

## Research Statement 2006

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My research can be divided into two areas; the theoretical study of delay and age-structure differential equations and HIV/HBV pathogenesis.

### Delay Differential Equations

Delay differential equations (DDEs) have been used for many years in control theory and only recently have been applied to biological models. Most biological systems have time delays inherent in them yet few scientists apply these equations due to the complexity they introduce. Investigation into the stability of delay differential equations was pioneered by the likes of Nyquist, Chebotarev and Pontryagin and more recently by Hale. I have been studying the stability of differential equations with both discrete and continuous time delays. In 2000, I mathematically analyzed a system of delay equations for HIV and showed the relationship between model parameters directly depended on the time delay. These results contradicted an earlier published hypothesis, however I was able to rigorously prove my conjecture [?]. In 2002, I developed one of the first continuous time delay models for HIV. Around the same time, other researchers began to introduce time delays in their models for HIV. While there was some controversy as to the proper location in the model of the time delay, I was able to show analytically that the stability and hence the dynamics of the various models was independent of its location [?]. My earlier papers on HIV have helped pave the way for others to use DDEs to model HIV and other infectious diseases as seen by the number of citations, currently over 147. I continue to study the application of delay differential equations to biological models with the focus on determining a general framework for analysis that theoretical biologists and other modelers will be able to apply to their research. My research in this area is now focused on:

(i) Characterizing the similarities and differences between the works of Nyquist and Pontryagin and determining how adjustments in their methods can lead to improvements in stability techniques.

(ii) Investigating the effects of including multiple time delays and time-varying coefficients in models?

My work on age-structured PDEs, which has numerous mathematical similarities to DDEs, is derived from the study of age effects on models for HIV. It is known that the model parameters for HIV are not constant and that there is a direct relationship between the the age of infection and the model prediction. I developed the first model for HIV with age structure and my results showed how varying certain parameters according to specific age distributions changed the estimated kinetic rates of the other parameters. I was able to show that the characteristic equation for the age structure PDE could be found using the Jacobian matrix and proved this through convolutions [?].

Recently, I have been applying my methods in two applications of DDE's; Tool chatter and HIV/HBV with Sturm Sequences.

## Tool Chatter

In Engineering, pure delays are often used to ideally represent the effects of transmission, transportation, and inertial phenomena. Delay differential equations 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 and graphical approaches. In September of 2005, Professor Galip Ulsoy, William Clay Ford Professor of Manufacturing contacted me to begin a collaboration combining my expertise on stability methods for DDES and his new analytic approach, based on the matrix Lambert function, for the complete solution of a system of linear constant coefficient DDEs. We are developing theory to account for systems with multiple time delays, time-varying coefficients, and specific nonlinearities. 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 our work 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 we are developing 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.

My 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. The following table summarizes my research in this area and my recently funded NSF grant with Professor Ulsoy.

## 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

## NSF CMS/DMS 0555765 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:

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  $\tau$  is the length of the discrete time delay, and  $P_1$  and  $P_2$  are polynomials in  $\lambda$ . 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  $\tau$  varies, these roots change. We are interested in any critical values of  $\tau$  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  $\tau$ , 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.

For the degree three problem, the general characteristic equation is

$$\lambda^3 + a_2 \lambda^2 + a_1 \lambda + a_0 + (b_2 \lambda^2 + b_1 \lambda + b_0) e^{-\lambda\tau} = 0. \quad (3)$$

The steady state is stable in the absence of delay if the roots of

$$\lambda^3 + (a_2 + b_2)\lambda^2 + (a_1 + b_1)\lambda + (a_0 + b_0) = 0$$

have negative real part. This occurs if and only if  $a_2 + b_2 > 0$ ,  $a_0 + b_0 > 0$  and  $(a_2 + b_2)(a_1 + b_1) - (a_0 + b_0) > 0$ .

Allowing,  $\lambda = \mu + i\nu$  and exploiting some facts of the polynomial we arrive at the following equation that we then can apply the Sturm Criteria to,

$$\mu^3 + A\mu^2 + B\mu + C = 0, \quad (4)$$

where

$$A \equiv a_2^2 - b_2^2 - 2a_1, B \equiv a_1^2 - b_1^2 + 2b_2b_0 - 2a_2a_0 \text{ and } C \equiv a_0^2 - b_0^2. \quad (5)$$

We then arrive at the following theorem,

**Theorem 1** *A steady state with characteristic equation (3) is stable in the absence of delay, and becomes unstable with increasing delay if and only if  $A, B$ , and  $C$  are not all positive and*

- i.  $a_2 + b_2 > 0$ ,  $a_0 + b_0 > 0$ ,  $(a_2 + b_2)(a_1 + b_1) - (a_0 + b_0) > 0$ , and*
- ii. either  $C < 0$ , or  $C > 0$ ,  $A^2 - 3B > 0$  and the condition (??) is satisfied, where  $A, B$  and  $C$  are given by (5).*

## HIV Research

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 21<sup>st</sup> 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. My results have provided quantitative support to several new hypotheses about the disease [?]. My 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,  $\delta$ , and the viral clearance rate,  $c$ . We have shown that the previously reported values for  $\delta$  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 can we learn about HIV-1 and immune system's dynamics through the analysis of these delay differential equation models and can we present this mathematical theory in a way that researchers, studying HIV-1, hepatitis C and hepatitis B, will be able to use?

2) How will changing the models by accounting for age dynamics, i.e., the age of an infected cell, affect parameter estimates?

3) Can we predict and prevent the imminent failure of drug treatment due to viral mutation?

4) What are the causative agents involved in the gradual decline of CD4 T cells, the main target cell of HIV-1, which eventually leads to AIDS?

5) What is the best way to incorporate sensitivity analyses, model identification and statistical analysis into our models?

Question one above has been addressed in the section on DDE Analysis and a new paper submitted to PNAS on HBV infection [?]. Question two is discussed in my paper, "An Age-structured model of HIV infection that allows for variations in the production rate of viral particles and the death rate of productively infected cells" [?]. I would like to comment that this paper besides presenting the first model for HIV cellular infection with age dynamics, contains some nice theoretical work about the structure of the Jacobian Matrix for an age structured PDE. Question three is the focus of my current work with Professor Ulsoy and our graduate student Sun Yi. Question four is the focus of my own research and is the reason why I began to work on Question five.

After some success with modeling HIV infection, I began to realize that there was a need to have more mathematical rigor to the model equations we were using. I noticed this after spending a year working in Dr. Kathleen Collins' HIV lab here at UM. I worked on my own experiments and began to question the models that I and other were using. Many researchers, including myself, 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 the publication of additional and/or alternative compartment formulations were proposed and the use of delay differential equations (DDEs) in modeling the eclipse phase was heavily debated. 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.

The focus of my research then changed temporarily to consider how confident we were with these models. The models were making profound impacts on the understanding of the disease and I wanted to make sure we were correct. Hence, I began to work on addressing 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 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 an 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* [?]. My research also focuses on model identifiability, observability and model sensitivity [?]. My group is currently working on numerous papers to address these issues and to make these techniques available to the infectious disease modeling community.