Statement of Research

As one of the relatively few experts in impulsive differential equations in North America, my current and future work directly arises out of the work that I did for my PhD on self-cycling fermentation. This work taught me the value and necessity of careful application of mathematics to real-world problems. I am fascinated by applied mathematics and the way in which it can be used to describe, predict and guide interdisciplinary research.

SEWAGE TREATMENT:

For my Ph.D. thesis, I investigated self-cycling fermentation, a computer-aided biological process that has applications to sewage treatment systems, toxic waste cleanup and analysis of cell growth. Prior to my research, scientists in self-cycling fermentation chose an arbitrary value of the emptying/refilling fraction for their experiments. My published work demonstrated that there was a unique optimal emptying/refilling fraction and developed a method for deriving this value. Researchers at McGill University in Montreal, Canada who run self-cycling fermentation processes have adopted my method for all experiments. This application of my results will enable a larger volume of polluted water to be cleaned more quickly, greatly reducing the expense.

BONE REMODELING:

My experience with self-cycling fermentation allowed me to take some of the mathematical tools I had acquired in differential equations and apply them to bone remodeling, working alongside scientists engaged in bone research, to answer questions motivated by very real and present demands of the scientific community. During the course of these collaborations, I learned the value of speaking a common language: the ability to communicate the power and versatility of mathematics to the broader scientific community is of extreme importance.

HIV IMMUNOLOGY:

Building on this work, I was able to use my expertise in impulsive differential equations to apply my mathematical skills to the application of dosage intervals in HIV models. This allowed me to develop a complex, but realistic, mathematical model of immunological HIV dynamics. This research resulted in the reformulation of an immunological problem - that of different classes of T cells, be they susceptible, infected or inhibited by one or more drugs - through an epidemiological framework.

I was subsequently able to incorporate drug resistance into this model. This involved further reformulating of the basic format. In addition to impulsive differential equations, I was then able to formulate a batch-like series of models, depending on whether the drug levels were low, intermediate or high. This application of fairly sophisticated mathematical ideas allowed for a considerably more realistic approach to the problem of formulating drug resistance models in HIV than had previously been studied.

The question of understanding adherence patterns to drug regimes has been described as "the most urgent unanswered question in HIV research today" by the U.S. department of Health and Human Services. I was recently able to describe the complex interplay of patient adherence using aspects of these models and became the first to answer the question "How

many doses can you miss before resistance emerges?", which was recently published in the Proceedings of the Royal Society B.

EPIDEMIOLOGY:

My epidemiological approach to immunological models led me to work in the area of mathematical epidemiology, using differential equations to make predictions about the impacts of low efficacy HIV prevention methods, such as vaccines and vaginal microbicides and address the question of whether such products could lead to an increase in epidemic severity. These models also took into account behavior changes and focused specifically on low efficacy prevention methods.

A combination of my mathematical expertise and my experience in epidemiological models led to my formulation of a complex model for drug resistance to nucleosides, nonnucleosides and protease inhibitors in triple-drug HIV therapy, in order to answer the question: has the introduction of antiretroviral drugs made the epidemic worse? This model incorporated a batch-like series of models tracing the evolution of drug resistance to one, two or possibly all three major drug classes. Equally as important, however, was the ability to work alongside medical specialists and communicate complex ideas to health professionals in a simple manner.

One of the foremost concepts in mathematical biology is the basic reproductive ratio, yet its derivation from ODE models is neither obvious nor biologically meaningful. After organizing a minisymposium on this topic, I was asked to collaborate on a paper that subsequently became an invited review for the Journal of the Royal Society Interface. This has recently sparked a number of discussions with experts in both mathematics and biology.

VECTOR-BORNE DISEASES:

My expertise in mathematical epidemiology led to my current position, where I was recruited to be the mathematical modeler for a group of biologists. I have been collaborating with scientists on a large, multi-institutional West Nile virus project, for which I am one of the coordinators and have developed a spatially explicit model. This research is ongoing, but has sparked my interest in vector-borne diseases. I have recently formulated a model for flight initiation for insects carrying Chagas' disease in Argentina and am also collaborating on projects involving schistosomiasis and avian influenza and was recently able to apply my HIV vaccine ideas to the question of malaria vaccines.

IMPACT:

My work has already had a significant impact on the field. My sewage treatment research was recently followed up in a Master's thesis [1] and current Ph.D. work is ongoing. My paper on bone remodeling has become a significant publication in the field, being the first to present a nontrivial mathematical model of osteoclast and osteoblast interaction. It has already been cited significantly [2]-[6] and has been described as "an important first step towards a systems biology understanding of bone remodeling and osteoporosis" [7]. My two papers on HIV immunology each reached #22 on the top 25 most downloaded articles from the Bulletin of Mathematical Biology in the Spring and Fall 2005 quarters. My drug resistance paper was the subject of a news article in Virus Weekly [8] and my analytical

results were used as the "gold standard" against which numerical simulations were tested [9]. My article on the impact of HIV vaccines has been cited in four publications [10]-[13] (including one by Alan Perelson, a leader in the field), was the subject of correspondence in The Lancet Infectious Diseases [14] and was included in a policy report by the International AIDS Vaccine Initiative [15]. Finally, my microbicides paper has been mentioned on a variety of websites, including the Medical Advocates Sexworker Infectious Disease prevention page [16], the Women, Children and HIV page [17] (including commentary by Arthur Ammann, MD), was cited in a conference paper at the Annual Bank Conference on Developmental Economics [18] and in an article in the Harvard Health Policy Review [19].

FUTURE RESEARCH:

My future research will be focused primarily on the complex question of adherence, which also includes further development of research involving drug resistance, patient behavior, social networks and treatment regimens. My specific plans include:

1. Develop a model to describe the effects that of HIV resistance to cytotoxic T-lymphocytes (CTL) responses. The body's natural immune system response via CTLs controls the virus to some extent, but resistance develops and models that account for the immune system response in HIV are rare. I intend to apply my results in drug resistance to the question of "natural" resistance. I am currently writing an R03 grant for NIH and have a joint collaborator, Elissa Schwartz from UCLA, who is an experimental scientist willing to devise and conduct experiments to test my model.

2. Developing a model to describe structured treatment interruptions (STIs), using impulsive differential equations to address the switching on and off of antiretroviral drug regimes. STIs have had some success in keeping drug resistance at bay in some patients, but the theory is not well understood. There are complex interactions, due to the fact that drug resistance rebounds quickly once treatment has been resumed. Knowing when to interrupt treatment is a key question that has barely been addressed, either by experimentalists or by mathematical modelers. I believe my expertise can assist in addressing this complex problem in a way that has not been done so far.

3. Adapting my complex drug resistance model to treatment juggling. Treatment juggling involves developing predictive tools to decide when to change therapies, before drug resistance has occurred. Like STIs, treatment juggling has not been studied in depth, but is a growing concern among medical professionals. Being able to predict when to switch treatments and which alternative treatment to recommend is a question that has had little theoretical development thus far. A model describing this phenomena would by necessity be quite complex, yet I believe my experience has equipped me to both develop such a model and communicate its properties to those most in need of predictive tools.

FUNDING:

As a junior faculty member, I will bring the ability to attract grants in the sciences to the department. I already have experience writing grants and anticipate receiving external sources of funding for my research. My work is highly attractive to funding bodies and I anticipate having students and postdocs of my own in the near future. As mentioned above, I have specific plans to collaborate with researchers in the field to attract external funding.

In summary, my expertise places me in an excellent position for collaborative research with other mathematical modelers, as well as researchers working in other disciplines. My specific expertise in impulsive differential equations and batch-like models allows me to contribute significant advances in an area that few mathematical modelers can, even fewer of whom are infectious disease modelers. Finally, my experience in communicating with scientists and medical professionals has yielded significant advances already, in my abilities to both address questions specifically to the needs of those in the field and to communicate the answers back to the scientific community in a straightforward way.

Citations:

[1] G. Fan "Analysis of a Model of Self-cycling Fermentation with Inhibitory Response Function " M.Sc. thesis, McMaster University, 2004.

[2] M.J. Martin, J.C. Buckland-Wright Sensitivity analysis of a novel mathematical model identifies factors determining bone resorption rates Bone. 2004;35(4):918-28.

[3] V. Lemaire, F.L. Tobin, L.D. Greller, C.R. Cho, L.J. Suva. Modeling the interactions between osteoblast and osteoclast activities in bone remodeling. J Theor Biol. 2004; 229(3):293-309.

[4] A. Inanir, K. Özoran, H. Tutkak, B. Mermerci. The Effects of Calcitriol Therapy on Serum Interleukin-1, Interleukin-6 and Tumour Necrosis Factor-a Concentrations in Post-menopausal Patients with Osteoporosis J Int Med Res 2004; 32(6):570-582.

[5] K. Tezuka, Y. Wada, A. Takahashi, M. Kikuchi. Computer-simulated bone architecture in a simple bone-remodeling model based on a reaction-diffusion system. J Bone Miner Metab 2005; 23, 1-7.

[6] S. Komarova. Mathematical model of paracrine interactions between osteoclasts and osteoblasts predicts anabolic action of parathyroid hormone on bone. Endocrinology 2005; 146:8, 3589-95.

[7] C. Holmes. Towards a Systems Biology Approach to Osteoporosis. http://www.ecf.utoronto.ca/~sdavies/sysbioldir/holmes.DOC

[8] "Dose interval decrease more effectively controls viral load than increasing dose." Virus Weekly, Aug 10 2005. http://abtweb.newsedge.com/1stbin/read_story/FIRST/050810/0/8/318/3

[9] J.M. Heffernan, L.M. Wahl, Monte Carlo estimates of natural variation in HIV infection. J Theor Biol. 2005; 236:2, 137-53.

[10] S.M. Blower, E.N. Bodine, J. Kahn, W. McFarland The antiretroviral rollout and drug-resistant HIV in Africa: insights from empirical data and theoretical models AIDS. 2005; 19:1, 1-14.

[11] S.M. Blower, E.N. Bodine, K. Grovit-Ferbas. Predicting the Potential Public Health Impact of Disease-Modifying HIV Vaccines in South Africa: The Problem of Subtypes. Current Drug Targets - Infectious Disorders, 2005; 5:2, 179-192.

[12] M.P. Davenport, L. Zhang, A. Bagchi, A. Fridman, T.M. Fu, W. Schleif, J.W. Shiver, R.M. Ribeiro, A.S. Perelson. High-potency human immunodeficiency virus vaccination leads to delayed and reduced CD8+ T-cell expansion but improved virus control. J Virol. 2005;79:15, 10059-62.

[13] K.C. Krebs, Z.Y. Jin, R. Rudersdorf, A.L. Hughes, D.H. O'Connor. Unusually High Frequency MHC Class I Alleles in Mauritian Origin Cynomolgus Macaques. J. Immun. 2005, 175, 5230-39.

[14] J.A. Bogaards, W.M. van Ballegooijen, G.J. Weverling, M.C. Boerlijst, J. Goudsmit. Is population-level perversity a likely outcome of mass vaccination against HIV? The Lancet Infectious Diseases 2005; 5, 254

[15] http://www.medadvocates.org/marg/sexworkers/prevention.html

[16] Modeling the Impact of AIDS Vaccines: A Review of the Literature, IAVI Public Policy Department, October 2005.

[17] http://www.womenchildrenhiv.org/wchiv?page=wx-jscandoc&pid=2&catid=pp&pmid=15750395

[18] J.M.A. Lange. Scaling up Access to HIV Prevention, Treatment, and Care in Resource-poor Settings: Challenges and Opportunities, Annual Bank Conference on Development Economics Amsterdam, The Netherlands May 23-24, 2005.

[19] K. Backes, A. Forbes and C. Polis. One Choice Is No Choice: The need for female-controlled HIV prevention tools for women and girls worldwide. 2005 Harvard Health Policy Review 6:1 19-30.