RESEARCH STATEMENT

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One of my research interests is the development of effective symbolic and numerical computation methods for investigating large scale biochemical networks. Symbolic computation techniques have led to new approaches for problem-solving in many areas of science and provide tools that enable an automatic and computerized solution of problems in ways that are not possible with conventional computing systems.

A second research interest of mine is the development of quantitative mathematical models of genetic regulatory networks that are directly comparable with experimental data. Many intracellular regulatory networks have been extensively studied using biochemical and genetic techniques. However, there have been relatively few attempts to integrate this knowledge into mathematical models. My goal is to determine the underlying functional mechanisms of such networks through the use of mathematical modeling. This is very important because mathematical models provide information about how components of these pathways are assembled and dynamically regulated. The mathematics I use to investigate these systems is highly interdisciplinary, drawing from dynamical systems theory, symbolic computation techniques, numerical methods and theory of reaction kinetics.

Symbolic computation approach to complex biochemical reaction networks

Multivariate systems of polynomial equations often arise in mathematical models of biochemical networks. These models usually consist of a number of parameters whose values are generally not known a-priori. This hampers both analytical and quantitative investigations of the mathematical model. Unlike other software packages, computer algebra systems are capable of manipulating symbols as well as numbers. This makes working with equations with unknown parameters easier.

My research focuses on using symbolic computations to derive rate equations for reactions catalyzed by single enzymes and to investigate the steady-state behavior of metabolic pathways. A mathematical description for the kinetics of a reaction catalyzed by an enzyme consists of a system of polynomial differential equations. The dimension of the models gets large for multi substrate/product reactions if one explicitly considers binding mechanisms of the enzyme. A standard way to reduce the dimension of the model is by a separation of time scales approach that assumes enzyme bound species reach their steady states fast as compared to product release. This reduces the differential equation model to a system of multivariate polynomials if one considers the time derivative of the final product as one of the variables. Although this system is “linear” in the concentration of enzyme bound species, the large number of parameters makes the derivation of rate equations that only involve substrate and product concentrations hard, sometimes impossible, if it is done by hand. Several methods have been developed to address this problem, and the most accepted one is the graphical method developed by King and Altman[1]. Although this method is quite general, it has the following disadvantage: if a rate equation is computed for a given scheme and the scheme is then amended, all calculations have to be carried out again. This makes the

method unpractical for predicting the general behavior associated with broad classes of binding mechanisms.

Mathematical models for the dynamics of metabolic pathways are systems of rational differential equations. These pathways start with a *source* of material and finish with an end product, the *sink*. In most cases, this will lead to the development of a steady state, where the concentration of the intermediates remains constant because their rate of formation balances their rate of degradation. This also requires that the flow through the pathway remains constant. Models for the dynamics of these systems reduce to a system of "nonlinear" multivariate polynomial equations if the flux through the pathway is considered as another variable.

There are many numeric algorithms for solving a system of multivariate polynomial equations. These algorithms ignore the geometric properties of the solution space and solve for one solution at a time and find an "approximation" to the solution. However, if a system can be transformed into an equivalent system that is easier to solve, then the computation of the solutions can drastically improve. The method of Groebner bases provides a uniform approach to solving a wide range of problems expressed in terms of sets of multivariate polynomials[2]. The general strategy of the Groebner bases approach is to transform a set of multivariate polynomial F into another set G of polynomials with certain nice properties, called a Groebner basis, such that F and G are equivalent (i.e. generate the same ideal). From the theory of Groebner bases we know that many problems that are difficult for general F are easy for Groebner bases G. The solution of the problem for G can often easily be translated back into a solution of the problem under consideration.

One of the nice properties of the Groebner bases technique is that the set of polynomial equations can be transformed into a system of multivariate polynomials in upper triangular form. This allows automatic derivation of the rate equations for an enzyme reaction scheme of any complexity under the quasi-steady state assumption for the enzyme bound complexes. My dissertation is a nice application of symbolic and numeric computation techniques used to analyze enzyme kinetics. In particular, I worked on the three step conversion of glucose and creatine into NADPH using *in vitro* measurements of NADPH in time. I estimated the kinetic parameters and control coefficients that determine how flux through the pathway is controlled by the three enzymes in the system.

Modeling of genetic regulatory networks and Lac Operon

The lac operon is a classic example of an inducible genetic network. The lac operon of `E.coli` consists of a small promoter–operator region and three larger structural genes lacZ, lacY, and lacA. Preceding the lac operon is a regulatory operon lacI that is responsible for producing a repressor protein. This control system functions in the following manner. In the presence of glucose, LacI represses the lac operon. However, in the absence of glucose, but in the presence of external lactose, lactose is transported into the cell by a permease. Intracellular lactose is then broken down into glucose, galactose, and allolactose by the enzyme β-galactosidase. The allolactose feeds back to bind with the lactose repressor and enables the transcription process to proceed.

It is known that the lac operon regulatory pathway is capable of showing bistable behavior. My research focused on how bistability arises in the lac operon system in E.coli and how time delays due to the transcriptional and translation process affects the dynamics of this system.

Among the various patterns of behaviour emerging from regulation associated with nonlinear kinetics, bistability is extremely interesting. Bistability allows a true discontinuous switching (with hysteresis) between alternate steady states that can convert graded inputs into switch-like responses. This permits a discontinuous evolution of the system along different possible pathways, which can be either reversible or irreversible, and may provide the system with a memory.

To investigate the role of time delays due to transcription and translation on the dynamics of the system, we developed a model of ordinary differential equations with discrete time delay. Our model is five dimensional and has three delay terms. We numerically investigated the model using published parameter values and demonstrated that this system is indeed capable of bistability under physiological conditions.

To investigate the origin of bistability further, we assumed that there is certain constant amount of lactose inside the cell. This reduced the five dimensional model to three dimensions by eliminating the equations for the permease and external lactose concentrations. By numerically solving the time-delay differential equations of the reduced model and by performing a local stability analysis we showed that it behaved similarly to the complete model and displayed bistability. From this, we conclude that the β-galactosidase regulatory pathway is the essential regulatory mechanisms for bistability in the lac operon. We showed that time delays do not affect the stability of the system in the sense that there is no evidence for a Hopf bifurcation. Although one was reported in a recent model developed for the regulation of lac operon by Mahaffy and Simeonov[3]. The analysis of our reduced model gives no grounds to expect a Hopf bifurcation or oscillatory behaviour. This last result supports the conclusion that the β-galactosidase regulatory pathway is the most essential of the regulatory mechanisms in the lac operon.

Future Projects

Over the past two years I have been working on a project involving the pheromone signaling pathway of yeast. The yeast pheromone response is one of the best characterized signaling pathways and contains several positive and negative feedback loops. I plan to develop mathematical models of this pathway to interpret time-dependent data for protein activity. This is an ongoing collaborative project with biochemists. The ultimate goal of this project is to construct a mathematical model to simulate the whole pathway. Experimental data for protein levels obtained from either population or single cell measurements will be used to validate the model.

I am also interested in stochastic modeling of biochemical networks, and the natural and artificial regulation of such networks. Deterministic models overlook the random nature of biochemical reactions. However, stochasticity is a significant effect in genetic regulatory networks because of the low copy numbers of molecular species such as DNA and mRNA. To consider the effects of fluctuations requires

the use of stochastic models. Stochastic models can capture important behavior that is not seen in deterministic models [4].

Estimation of parameters values in models of biochemical networks is often difficult because the data are noisy and our knowledge of the network topology and participating molecular species is incomplete. Additionally, determining how well the model parameters are constrained by the experimental data is as crucial as finding optimal fits to the data. Both of these issues can be addressed using Monte Carlo methods. Because these methods determine which parameters are least constrained by the data, that often suggest new avenues for experimental analysis to measure the unknown parameter values.

There is a wealth of new experimental techniques in molecular and cell biology, such as biosensors and microarrays, that have created an incredible amount of novel data. I plan to continue applying mathematical, statistical and computational methods to interpret and analyze these new data.

References

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TEACHING STATEMENT

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Every professional believes that his/her profession is the most important of all. I think so too, but I have a different approach. From my perspective, I see mathematics as a real basic science. Not only hypothetically, but in practice it is a real life science. Man did not invent math, he just discovered it because in everyday life we need it desperately. I want to show students that math is not only a fixed formula of facts.

When I tell people that I am a mathematician and doing research in math, many of them respond in exactly the same way: Math is hard. It is widely believed math is inapproachable to all but except a few. I think this false concept takes its roots from negative stereotypes, scaring to fail, and many more reasons. One of the most challenging things is to overcome the lack of confidence some students have in their math abilities and show them how math is useful and how it makes life easier for us. There are many methods to engage the students' interest in the subject of math. The most obvious way to do it is to show them how math actually interfere with our life. I find that it increases students' understanding when I show them how the topics of interest have applications in other sciences. I want to show them that math is a language; it uses numbers and theorems, functions, instead of letters.

I like teaching math. Before starting my PhD program, I used to teach at colleges. And now I am teaching again at the undergraduate level. I can make a long list of why I like teaching. First of all, I am not only teaching it to others, I am exploring the math myself. After all those years in undergraduate and graduate training, I still think that there is much more things to explore. Second, I believe mathematics is one of the most enjoyable things to teach, since a math instructor not only carries mathematical knowledge, but is given an opportunity to stimulate logical thinking and reasoning among the students. One can forget all equations and formulas once the class is over, but, students who have learned "thinking like a mathematician" will have a precious skill for the rest of their life.

Teaching is a dynamic profession. Especially in a science that is at a crossroad, like math, one should know how to deliver the material to students. Students and instructor both have responsibilities in a class. As an instructor, it is my job to provide well-prepared material, encourage students to learn and do the necessary work. Careful preparation of class material is the first step in being able to explain complicated topics clearly.

Since my research interest is in applied math, I often incorporate applications and ideas from other sciences. I always spend enough time to prepare and up date my material. My teaching approach depends on the course I teach. In advance classes, students are prone to learn more effectively with take-home examinations or projects. I always encourage students complete projects that involve real life problems. I believe that applications of formulas and complicated theorems to another science and seeing a concrete results of their effort will show them that math is more than just two plus two. When students realize that they can use simple math to understand and solve problems relevant to their lives, they will discover that math is stimulating. I also try to give plenty of time to students for discussion inside or outside the class.

My principal is to know interest, strengths and weakness of each individual in my class. Because I believe teaching works best when adjusted to each student's needs. Key aims of my teaching philosophy are interaction, waking and nurturing interest in math, supportive use of technology in the class. My enthusiasm for math and teaching are my strengths. My major goal as an instructor and research advisor is to transfer to students understanding and joy of applied math.

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