

Research Statement 2007

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1 What has defined my research

Since my earlier success with modeling HIV, I have begun to explore ways to substantially improve modeling and its application to infectious diseases and Diabetes. We are at the beginning of an era where mathematical modeling, if done correctly, will lead to important discoveries about the pathogenesis of disease. While we have been very successful defining the kinetic rates of disease parameters in models for HIV and HBV, to really advance the science is going to require a new way of thinking about modeling. Hence, we cannot simply allow ourselves to generate various complex system models without any real mathematical proof that the model is the "best" model for the system. Hence, my group is pioneering the application of theories associated with model selection, model identifiability, model observability and controllability, and model sensitivity. All of these tools are crucial to advance the understanding of HIV, HBV, and Diabetes.

Secondly, in many of these applications it is necessary to incorporate time delays into the model. Time delays are inherent in any biological system and we are developing novel ways to study these difficult equations. A properly derived mathematical model must be built from the basis of the biology. One cannot alter the model based on limited abilities with mathematical theory. Hence, the main reason for my work on the theory of delay differential equations.

2 HIV

Understanding how the HIV-1 virus actively diminishes the immune system's capability of response, and HIV-1's ability to mutate, which ultimately leads to drug therapy failure, are arguably some of the most important medical problems of the 21st century. In fact, while researchers worldwide are actively combating this disease, we still lack an understanding of many of the fundamental properties of its pathogenesis. My research has focused on developing several mathematical models that account for many stages of the HIV-1 infection process. My mathematical models of the dynamics of HIV-1 infection after the initiation of drug therapy have already assisted in determining many quantitative features of the interaction between HIV-1 and the corresponding immune response. Our results have provided quantitative support to several new hypotheses about the disease. Our research has focused on the use of models which account for intracellular delays in the infection process and have shown that this more accurate representation of the cell biology substantially changes the estimates of the death rate of productively infected T cells, δ , and the viral clearance rate, c . We have shown that the previously reported values for δ were underestimated by nearly 23% and then showed quantitatively how the average life span of infected T cells is partitioned between infected but not producing virus and productively infected. Also, we have shown that the levels of drug effectiveness in patients on antiviral therapy can be as low as 70%, which implies the need of better drug therapies. Some of the main questions I am attempting to answer are:

1) What causes the gradual depletion of CD4⁺ T-cells during latency? Recently experimental work on regulatory T cells, a CD4⁺ subset of T cells, has been implicated as a possible mechanism for this gradual decline. Other work has suggested that these cells are highly vulnerable to HIV infection. With all the varieties of interdependent cells that regulate and protect the body during

infection, mathematical modeling is key to providing a road map to understanding the immune systems response to infection.

2) How can we optimize drug therapy by minimizing viral mutation and maximizing drug effectiveness? HIV drug resistance results possible from a combination of three factors; HIV diversity, HIV replication, and HIV selection. Advances in understanding the HIV genome, such as HIV nef and HIV rev, two specific genes that mutate to give an advantage to HIV replication, can now be applied to mathematical modeling to predict outcome. By predicting mutation ahead of time, one can better prescribe drug therapy that in the long run minimizes the total amount of mutations. Recent advances in modeling using control theory, model selection and identifiability, makes this area ripe for new interactions.

Many researchers, including my self, were trying to make biological conjectures based on the given model. In many of these papers, researchers argued over the importance of a variety of biological effects as well as for the inclusion or exclusion of the corresponding representations in their mathematical models. Following our publications of additional and/or alternative compartment formulations including the use of delay differential equations (DDEs) in modeling the eclipse phase much debate was generated on the correctness of the model. The knowledge gained from using models of disease pathogenesis has, in many cases, suggested novel design ideas for treatment strategies as well as laboratory experiments. My research on HIV now focuses on how confident we are with these models. The models are making profound impacts on the understanding of the disease and I wanted to make sure we were correct. Hence, my group now addresses model identifiability, model selection and model sensitivity. Issues highly important to understanding our models and hence understanding their impact on HIV and other diseases.

For example, in many of the these earlier works, the viral clearance rate was identified by modeling the disease pathogenesis with a system of deterministic differential equations, numerically calculating a solution, and then fitting the results with plasma viral load data (using a ordinary least squares (OLS) approach). Two statistical issues rarely considered when studying disease pathogenesis using dynamical systems are the modeling of variability within and between individuals as well as the estimation of statistical evidence for the superiority of one model over others. My group then began to focus on this topic. We began to employ hierarchical nonlinear mixed-effects (NLME) modeling approach to address the first issue and model selection criteria for the second. Little work has been done on this topic and we have just had our first paper on "Model selection and mixed-effects modeling of HIV infection dynamics" accepted for publication in the Bulletin for Mathematical Biology. We are only beginning to scratch the surface of what mathematical modeling can answer about biological systems. The next decade is going to be very exiting.

3 HBV

Acute hepatitis B infection (HBV) is cleared in 85% to 95% of infected adults, while the rest progress towards chronic infection. Why some people clear the virus, while others do not is still not well understood. The quality and the dynamics of the immune response have been implicated, but a precise quantitative understanding of this response is still lacking. We were able to analyze data from a set of individuals identified during acute HBV infection, and developed mathematical models to test the role of immune responses in various stages of early HBV infection. Fitting the models to the viral load data we are able to separate the kinetics of the non-cytolytic and the cytolytic immune responses thus explaining the relative contribution of these two processes. The

non-cytolytic phase occurs around the peak of viral load and helps reduce it, whereas the cytolytic processes are crucial for a second phase of viral decay, which eventually may lead to control of the virus. The model also demonstrates the difficulty of controlling the infection in a setting of regeneration of uninfected hepatocytes, and requires us to introduce a class of cells refractory to viral production that confer protection against re-infection of the liver. Taken together these results contribute to a clearer picture of acute HBV dynamics. We are now studying the sensitivity of these models by considering that the best fit parameters we found have a degree of uncertainty. This uncertainty can greatly effect the model predictions by changing the eigenvalues. While we showed the real part of the eigenvalues remained in the left half of the complex plane we must be able to show that this is true when taking into account the uncertainty of each parameter. Hence, my group is studying this problem from an engineering perspective were we are considering techniques such as eigenvalue assignment and pole-placement. Together, these ideas will lead to a better model for HBV.

4 Diabetes

Type 1 diabetes (T1DM) is a chronic autoimmune disease characterized by dysfunction and ultimately destruction of β cells in the islets of Langerhans. Type 1 diabetes presents a complex interaction between genetic and environmental factors, most of which have yet to be identified. This disease that typically affects children and young adults, is the result of a protracted process of autoimmunity leading to dysfunction first and eventually ablation of the insulin secreting beta cells of the pancreas. When the level of beta cell function is no longer sufficient to maintain metabolic homeostasis, the individual is then dependent on endogenous insulin to sustain life. Recent evidence suggests that in T1DM there is a relative excess of islet β -cell specific autoreactive T cells and a deficiency of regulatory T cells (Treg). Regulatory T cells (formerly suppressor T cells) are a specialized subpopulation of T cells that suppress activation of the immune system and thereby maintain the immune system homeostasis and tolerance to self molecules. For many decades the existence of a specific subpopulation of "suppressor" T cells was the subject of significant controversy. Recent advances in the molecular characterization of this cell population have convincingly demonstrated their existence and their key role in the pathoetiology of several autoimmune diseases such as Type 1 diabetes. Interest in regulatory T cells has been heightened by evidence from experimental mouse models, such as the non obese diabetic (NOD) mouse, demonstrating the immunosuppressive potential of these cells. Using a number of experimental protocols, Treg cells can be expanded in vitro and in vivo and eventually could be harnessed therapeutically to treat Type 1 diabetes or facilitate tolerance of transplanted pancreatic islets. In collaboration with Dr. Pietropaola, an expert on T1DM we have begun to develop a mathematical model in an effort to quantify the influence of regulatory T cells (Treg) on Type 1 diabetes progression. This work is in an early stage.

5 Arabidopsis

Molecular genetic studies from John Schiefelbein's lab and others have uncovered a large number of components and regulatory interactions that influence the pattern of root epidermal cell types. As our experimental knowledge of this network has grown, the system behaviors have become sufficiently complex (largely due to multiple feedback loops) so as to preclude intuitive understanding. As a result, we have necessarily become interested in developing a mathematical model to depict these dynamic regulatory interactions, enable us to study them, and provide predictions and hy-

potheses for biological testing. In considering an appropriate mathematical model, our current knowledge suggests that, at its core, epidermal cell patterning relies on lateral inhibition and local self-enhancement to generate stable spatial differences in the relative abundance of two types of transcription factors; an active, less-mobile type (WER and MYB23) and an inactive, mobile type (CPC, TRY, and ETC1). In a landmark paper, Turing used differential equations to mathematically describe how the reaction and diffusion of two chemicals may spontaneously produce steady-state heterogeneous spatial patterns of chemical concentration. Gierer and Meinhardt expanded on this fundamental concept and described in detail the features of an activator-inhibitor mechanism, which emphasizes the interplay between the local autocatalysis of one component (the activator) and the long-range inhibition by another (the inhibitor). They and others have shown that Turing-type models can exhibit an array of patterns and may theoretically account for many physical and biological patterning phenomena. Using the activator-inhibitor concept as a starting point, we are focusing on devising a model that is simple, yet maintains the essential elements of the system. We combined WER and MYB23 into a single component (called the activator A) and CPC, TRY, and ETC1 into another component (called the inhibitor I). These simplifications are justified by the known functional similarity of the WER/MYB23 proteins and the CPC/TRY/ETC1 proteins. Using available biological information, we constructed simple rules for the behavior of A and I. Further, we define a relatively high A/I ratio as specifying a non-hair cell and a relatively low A/I ratio as specifying a hair cell. From this we are devising systems of differential equations that will allow us to predict necessary interactions involved in the development of pattern. We are approaching this task as an inverse problem since we have no real data at this point, only output. It is our goal to generate discussion on the possible hidden interactions.

6 Delay Differential Equations

Delays are inherent in many physical, biological, economic and engineering systems. My research in this area is focused on both finding solutions to these equations and finding stability manifolds, with an emphasis on developing methods that are practical and useful for others. I have two main projects in this area; one in Engineering on the study of Machine Tool Chatter and the other in HIV and HBV.

In Engineering, pure delays are often used to ideally represent the effects of transmission, transportation, and inertial phenomena. Delay differential equations (DDEs) constitute basic mathematical models for such real phenomena. The principal difficulty in studying DDEs lies in their special transcendental character. Delay problems always lead to an infinite spectrum of frequencies. Hence, they are often solved using numerical methods, asymptotic solutions, approximations (e.g., Pad) and graphical approaches. I collaborate with Professor Galip Ulsoy, Henry Ford Professor of Mechanical Engineering. Professor Ulsoy developed a new analytic approach, based on the matrix Lambert function, for the complete solution of a system of linear constant coefficient DDEs. We are applying this theory to study eigenvalue assignment, pole placement, controllability and observability, and time varying coefficients. We have validated the method for stability, free and forced response, by comparison to numerical integration for selected examples. The method is applied to an engineering problem where delay is significant: regenerative chatter in a machining operation on a lathe and a biological problem: control of drug therapies. The matrix Lambert function based solution approach for DDEs is analogous to the use of the matrix exponential for the free and forced solution of linear constant coefficient ordinary differential equations. Systems with multiple time delays and nonlinearities arise quite naturally in engineering and biology and yet little attention has been paid to their analyses. Our method should provide a framework for others to use in

studying these complicated systems. The intellectual merit of this proposal lies in the potential development of specialized methods, based upon the proposed matrix Lambert function approach, for solutions to important problems in systems of delay differential equations (e.g., observability and controllability criteria, controller and observer design, multiple delays, time-varying coefficients, or nonlinearities) that would facilitate the analysis of dynamical systems characterized by such equations. The new method developed in this project will be demonstrated and validated by application to significant problems in science and engineering, for example, the dynamic modeling of HIV with delay and to regenerative chatter in the milling process.

The proposed research on the analytical solution of delay differential equations using the matrix Lambert function promises to be of wide interest to the mathematics, engineering and science communities. The application to HIV will be of benefit not only to researchers in related fields, but will also benefit patients under medical care. For example, the proposed method will be used to establish the best lab testing and drug therapy procedures for HIV treatment. Similarly, the chatter stability results will be of benefit to the manufacturing industry. Those results will enable manufacturers to determine the best spindle speeds and depth-of-cut for their machines for chatter-free high-productivity operation.

Summary of Research on DDEs

Topic	Problem Formulation	Approach	Applications
Nonlinear	$\dot{y}(t) = f(y(t), y(t - \tau), u(t))$	Perturbation Method with Lambert function	HIV, Chatter
Multiple delays	$\dot{y}(t) + \sum_{i=1}^N A_i y(t - \tau_i) + B y(t) = u(t)$	Superposition or Modified Lambert function	HIV, Multiple regenerative effect in chatter
Time-varying	$\dot{y}(t) + A(t)y(t - \tau) + B(t)y(t) = u(t)$	Floquet theory, Wronskian matrix with Lambert function	Milling chatter

Table 1:

6.1 Sturm Sequences

My second area of interest in DDEs is developing algorithms to determine stability manifolds. When one introduces a time delay into a system of differential equations, it is often of interest to determine whether or not bifurcations occur for various lengths of the delay. In particular, a stable steady state can become unstable if, by increasing the length of the time delay, the eigenvalues of the system go from having negative real parts to having positive real parts, and this occurs only if they traverse the imaginary axis. Many authors have utilized certain geometric methods for determining if and when a bifurcation occurs about a steady state. Our research focuses on analysis in polynomial form. Once the standard polynomial results are developed, we have been able to show how these techniques can extend the analysis of a system of delay differential equations by Nelson and Perelson.

The transcendental equation of the delayed differential equation, at the steady state determined for $\tau = 0$, will have the form

$$P(\lambda, \tau) \equiv P_1(\lambda) + P_2(\lambda)e^{-\lambda\tau} = 0, \quad (1)$$

where τ is the length of the discrete time delay, and P_1 and P_2 are polynomials in λ . We can rewrite (1) as

$$\sum_{j=0}^N a_j \lambda^j + e^{-\lambda\tau} \sum_{j=0}^M b_j \lambda^j = 0 \quad (2)$$

and assume that the steady state about which we have linearized is stable in the absence of the delay. Then for $\tau = 0$ all of the roots of the polynomial have negative real part. As τ varies, these roots change. We are interested in any critical values of τ at which a root of this equation transitions from having negative to having positive real parts. If this is to occur, there must be a boundary case, a critical value of τ , such that the characteristic equation has a purely imaginary root.

Early stability methods developed and presented in the classic papers of Pontryagin and Nyquist have been used for many years to study bifurcations in transcendental equations. However, these methods rely heavily on the principal of the argument for determining where the poles of the transcendental equations are located. In other words, they use geometric principles to determine the number of roots of these equations. The monograph by Chebotarev and Meiman shows how to extend the Routh-Hurwitz criteria for polynomials to quasi-polynomials. However, it has been noted that the application of the Chebotarev criterion as an analytical tool is not effective practically. The results that we present using Sturm sequences relax the need for the application of the argument principle and provides an analytical criterion that is practical to use. The Sturm Sequence provides a novel algorithm for determining stability of low degree, i.e., less than degree 4, polynomials that may be useful to anyone interested in stability analysis.

Currently, my research in this area is focused on developing a method that will allow us to consider systems with multiple time delays and/or time varying coefficients.