Research Interests

High throughput cell and molecular biological tools have dramatically altered the way in which we explore living systems and have significantly enhanced our knowledge of the specific genes and proteins involved in various biological processes. Indeed, we have now entered a period of biological research in which we are no longer data limited, but are instead restricted by our inability to intuitively organize, explore, and understand the complexity of living systems. My interests revolve around using computational methods to explore the function of complex cellular systems in both normal and diseased states. I will focus my research on two such problems – an analysis of the kinetics of cell loss due to inherited and acquired neurodegeneration (ND), and an investigation of the dynamics of the insulin-dependent signal transduction network in muscle and adipose cells.

Apoptotic Cell Death and ND Kinetics: Neurodegenerative disorders can have devastating physical and psychological consequences for the lives of those affected. Although we know little regarding the mechanisms by which physical, environmental, and genetic insults ultimately lead to neuronal attrition, a common feature of many forms of ND is that affected cells undergo apoptotic cell death. Remarkable progress in elucidating the molecular details of apoptosis and of ND has been made in recent years, but little attention has been given to higher order, system level properties of the affected cells. I have been using mathematical analyses to explore one of these properties, the kinetics by which cells undergo apoptosis in response to various genetic and acquired injuries, and have made significant discoveries that I will elaborate on with my proposed research.

My original analyses showed that the risk that any neuron will undergo apoptosis was constant, thereby challenging the prevailing idea that ND results from a gradual accumulation of damage that progressively increases the probability that a cell will undergo apoptosis [1]. To explain this observation, we hypothesized the existence of an alternative homeostatic state – the Mutant Steady State (MSS) – the exit from which was regulated by stochastic fluctuations in biochemical events. I later demonstrated (in collaboration with a graduate student from the Dept. of Mathematics) that by assuming dying photoreceptors release toxic factors into the surrounding environment, our model could produce degenerating cell patches of histologically observable size, thus reconciling the constant risk MSS model with the spatially heterogeneous cell loss observed in under clinical settings [2]. More recently, I was able to show that available ND data were better described by a stretched exponential (SE) function than the single exponential function of the original MSS model, and that the distribution of risk across affected populations could be described by a power law [3, 4]. We have interpreted these results as an indication that individual neurons experience a unique yet constant probability of dying that is determined by scale-free heterogeneities in the tissue environment.

To date, my hypothesis that fluctuations of cellular events result in the constant risk of cell loss during ND has not been tested directly. As one part of my research I will explore this possibility by generating models of the vertebrate apoptotic network and analyzing their dynamics using established stochastic-simulation procedures [5, 6]. Published models (see [7-10], for example) that exhibit behaviour consistent with empirical evidence will be used as a foundation for the stochastic models, and the consequence of random variation in reactant number densities will be evaluated. A related possibility, based on recent analyses of single enzyme molecules [11], is that the constant risk of cell loss might reflect fluctuations in the activities of individual proteins of the apoptotic cascade. To explore this possibility, the stochastic models described above will be modified so that reaction rates are randomly selected according to activity distributions reported for single enzymes. For both sets of simulations, neuronal lifetime distributions will be obtained and fit to both the constant risk and SE models of cell loss to examine whether fluctuations in molecular properties can account for the temporal patterns of neuronal attrition.

More abstract models will also be used to explore mechanisms of neuronal death. I previously suggested [1], based on the observation of a constant risk of cell death, that if damage accumulation occurred during ND then it did not affect the chance that a cell would undergo apoptosis. However, an alternative explanation is that the accumulation of intracellular damage does occur, but can only trigger apoptosis once a specific threshold is passed. If it is assumed that all intracellular molecules are damaged with equal likelihood yet affect the overall risk of death differently, and if all forms of damage are equally likely to be repaired by cellular defense mechanisms, then the instantaneous apoptotic risk experienced by a cell will be dependent on its history of damage and repair. Random walk models based on these concepts will then be used to make qualitative predictions regarding the temporal patterns of cell loss, which can then be compared with empirical data.

Computational Analysis of Insulin Signaling Networks: The prevalence of type 2 diabetes, which currently affects on the order of 3% of the global population, is increasing at an alarming rate. Progression from normal glucose homeostasis to type 2 diabetes involves severe insulin resistance in peripheral tissues [12], and although genetic predisposition has been suggested as an important contributing factor, the mechanism by which resistance develops is unclear. Under normal conditions, the binding of insulin to its receptor initiates an intracellular signaling cascade that triggers the movement of the GLUT4 glucose transporter from intracellular stores to the plasma membrane (PM) [13]. As the abundance of GLUT4 at the muscle cell PM is dramatically reduced in patients with type 2 diabetes [14], and chronic exposure of cultured adipocytes to insulin reduces the activity of several response network components [15], it is likely that abnormalities in this signaling network are involved in generation of the resistant state.

Although enormous advances have been made in identifying insulin-responsive signaling molecules, many gaps remain in our knowledge regarding how the complete system performs under normal conditions, and how changes to the network lead to insulin resistance. For instance, modifications to network organization or to reaction parameters may decrease network sensitivity to normal stimuli, may decrease the robustness of the system to inappropriate stimuli, or may affect the ability of the network to adapt to chronic stimulation. While each of these scenarios may have a role in the etiology of insulin resistance, it is not clear if, or how such features arise from the interaction of the network components. To address this question, I will generate simplified model networks based on known components of the insulin response cascade with the goal of determining the network features that are the most likely agents responsible for insulin resistance.

Skeletal muscle and adipose cells are responsible for the vast majority of postprandial insulin-dependent glucose uptake [12, 16]. My analysis will therefore focus on developing simplified networks consisting of validated biochemical interactions and known regulatory loops from these experimental systems. The networks will initially be analyzed using traditional deterministic models, and system dynamics will be followed by numerically solving the pertinent systems of differential equations. The validity of these models will be tested by comparing the predicted rates of GLUT4 translocation and glucose uptake with known behaviour in the basal and insulin-stimulated states, and by evaluating the ability of the models to accurately predict the phenotypes resulting from known pharmacological and molecular genetic treatments. These simplified network models will continually be updated so they qualitatively and quantitatively reproduce available empirical data.

To explore how insulin resistance might arise due to network changes, these models will be further studied by sensitivity analysis, which will enable the identification the reaction parameters and network motifs that are most critical for maintaining normal insulin responsiveness. Because circulating insulin levels increase in the resistant state, yet peripheral tissue cease responding to the hormone, a particularly important analysis will be focused on determining the signaling motifs that

normally contribute to, or inhibit the network's ability to adapt to increasingly intense stimuli. In other words, does the signaling network respond to changes in the insulin signal, or does its output reflect only the absolute value of the input signal?

I am presently analyzing a simplified deterministic network model, first described by Sedaghat and colleagues [17], that can reproduce empirically available data regarding glucose uptake with a reasonable degree of fidelity. I have been able to reproduce their results using independent methods, and have thus confirmed the stability of their model system. However, preliminary comparisons between this model and results from experimental perturbations indicate that this simplified network is unable to fully reproduce the responses observed *in vivo*. Consequently, I am generating alternate deterministic models that, although simplified relative to recognized biochemical detail, incorporate a larger cohort of signaling molecules that more faithfully depict the feedback and regulatory modules that have been identified empirically.

Long term projects will explore biologically relevant variations of the models described above. First, because the cellular reaction volumes relevant to signaling processes are often small in comparison to whole-cell volumes, few molecules of each reacting species are normally available to respond to incoming signals and fluctuations in number densities can effects network output. To explore the role of such fluctuations in insulin signaling, I will analyze the simplified models described above using established stochastic simulation procedures [5, 6]. Second, because the redistribution of signaling components is a major event in the insulin response [13], the network models will be modified to explicitly account for spatial reorganization of signaling components. Finally, a more detailed large-scale network model that includes all known molecules that interact with components of the insulin-response network will be generated and analyzed in a manner similar to that discussed above. Many of the proteins involved in insulin signaling also mediate the effects of other cellular signals. Consequently, these large-scale models will enable the analysis of the role that other cell signals (such as PDGF and adipokines) play in modulating the metabolic effects of insulin in peripheral tissues. The quantitative understanding of insulin signaling in muscle and adipose cells obtained by these approaches will no doubt provide valuable insights into the role of both individual molecules and specific network motifs in the development of insulin resistance, and likely enhance our ability to develop effective therapeutic interventions.

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Teaching Interests and Experience

I consider a university faculty member's role in education to be far more than a provider of information during the training of a skilled workforce. I believe that learning is a life-long undertaking and that the role of faculty is to encourage and facilitate deep self-directed learning in addition to enabling critical thinking and creativity in all endeavours. Necessarily, this extends beyond teaching at the undergraduate and graduate level to include involvement with both continuing education of adult learners, and with secondary school students as well.

Accordingly, I am interested in teaching at several levels. At the undergraduate level, I would be interested in involvement with both introductory biology courses – specifically cell and molecular biology – and with more specialized, senior level courses. One possibility would be a course in emphasizing the use of computational methods normally associated with math, physics, and chemistry to gain understanding of cell and tissue function. Such a course focusing on understanding cellular organization and function will provide students with a biological perspective that will be increasingly important as the paradigm of systems biology takes hold in modern research. Moreover, if open to students from a variety of traditional subjects, the appropriate choice of problems would encourage the biologist to call upon their colleagues from other disciplines, and *vice versa*. Consequently, students from different fields would have a unique opportunity to work with each other, and to learn scientific approaches different from their own. Hopefully this would be a step in educating scientists that 'speak the same language' regardless of their research specialties.

In addition to these more formal teaching interests, I am also interested in teaching outside of the usual university curriculum in the form of outreach in the community. As biology becomes more visible to the public through mainstream media, it becomes increasingly important that experts in the field also become visible and encourage intelligent debate over social issues that arise in response to advances in knowledge and technology. Continuing education courses designed to help community members learn about and discuss such issues with experts will no doubt increase their ability to make rational decisions when confronted with choices involving scientific issues.

The majority of my teaching experience has been informal, centred predominantly around in-lab teaching of research colleagues. These colleagues have spanned different levels of educational experience – from summer students becoming familiar with research methodologies, through graduate students and postdoctoral peers, to my own research supervisors – thereby providing a significant range of teaching experiences from which to draw. As my research interests and experiences have often been somewhat different from those of my closest colleagues, one of the noteworthy skills I have developed is an ability to effectively teach colleagues material from disciplines to which they have not been exposed. For example, I first became interested in utilizing computational approaches in cell biology during my doctoral studies, when I worked in a lab composed entirely of molecular biologists. Therefore, I not only had to learn the appropriate mathematical tools myself, but I also needed to learn how to accurately communicate their importance and details to individuals not familiar with these concepts. Similarly, during postdoctoral training in a research group comprised of a diverse group of applied mathematicians, engineers, physicists, computer scientists, and graphic artists, I was the only researcher trained in experimental biology.

During these experiences, feedback regarding my teaching abilities has been uniformly positive. I have always attempted to be as approachable and collaborative as possible, trying to facilitate the discovery of questions and answers rather than simply providing quick responses. As a self-directed learner, I have consistently found that teaching others how to recognize solutions and make progress themselves is far more rewarding and productive in the long term.