Research Statement

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I am an applied mathematician who specializes on using mathematical tools to study problems that arise in biology. I am particularly interested on developing models that can help to understand physiologic and metabolic processes, as well as the dynamics of infectious diseases in both, at population and in-host levels. When the complexity of the model allows it, I use dynamical systems theory and applied analysis techniques like singular and regular perturbation theory to extract information about the problem. In most cases however, these models cannot be solved analytically and it is necessary the use of existent or own written numerical packages. In either way, analytic or numerical analysis of the model can reveal rich insights about the biology of the problem that would allow us to draw important conclusions.

Usually the conclusions that can be drawn from these models depend on how well parameters can be estimated from real animal or human data. However, biological models usually come with a large number of unknown parameters and in practice only some of them can be estimated given a model and available observations. For parameter estimation, I use Ordinary Least Squares and Maximum Likelihood Estimators as well as Bayesian techniques such as Markov Chain Monte Carlo, Metropolis, Metropolis-Hastings or variations of these like Delayed Rejected Adaptive Metropolis (DRAM) to construct posterior densities for model parameters. In order to reduce the number of parameters to be estimated, I also perform sensitivity analysis and study of correlations computed from the covariance matrix which allows us to determine parameters that are pairwise correlated as well as computing standard error and confidence intervals.

Previous work

Over the years, I have worked on mathematical models to describe the dynamics of certain diseases and conditions. As part of my Masters thesis, I worked on applying an existent differential equation model to study the interactions between hepatitis C virus (HCV) and the immune system cells in the human body. Also, therapy was addressed as an optimal control problem to determine best treatment strategies, [1]. Further, model parameters were estimated using ordinary least squares fitting from longitudinal data (serum HCV RNA measurements) given in reported literature. In the summer of 2016, I attended a Mathematical Research Communities on which, together with other colleagues and under the supervision of Dr. M.S. Olufsen, we developed a mathematical model that couples the interactions of the inflammatory response with cardiovascular dynamics, [2].

Current and future work

Currently, I am working on the development of mathematical models consisting of ordinary differential equations to explore the dynamics of the acute inflammatory response against infections caused when a pathogen makes its way into a host. In particular, I am interested in studying disorders in energy metabolism, such as low levels of adenosine triphosphate (ATP), lactate accumulation, and nitric oxide (NO) overproduction, which can trigger organ dysfunction and is characteristic in patients with sepsis.

Sepsis is an overwhelming systemic inflammation that may occur whenever pathogens enter the body. This condition can lead to tissue damage, organ failure, and death. Every year more severe sepsis affects more than 1.7 million of people only in the U.S. and over 30 million of people worldwide [3]. Several studies have found association between sepsis, mitochondrial dysfunction and nitric oxide [4], [5].

We recently published a paper entitled "Mathematical modeling of energy consumption in the acute inflammatory response", on which we present a computational model to study the dynamics of acute inflammation that incorporates a reduced representation of relevant metabolic pathways and energy resources and demands, [6]. This model represents a significant extension of previous models in that takes into account the dynamics of the immune system in the presence of pathogens and incorporates energy production along with the energy requirements that arise when fighting such an infection. In particular, we investigate the role of energetics during infection and explore the relation between overproduction of NO, lactate, altered ATP levels, and sepsis. See Figure(1). New mathematical formulations needed to be developed to handle such complex interactions and to help have a better understanding of the role of energetics in sepsis and the impact in some metabolic conditions.

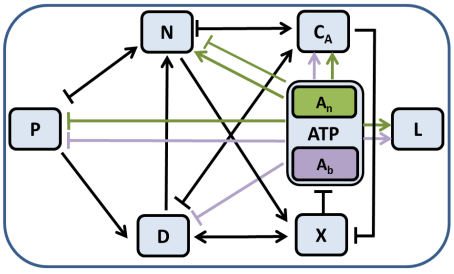

Figure 1: Interactions between the eight variables of the system of equations in the model. Arrows and bars indicate up and down regulation, respectively. P corresponds to pathogens, N to activated neutrophils, C_A anti-inflammatory mediators, D measures levels of tissue damage, X is nitric oxide, L lactate, and ATP is subdivided into two categories, A_n which is produced through glycolysis and A_b, which is produced through mitochondrial respiration. The actions of A_n are indicated by green arrows and bars while the actions of A_b are denoted as purple lines.

The model provides a helpful tool for evaluating the outcome of virtual patients which eventually can be used to better treat real patients. In fact, we created a set of virtual patients by introducing variability in some parameters and then classified them into non-survivors and survivors. Assuming no treatment is administered, the model predicts the times of death for each patient. This information will provide an idea of when is best to administer treatment to real patients. This model was also applied to study metabolic conditions such as hypoglycemia (low blood glucose), hyperglycemia (high blood glucose) and hypoxia (low oxygen availability). All of which have been reported to have a negative impact on the immune system, increased mortality, and benefit sepsis [8]-[13]. By understanding how these conditions interact with the immune system we can also suggest treatment strategies to reduce the risk of a patient becoming septic.

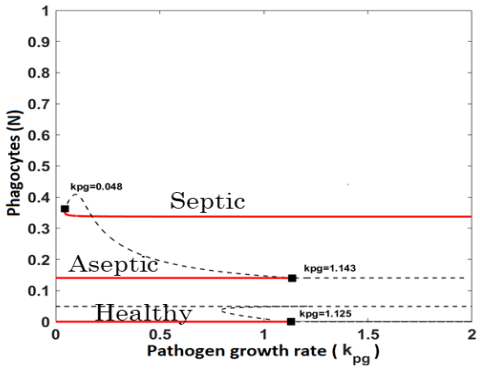

Figure 2: Bifurcation diagram for model equations (1)-(8) on [6]. Equilibrium states are illustrated with red solid curves (stable), shown with dashed curves (unstable), or not shown at all if non-physiological. The three stable equilibrium states correspond to healthy, aseptic, and septic states.

The model exhibits three biologically significant equilibrium states: healthy, aseptic, and septic. As depicted in Fig.2, a bifurcation analysis of the system shows that for our baseline parameter set, tri-stability can be achieved for fixed values of the pathogen growth rate k_{pg}, which reflects realistic tuning in that the same patient could end up in any one of these three states, depending on infection severity. We also observed that the insufficiency of ATP production plays an important role in the developing of sepsis.

Most recently, we have developed an extended model that builds up on the work done in [6]. We are currently working on the detection of identifiable parameters in order to reduce the number of parameters to be estimated when fitting the model to animal data. Parameter identification consists of finding a set of parameters that can be estimated given a model and data. This is however not an easy task since data is limited and only a subset of model outputs have been measured, and consequently only a subset of model parameters can be identifiable, [7]. Further, the high dimensionality of the parameter space makes the problem

highly nontrivial. As a result the use of global search optimization methods and Monte Carlo algorithms for estimation of the model parameters is necessary.

Future directions include:

- **Parameter identification and parameter estimation.** We are currently applying parameter identification and estimation techniques, to properly tune our extended model with available animal data. In particular, we are interested on determining main differences across survivors and non-survivors on a study done on thirty-two baboons that 2×10^9 colony forming units per kilogram of Escherichia coli were infused IV into each subject over 2 hours. Our main goal is to identify the role of energetics on each of the groups and to determine the cause of death of the non-survivor cohort. Once the model is well tuned, it will allow us to predict patient outcome and to prescribe therapy at the right moment to help reduce mortality.

- **MODS**. Multiple organ dysfunction syndrome (MODS) is a condition primarily caused by sepsis and may result in septic shock. The precise reasons of why this syndrome occurs have yet to be found. Compartmental models that include the acute inflammatory response within organs, blood and tissue can be considered as an attempt to try to explain MODS.

- **Optimal control**. Computational models, like the ones mentioned above, can be used to generate virtual patients on which treatment can be artificially administered. Moreover, optimal control can be applied to determine optimal treatment regimes to fight infection while simultaneously reduce side effects. Hopefully, designing these treatment strategies will allow for approaches that are tailored to individual patient characteristics, allowing for a much more extensive exploration of options, with a more refined capability to address specific patient needs, that can be achieved in clinical settings.

- **Treatment to address metabolic conditions**. Adaptations of our extended model, such as increasing or decreasing the production rate of glucose, can be used to address metabolic conditions such as hyperglycemia and hypoglycemia. Similarly, we can induce hypoxia by imposing conditions that simulate lower oxygen availability that will compromise the aerobic production of ATP. Further, with these extensions in the model, we can explore the effect of treatment of either of these conditions when combined with sepsis.

- **Warburg Effect**. Contrary to most other cells in the body, certain immune cells even in aerobic conditions, rely their production of ATP mostly on anaerobic respiration rather than the much more efficient oxidative phosphorylation pathway. This phenomenon, called the Warburg Effect, also occurs in cancer cells and it has been studied and documented for over 90 years. The reason why immune and cancer cells experience this

metabolic switch remains unclear. Through bifurcation analysis and numerical simulations, the models mentioned above or adaptations of them, can be of great help to study this mechanistic switches in cell metabolism.

As I move forward on my career, I am open and exited to collaborate with colleagues of different areas of science to use the previously mentioned as well as new methods to explore the underlying biology of a variety of problems arising from immunology, oncology, epidemiology, population dynamics, infectious diseases, ecology, and many other areas of life sciences.

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