Introduction

My graduate research in the field of mathematical biology involves modeling cardiovascular dynamics. In particular, my dissertation has focused on assesing the state of the cardiovascular system for individuals suffering from orthostatic intolerance (OI). The ultimate goals of my research are to apply techniques of mathematical modeling, parameter identification, numerical optimization, and control theory to understand how disorders alter the biological function of the cardiovascular system, and to use these methods to aid clinical professionals to assess the state of the cardiovascular system within and between groups of subjects.

My work focused on three aims: 1) development of a patient-specific pulsatile model that interprets the effect on the cardiovascular control system for patients suffering from OI 2) development of a non-pulsatile model that accuratley coincides with the pulsatile model; and 3) regulation of efferents in response to the head-up tilt (HUT) test using time-varying parameters via the use of piecewise splines and an optimal control method. The dissertation is organized as follows.

A compartmental model analogous to an electrical circuit was developed, along with a physiologically based sub-model describing gravitational pooling of blood into the lower extremities utilized for aim 1. A simpler non-pulsatile model that can be interchanged with the pulsatile model is developed, which is significantly easier to compute, yet it still is able to predict internal variables for aim 2. For aim 3, a cardiovascular regulation model using piecewise linear splines is compared to an optimal control approach using a collocation method to adjust those efferents impacted. Newly developed methodology for sensitivity analysis, parameter subset selection, and parameter estimation (13) is used to choose model parameters that are to be estimated, while the technique developed in (9) is utilized for the numerical optimization of model parameter values. A methodology for the optimal control approach to estimate model parameters was developed that is implemented using the general pseudospectral software, GPOPS (14).

The results of my work showed that simple pulsatile and non-pulsatile models can be made patient-specififc and used to interpret the effect of OI on the very complicated cardiovascular system. I was able to determine a set of parameters that when regulated can predict changes in the cardiovascular system impacted by OI. It is also shown that regulating these parameters using the optimal control approach provides a more proficient prediction of efferent changes in comparison to the piece-wise linear spline method. Several publications have been submitted on this study, and thus my dissertation is composed of those published works as contributing chapters.

Although my dissertation focuses on the cardiovascular system, the techniques utilized are applicable to the study of any system that can be modeled by ordinary differential equations. My future interests include using mathematical techniques to model various biological systems, allowing model based predictions as well as model based data analysis.

Future Research and Interests

My models were developed to be very simple while still having the necessary components to correctly model the effects of blood pressure during HUT. Therefore, numerous future studies could be developed to advance my current study. Future work can consist of:

- Develop a model for autonomic regulation to avoid using optimal control or linear piecewise splines to regulate efferents.

- Coupling this simple compartmental model with a fluid dynamics model that can predict the wave reflections seen in the blood pressure data, thus giving more accurate depictions of the controlled efferents.

- Developing a global subset selection strategy that may be better suited for analysis of many systems. The parameter identification techniques utilized in this study are inherently local in nature. These methods can be sensitive to large differences in parameter values.

- Use results obtained from optimal control method to develop an empirical feedback to predict the control.

I would love to continue to use mathematical models and parameter identification techniques to understand the cardiovascular system and aid clinical professionals in determining answers to their medical questions. I am also interested in studying related aspects of the human body involving not only the cardiovascular system, but the renal, reproductive, respiratory, and immune systems. I was privileged in my undergraduate career to assist in some research involving infectious disease modeling. Infectious diseases effect several of the body's systems, all of those I mentioned that interest me. My ultimate desire is to use mathematics in research to study biological systems so that I may contribute to enhancing the life of people all over the world, whether it involves rather simple disorders or deadly diseases.

Background and Significance

Orthostatic intolerance occurs when the act of standing upright causes an imbalance in blood pressure and flow in the body. When a human stands, approximately 750 mL of thoracic blood is abruptly translocated downward, reducing the venous return and cardiac filling (10; 15). People who suffer from OI lack the basic mechanisms to compensate for this deficit. Changes in heart rate, blood pressure, and flow that produce OI may be related to abnormalities in the interplay between blood volume control, the cardiovascular system, the autonomic nervous system and local circulatory mechanisms that regulate these basic physiological functions.

The most common symptom of OI is syncope, the clinical term for fainting. This loss of consciousness is caused by a severe drop in arterial blood pressure. OI is difficult to diagnose. As a result, many patients have gone misdiagnosed or treated for other disorders. Head-up-tilt (HUT) testing has become the standard to diagnose syncope and other orthostatic disability (10; 12). The test is simple – using a motorized table with a foot support to raise the patient from supine to approximately 60-70 degrees upright without the use of the patient's own muscles.

As a response to tilting, blood pressure in the upper body (above the center of gravity) is decreased, while blood pressure in the lower body (below the center of gravity) is increased. During HUT the baroreceptors located in the carotid sinuses sense the drop in blood pressure causing sympathetic activation and parasympathetic withdrawal. This in turn leads to an increase in heart rate, along with changes in cardiac contractility and vascular resistance (7; 18).

Patterns of blood pressure and heart rate during HUT take diverse forms which relate to the underlying mechanism of disease and which may help individualize specific therapy. Most patients experience an improvement of their symptoms, but for some, OI can be gravely disabling and can be progressive in nature, particularly if it is caused by an underlying condition which is deteriorating. The ways in which symptoms present themselves vary greatly from patient to patient; as a result, individualized treatment plans are necessary. In order, to develop effective treatment plans, various measurements and experiements must be performed with the cardiovascular system to gain data and knowledge of the phenomenon. As a consequence of the system being so complex, measurements and experiments are difficult to perform.

Thus, our goal is to develop pulsatile and non-pulsatile patient specific compartment models that predicts dynamic changes in arterial blood pressure, using time-varying parameters to predict the effects of the cardiovascular control system. Parameters are to be made time-varying by use of piece-wise linear splines and an optimal control approach. Understanding cardiovascular regulation during HUT involves invasive measurements that are experimentally difficult to achieve, hence the use of mathematical modeling is a great alternative to study cardiovascular dynamics. Moreover, the patient specific model may be used to learn about the impact on treatment of disease.

Dissertation Summary

The cardiovascular system is a very complex structure and its regulation makes it difficult to model the system as a whole. Simplifying assumptions are made according to the objective of a given study. The cardiovascular system can be modeled using approaches ranging from detailed three-dimensional models of local structure to system level models assuming spatial consistency. Futhermore, the cardiovascular control can be modeled using anything from empirical models down to elaborate molecular models. We chose to develop system level models that involve parameter estimation techniques to render the models patient specific.

Modeling HUT and Parameter Estimation

I developed interchangeable pulsatile and non-pulsatile patient specific models formulated using a system of ordinary differntial equations. The models use heart rate as an input to predict dynamic changes in arterial blood pressure during HUT (19; 20). My model consists of five compartments representing arteries and veins in the upper and lower body of the systemic circulation, as well as the left ventricle facilitating pumping of the heart for the pulsatile model. An empirical law called the Frank-Starling mechanism (3) provides a model for the left ventricle for the non-pulsatile model. A physiologically based sub-model describes gravitational pooling of blood into the lower extremities during HUT, and a cardiovascular regulation model adjusts the efferents, cardiac contractility and vascular resistance, in response to the blood pressure changes. These efferents are first adjusted in an indirect manner by expressing these parameters as linear piecewise splines that change with time. Two publications (19; 22) as well as an conference papers (20) have been developed illustrating this work. The efferents are also adjusted using an optimal control method that is discussed subsequently. A publication (23) and a conference paper (21) have been developed to describe the optimal control approach.

The models are rendered patient specific via the use of parameter estimation techniques. This process involves sensitivity analysis, prediction of a subset of identifiable parameters, and nonlinear optimization to fit the arterial blood pressure data. The approach proposed was applied to the analysis of aortic and carotid HUT data from 5 healthy young subjects. The blood pressure drop that is seen during HUT is via the blood pressure in the carotid sinusues. Thus carotid data is needed for analysis using my model, however most clinicians measure blood pressure at the level of the aortic arch. Therefore, I developed a novel simple model that can estimate carotid pressure values from given aortic data, based on the hypothesis that the two pressures only differ due to gravity. For this part of the study, I used the aortic blood pressure data as a reference and added a gravitational term to simulate the calcualted carotid data. Then I performed the same analysis as done on the original carotid data to compare results.

Pedicting the gravitational response of HUT by accounting for hydrostatic pressure due to gravity, is a novelty in my model. When HUT is initiated, blood is pooled in the lower body leading to an increase in pressure in the lower compartments, while pressure decreases in the upper body. Gravity is accounted for by using the carotid arteries blood pressure as a reference pressure and a term representing gravity is added to the flow terms in the differential equations. Another novelty is the use of time-varying parameters to model the effects of HUT. This was accounted for using two methodologies: piecewise linear functions and treating the time-varying parameters as controls. The advantage of the first method is that implementation is fairly simple using MatLab. However, the smaller the time steps of the parameters, the better the estimate, which in turn makes computations very expensive.

My results showed that it is possible to estimate a subset of model parameters that can predict changes in arterial blood pressure at the level of the carotid sinuses, using both clincal carotid pressure data and the computed carotid data. Moreover, the model estimates physiologically reasonable values for arterial and venous blood pressures, blood volumes, and cardiac output for which data are not available. This work has been compiled into a paper and is in the final stages of revision to be published. The mathematics I utiilized consists of differental equation and numerical analysis theory, as well as some statistical elements. Computations was done using MATLAB.

Regulating Efferents Using Optimal Control

One of the disadvantages of representing time-varying parameters using piecewise linear splines is that the number of parameters to estimate grows with the time-span simulated. Moreover, it is necessary to specify where nodes should be placed. This requires a priori knowledge of the system. To avoid these pit falls, I used optimal control theory to predit cardiac contractility and vascular resistance in response to the changes in aterial blood pressure. Cardiac contractility and vascular resistance, which were parameters in the previous model mentioned, are now considered control variables. The set of differential equations are to describe the paths of these control variables that minimize a cost functional. To solve the optimal control problem, a pseudo-spectral method involving collocation is utilized with the simpler non-pulsatile model.

A collocation method is a method for the numerical solution of ordinary differential equations, partial differential equations and integral equations. The idea is to choose a finite-dimensional space of candidate solutions (usually, polynomials up to a certain degree) and a number of points in the domain (called collocation points), and to select that solution which satisfies the given equation at the collocation points. Computer software written by a third party named GPOPS is employed to solve the optimal control problem.

GPOPS, which is an acronym for General Pseudospectral Optimal Control Software, is an open-source MATLAB optimal control software that implements the Gauss and Radau hp-adaptive pseudospectral methods. These methods approximate the state using a basis of Lagrange polynomials and collocate the dynamics at the Legendre-Gauss-Radau points. The continuous-time optimal control problem is then transcribed to a finite-dimensional nonlinear programming problem (NLP) and the NLP is solved using well known software tools (5). The benefits of this optimal control approach is that it allows for finer tracking of the efferents in time, as well as being more computationally efficient than the the previous interpretation. Although the optimal control method is performed with the non-pulsatile model, I input the optimal control method results for regulating the efferents from the non-pulsatile model into the pulsatile model and compared results with the piece-wise linear spline results (23). This analysis was appropriate since the pulsatile model and non-pulsatile models are interchangeable.

Work in Progress

My current research focuses on applying the model, coupled with the optimal control regulation of efferents, to analyze data-sets within and between different groups of subjects. The goal is to predict differences in regulated efferents so that we may assess the state of a subject's cardiovascular system. The subjects include patients who lack control of their autonomic system, hypertensive patients, diabetics, and stroke-subjects. This work has been in colloboration with medical professionals who are attempting to understand the dynamics of the cardiovascular system for people suffering from orthostatic intolerance and establish the optimal treatment. I have visited the medical center in Denmark that performs HUT, as well as other tests, on patients to investigate the state of patients' cardiovascular systems. These professionals at the center have theories on what components of the cardiovascular system are most effected by this condition and what treatments are most beneficial. However, testing these theories and treatments on actual people is not always feasible. Therefore, we have discussed using my model to predict the impact of tissue and colloidal osmotic pressure on OI, as well as the impact of heart rate, contractility, and vascular resistance. Thus, my model can be instrumental in providing reasoning and insight on the components of the cardiovascular system that are most important, as well as treatment ideas.

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