractable research hypotheses, fosters critical thinking, and above all, encourages an educational and rewarding experience.