MODELING AND ANALYSIS OF PATIENT-SPECIFIC CARDIOVASCULAR CONTROL

by

Julia Hatoum

A thesis submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Honors Degree in Major with Distinction

Spring 2024

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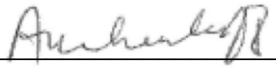
Approved: 

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ABSTRACT

High blood pressure is a significant risk factor for cardiovascular diseases. To help analyze the causes and effects of high blood pressure, we develop a patient-specific cardiovascular and nervous system model. By utilizing patient-specific continuous blood pressure data and heart rate data from healthy and hypertensive individuals, future steps of this project will seek to gain insights into potential hypertension therapies and inter-patient variability through *in-silico* trials. Our approach involves integrating the frameworks and equations from two existing but distinct cardiovascular models. By merging the models, we aim to leverage the comprehensive capabilities of the first with the personalized, adaptive features of the second, creating a model that enhances our understanding of how inter-individual variability contributes to diversity in therapeutic responses and capabilities for individualized treatments. Our project builds primarily on the first model, which incorporates desired cardiovascular and nervous system components. The second model has been tailored to capture patient-specific variations, offering the ability to incorporate individual physiological differences into our simulations. The model is developed and almost fully integrated with only a few module connections remaining; once the model is closed, it will serve as a strong tool for future extended patient-specific research.

Chapter 1

INTRODUCTION

High blood pressure is a pervasive health issue and, according to the World Health Organization, it is a leading cause of cardiovascular diseases globally[12]. The complexity of the cardiovascular system and its regulation makes advanced modeling techniques a valuable tool for understanding the underlying mechanisms and developing effective treatments. For example, patients often respond differently to hypertension medications and treatments based on physiology, potentially experiencing adverse side effects and drug reactions. Additionally, most treatment plans are generalized and not optimized for each individual patient's care. Predicting reactions and tailoring treatments can both be accomplished through a computational model and *in-silico* clinical trials. With this approach, it is also easier to regulate blood pressure despite confounding system factors and the influence of comorbidities like diabetes, kidney disease, and cardiovascular disease. In many computational models, the timestamp can also be elongated to evaluate the long-term effects of treatments and specific conditions–a capability that does not exist with traditional clinical trials. Additionally, having a reproducible and accurate way of modeling patient-specific cardiovascular systems can allow for more predictive modeling to identify at-risk patients before hypertension develops.

Patient-specific models employ a generic modeling framework but leverage data from individual patients to tailor the model. As mentioned, patient-specific models hold promise in informing about potential therapies, crafting personalized treatment regimens, and conducting *in-silico* clinical trials. For our project and to test

patient-specific systems with high blood pressure, we can develop a closed-loop disease model using data from hypertensive and healthy individuals and explore the effects of therapeutic intervention to see how interpatient variability affects our results. We focus on the integration of the cardiovascular and nervous system model, using the CellML language and OpenCOR software. The approach includes translating an existing Simulink model into CellML, integrating the model with a patient-specific model created by a partner group at the University of Auckland, and creating patient-specific models to analyze the effects of high blood pressure and interpatient variability. Hypertensive and baseline patient-specific data are provided for model calibration and analysis. This approach allows for a detailed examination of system dynamics and the potential for personalized treatment strategies.

1.1 MODELS

Existing computational models of the cardiovascular system and its regulation via the autonomic nervous system have served as useful tools for studying short-term hemodynamics. Initial models included parasympathetic (rest and recover response) and sympathetic (fight or flight response) regulation of cardiovascular function.[3] Older works have integrated various physiological elements of the cardiovascular system to provide a comprehensive system representation and insights into complex interactions between the heart, blood vessels, and other mechanisms under different conditions.[3] This includes detailed mathematical descriptions of the heart, systemic circulation, and pulmonary circulations.[3] This computational work set the foundation for future computational physiology as it provides a mechanistic approach to simulate cardiovascular functions, which allows for research and exploration of the underlying causes of various cardiovascular phenomena.

More recently, detailed representations of the brainstem and peripheral autonomic circuits have been included in models.[1] The Gee model focused on incorporating the intrinsic cardiac nervous system (ICN) into a computational model of the baroreflex, which regulates short-term blood pressure. Computational models of closed-loop control systems that regulate blood pressure by modulating nerve activity between the brainstem and heart already existed before this project, but the incorporation of the ICN within central control reflex circuits (which mediate central control of the heart function), was not included in such models.[14,15] This model was used to examine central and local contributions to the control of heart rate, ventricular functions, and respiratory sinus arrhythmia, test relationships between the respiratory sinus arrhythmia and lung tidal volume, and predict contributions of the sensory and motor neuron pathways to changes in the heart rate.[14,15]

Additionally, some more recent computational models have focused on fitting computational physiological models to clinical data, allowing for the generation of patient-specific models.[2] Markov chain Monte Carlo (MCMC) analysis is used to find optimized parameter values and determine confidence intervals of predictions.[2] To approach this, a lumped parameter model of the cardiovascular system was calibrated to brachial artery cuff pressure, echocardiogram volume measurements, and synthetic cerebral blood flow data to approximate 4D-flow MRI data.[2] The results provided cerebral arterial pressure prediction that can be useful for determining the risk of hemorrhagic stroke.[2] This system was applied to three patients, and it successfully reduced the number of parameters required for the cardiovascular system model from

12 to 8-10; this improvement allows for more efficient simulations and determining confidence intervals for pressure in comparison to running the model with a full parameter set.[2]

In their work, Argus et al. discussed some limitations regarding the convergence of the MCMC analysis to their posterior chains, the their model's compatibility with clinical echocardiographic measurements, and some uncertainty due to a mismatch between model outputs and measurements.[2] Nonetheless, the work proposes a high-performance computational model that allows for automated calibration of a parameter set specific to available structurally identifiable patient data with minimal patient interaction.[2]

This thesis aims to advance the field of computational physiology by developing a comprehensive and patient-specific model that integrates cardiovascular and nervous system dynamics. The first objective of this work is to provide a deeper understanding of the motivation for this work, how patient-specific data is leveraged to refine predictions and enhance treatment personalization, and a detailed description of the physiology of the system. The subsequent sections will detail the methodologies employed, present the results obtained, and discuss the implications of our finalized model. Ultimately, this thesis offers insights that could lead to more effective and tailored treatments for hypertension and other cardiovascular diseases.

Chapter 2

METHODS

2.1 MODEL DESCRIPTION

The cardiovascular system is a closed-loop modularized system in which each portion of the system (or module) is defined by mass balances and ordinary differential equations (ODEs) that characterize different physiological parts. In this model, there are over 80 equations representing the systemic and pulmonary circulation as well as relevant aspects of the nervous system.[1]

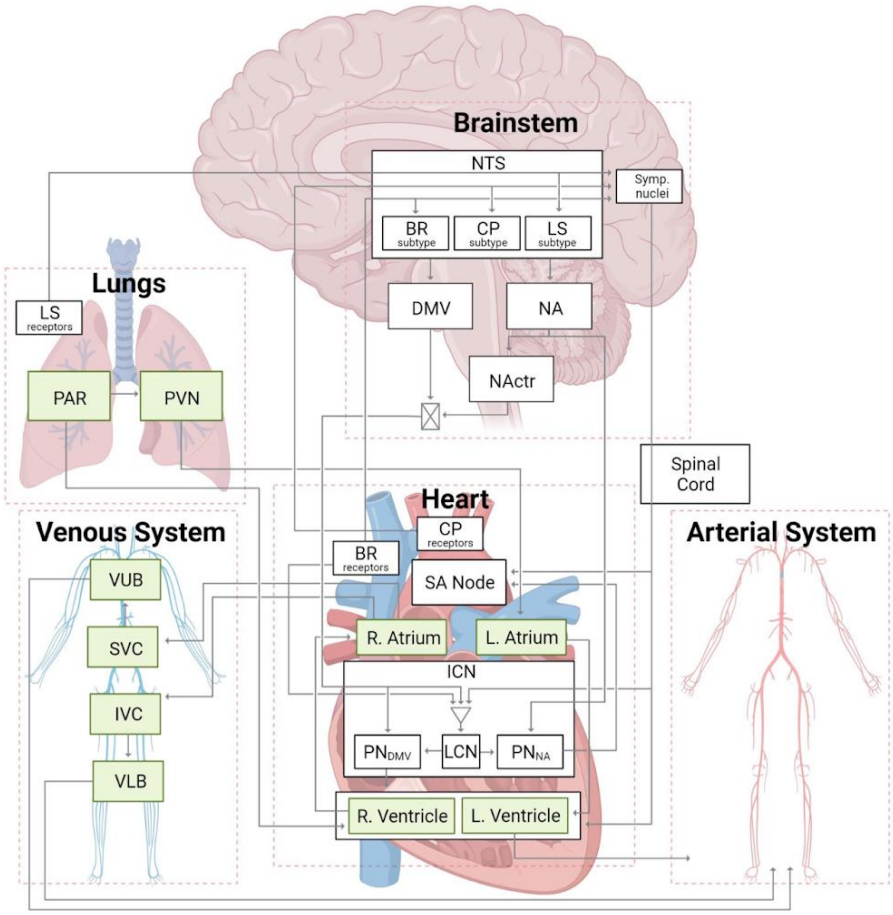

Figure 2.1: System diagram depicting the model both physiologically and modularly.

Figure 2.1 is a diagram of larger modules and/or physiological components made up of smaller modules that are accounted for in our model. The diagram aims to be physiologically accurate; however, a lot of these modules overlap or spread

throughout multiple body parts and organs, making it difficult to fully demonstrate where each module resides in the body. The white blocks are based on the Gee model[1] while the green blocks come from the Argus model[2].

The model describes components of the autonomic nervous system (ANS). The ANS controls involuntary body functions and is often called the involuntary motor division.[1,16] It consists of neurons that carry signals primarily to the thoracic and abdominal viscera. The ANS regulates many things, including the contraction of cardiac muscles, creating the heartbeat. This system includes the parasympathetic nervous system (PNS) and the sympathetic nervous system (SNS).[16] The PNS is often referred to as the "rest and digest system" as it ensures the maintenance of normal bodily functions, for example, energy conservation, slowing down the heart rate, increasing intestinal and gland activity, etc.[16] The SNS is conversely referred to as the "fight or flight system" because it prepares the body for stressful situations by increasing the heart rate, dilating the pupils, redirecting blood flow to the muscles, and reducing digestive activity.[16] Additionally, the intrinsic cardiac nervous system (ICN) is included in this model. It is a network of neurons within the heart that helps regulate heart function. The ICN is not typically included in many computational nervous system models, setting this project apart from similar models.[1]

Included in the model are afferent pathways, which are sensory neural routes that carry information on blood pressure and respiration from sensory receptors in the body towards the central nervous system like the brain and spinal cord.[1] There are also three important sets of sensors within the system: the baroreceptors, cardiopulmonary

receptors, and lung stretch receptors, which are clearly labeled in the heart and lungs in Figure 2.1.[1] The baroreceptors are located in the aortic arch and are sensory for blood pressure. The cardiopulmonary receptors are located in the walls of the atria of the heart and the pulmonary veins and are sensitive to the stretch caused by the filling of these cardiac chambers and veins. And the lung stretch receptors are located in the smooth muscles of the airways in the lungs and are activated by the stretch of the lung tissue during inhalation.

Connected to the afferent pathways are the efferent pathways, which are motor neural routes that carry commands from the central nervous system to effectors, such as the heart muscle, to initiate actions.[1] We incorporated portions of the nervous system located in the medulla oblongata of the brainstem, including the dorsal motor nucleus of the vagus (DMV) and the nucleus ambiguous (NA), both of which are essential to the PNS.[16] The DMV is a nucleus that sends parasympathetic fibers to the heart, and primarily regulates cardiac contractility.[1] The NA contains motor neurons that regulate the heart rate on beat-to-beat time scales.[16]

Regulation of the heart rate and contractility then affects blood pressure in the systemic circulation, which describes the circulation of blood throughout the body, as well as the pulmonary circulation, which involves the blood flow between the heart and lungs.[13] However, these two components were integrated from the Argus model instead. Both the systemic and pulmonary circuits are important to our model as they are essential in effectively connecting other parts of the model, creating a closed-loop system.[13] The pump for the pulmonary circulation is the right ventricle, which

circulates blood through the lungs.[13] The pulmonary circulation is essential to the body as it transports oxygen-poor blood to the lungs and returns oxygen-rich blood to the left atrium.[13] In contrast, the pump for the systemic circulation is the left ventricle, which circulates blood through the arteries and to the capillaries, from which mass transfer occurs to cells in different tissue types throughout the body.[13] The blood carries oxygen and nutrients to the cell while picking up carbon dioxide and other waste products, and then returns as deoxygenated blood through veins to the right atrium.[13] The traveling blood through these two circulations is depicted in Figure 2.1 with arrows.

The model also contains modules for the left and right heart and the pulmonary arteries, which lead to the lungs, as well as different pressures and variables related to the lungs: The lung volume measures the lung capacity.[1] The thoracic pressure is the pressure within the thoracic cavity, which is the area enclosed by the rib cage, containing the heart and lungs; changes in the pressure can have significant effects on the cardiovascular system.[1] The abdominal pressure is the pressure within the abdominal cavity and can have implications for blood flow among other factors.[1] Changes in thoracic and abdominal pressure drive respiration, while also changing the external pressure against which the heart pumps blood.[1]

2.2 MODELING AND SIMULATION PLATFORMS

OpenCOR is an open-source software package with an interface designed to work with either CellML or Python coding languages. CellML is an XML-based language that is primarily used within OpenCOR. CellML provides a standardized way of defining models, ensuring that they can be shared, reused, and extended by

different people across various platforms. This standardization promotes consistency in how biological models are described. Additionally, the software is used for modeling, simulating, and analyzing biological systems, like the cardiovascular and nervous systems. Its niche specialty and variety of tools to characterize and display biological system behaviors allow for efficient model analysis, superior project results and figure generation, as shown in Figure 2.2 and Figure 2.3.

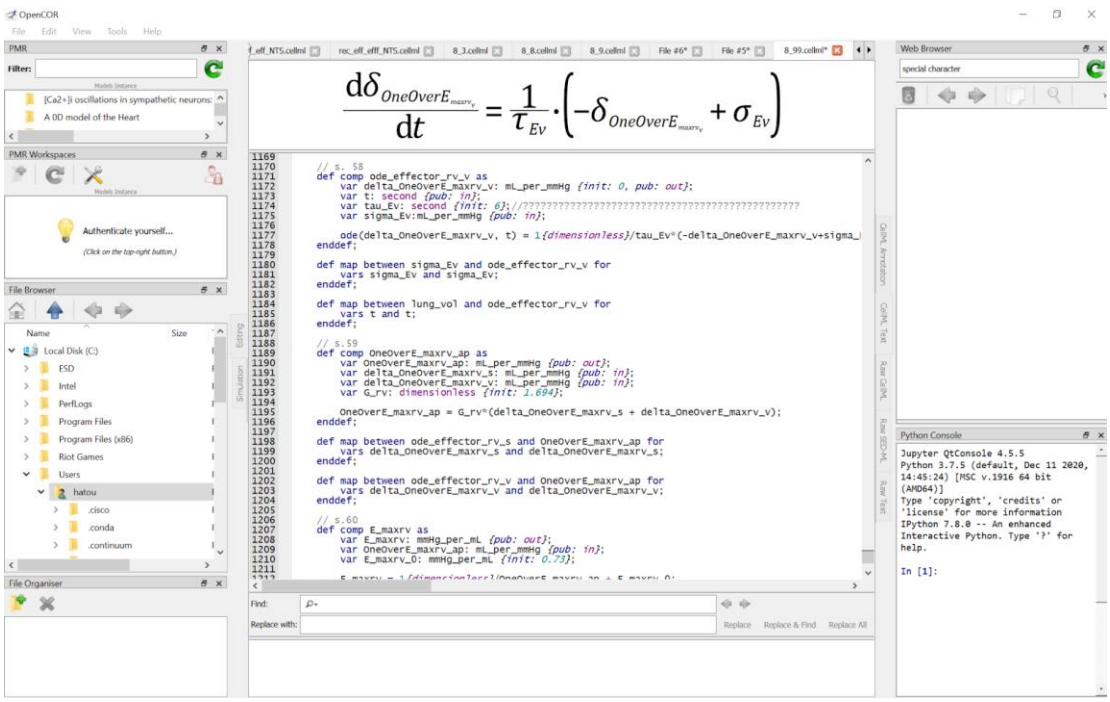

Figure 2.2: OpenCOR interface where CellML scripts are written under the “Editing” tab. This code screenshotted directly from the code used for this model.

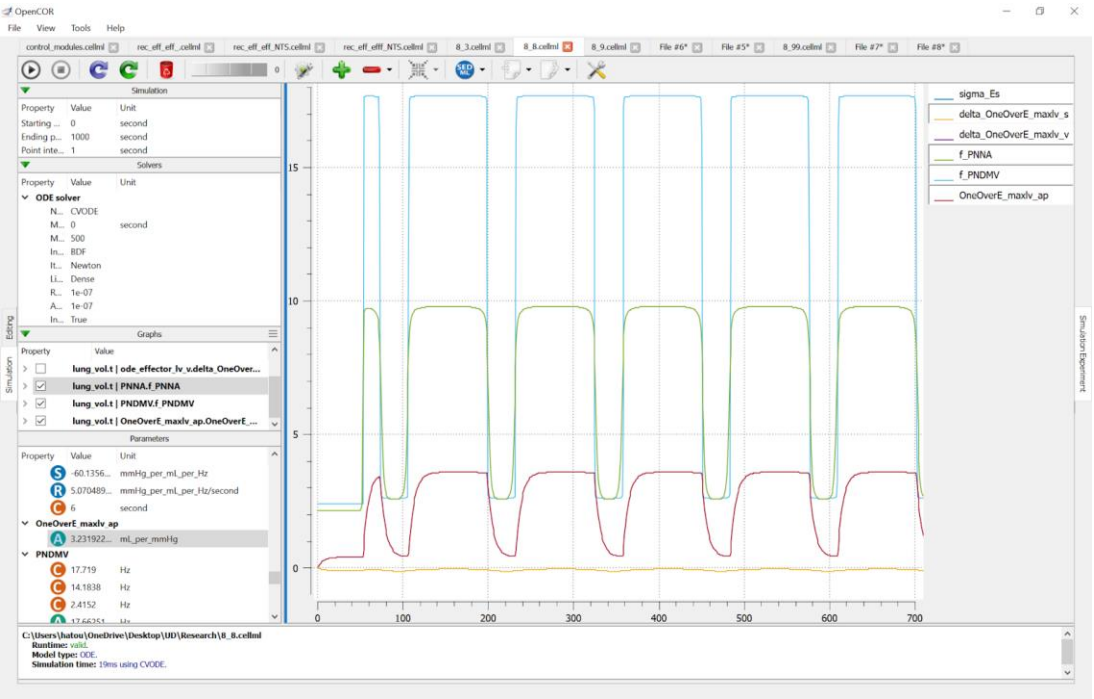

Figure 2.3: OpenCOR "Simulation" tab where variables of CellML code can be plotted. These trends are plotted based on code used to simulate this model.

2.3 TRANSLATING THE MODEL

The Gee model was initially designed and formulated in Simulink, but that did not allow for integration with the Argus model or parameter estimation with patient-specifc data. As a result the Gee model had to be translated into CellML for use in OpenCOR software. Translation to CellML is beneficial because it allows us to perform a more in-depth analysis since OpenCOR has a variety of tools to characterize and display biological system behavior in ways that Simulink cannot.

To perform the translation, each equation of the Simulink models was coded in OpenCOR and then run in parallel to ensure that trends in the translated model mimicked those in the original model.

2.4 INTEGRATING THE MODEL

Once the translation of the Gee model to CellML was complete, the model was sent to the University of Auckland for model integration with the patient-specific Argus model. The Argus model uses a platform that is under development to create modules for cardiovascular system and neural regulation components. The modules correspond to physiological components such as the brachial artery or baroreceptors. Users can choose modules from a library, then couple the components using appropriate boundary conditions to build a model. The components translated from the Gee model were incorporated into the library of modules by the University of Auckland collaborators.

To run the integrated model using OpenCOR, there is a multi-step process, including initialization, establishment of the directory structure, determination of software dependencies, and step-by-step instructions for generating and simulating models. To initialize the setup, the software requires a Linux operating system, but it can be run on Windows using a virtual machine like VirtualBox Oracle and Ubuntu. The code is cloned from the virtual machine using git commands; Python and required libraries and packages are installed in the OpenCOR environment.

For the model, respective vessel array and parameter files in CSV format are created and a YAML file is used to configure the model generation settings. A JSON

file is rewritten to incorporate appropriate data and to link corresponding modules and CellML files. Based on the Gee model, each physiological “Component” defined in the CellML code was defined as a module in the JSON file. Each module was then compiled in the model’s comprehensive CSV file, which lists all connected modules necessary to form the closed-loop system; this includes modules from the Gee file as well as those from the Argus model, like the pulmonary circulation, circulatory circulation, and lung bond graph.

Once everything is prepared and rewritten with appropriate parameters, boundary conditions, connected input and output variables, and other necessary initial conditions, the script, prompting Unix shell is run in the terminal to generate the CellML file for the integrated model, which can then be simulated using OpenCOR.

2.5 PARAMETER ESTIMATION

To prepare patient-specific models, there is a parameter identification feature allowing for the calibration of the model to experimental or clinical data. This requires creation of additional CSV and JSON files to define which parameters will be varied to fit given data. The corresponding YAML file is then used to configure the parameter identification settings and to ensure the optimization of results.

Chapter 3

RESULTS

There were two large milestones in developing this model: the translation of the model and the integration and generation of the model, which can now be utilized for model analysis and *in-silico* trials.

3.1 TRANSLATION OF GEE MODEL

As mentioned previously, the process for translating the Gee model from Simulink to CellML was tedious and required considerable time, comparing each of the more than 80 coded equations and their trends in OpenCOR to the respective corresponding trends in Simulink.[1]

A good example of the outcome of compared variables and their outputs are the three classes of receptors in the system, the baroreceptor, the lung stretch receptor, and the cardiopulmonary receptor. When translating the model, the Simulink block diagram and CellML code were left as an open-loop system (as the system could not be closed due to incomplete code). However, in order to make appropriate comparisons, inputs approximating the Simulink model inputs were generated as inputs to the receptors. These inputs were kept throughout the entirety of the model translation and modified in the Simulink model to make appropriate model comparisons. This included a lung volume input of a step from 0 mL to 0.6 mL in the lung volume, a sine wave of 25sin(0.05t)+125 mmHg for arterial pressure measured by the baroreceptors, and a step input from 6 mL to 13 mL in the transmural pressure at the pulmonary vein.

Figure 3.1 and Figure 3.2 both plot the firing frequencies of the baroreceptors (f_br), lung stretch receptors (f_lr), and cardiopulmonary receptors (f_cp) in OpenCOR and Simulnk, respectively. Firing frequencies are rates at which neurons produce action potentials over time; these electrical signals are how neurons communicate throughout the nervous system. In the lung stretch receptors, the firing frequencies correspond to the amount of pressure in the baroreceptors, the degree of lung inflation in the lung stretch receptors, and the pressure in the pulmonary veins.[1] Based on Figures 3.1 and 3.2, it is evident that the trends and values shown in OpenCOR mimic those in Simulink. It is even more notable that the ranges for the firing frequencies are within an appropriate 0-50 Hz range given the random input functions.

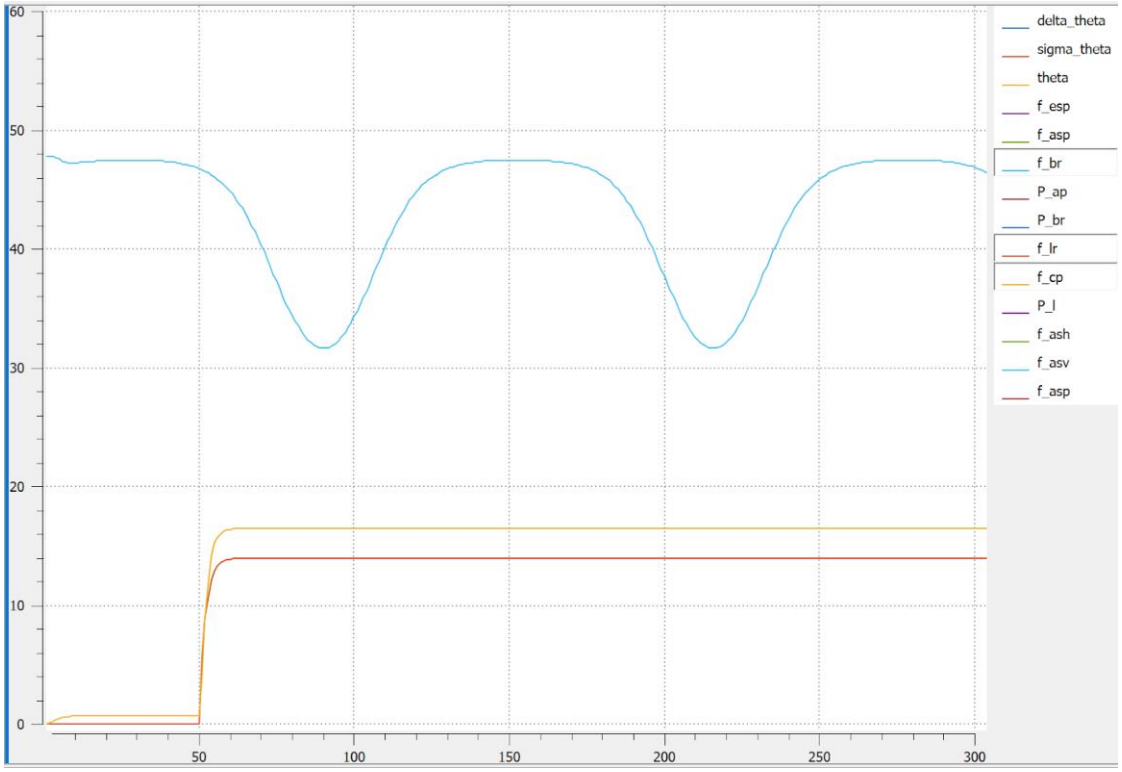

Figure 3.1: Firing frequencies within the baroreceptors, lung stretch receptors, and cardiopulmonary receptors simulated in OpenCOR.

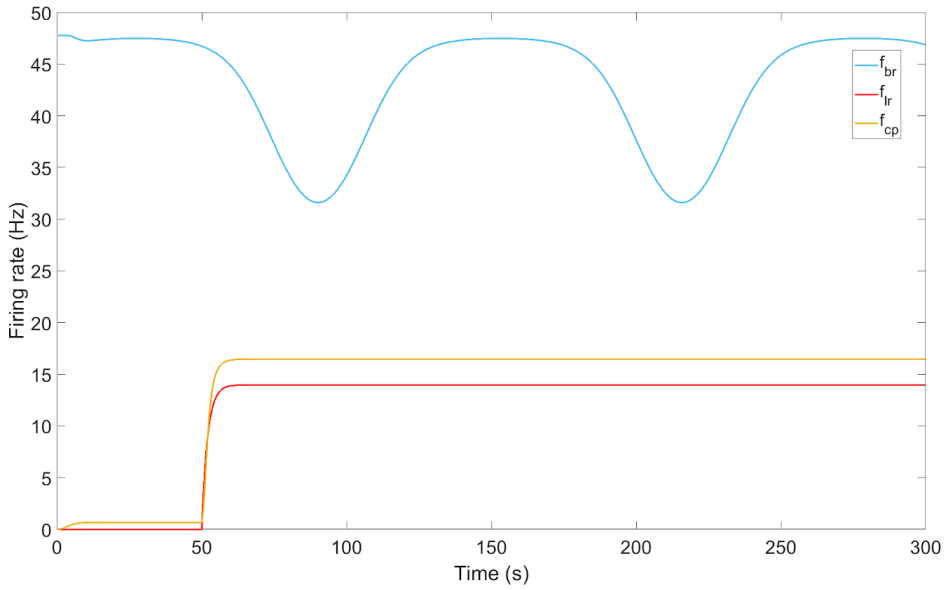

Figure 3.2: Firing frequencies within the baroreceptors, lung stretch receptors, and cardiopulmonary receptors simulated in Simulink.

Figure 3.3 and Figure 3.4 both show plots of afferent pathway firing frequencies that are based on signals sent by the baroreceptors, cardiopulomanry receptors, and lung stretch receptors and used to determine the sympathetic efferent outflow signals to effector functions associated with the heart (f_ash), peripheral circulation (f_asp), and unstressed volumes (f_asv), respectively.[1] Figure 3.3 is plotted using OpenCOR while Figure 3.4 uses the Gee Simulink model; these figures are another example of successfully translated equations out of the 80+ equations in the model.

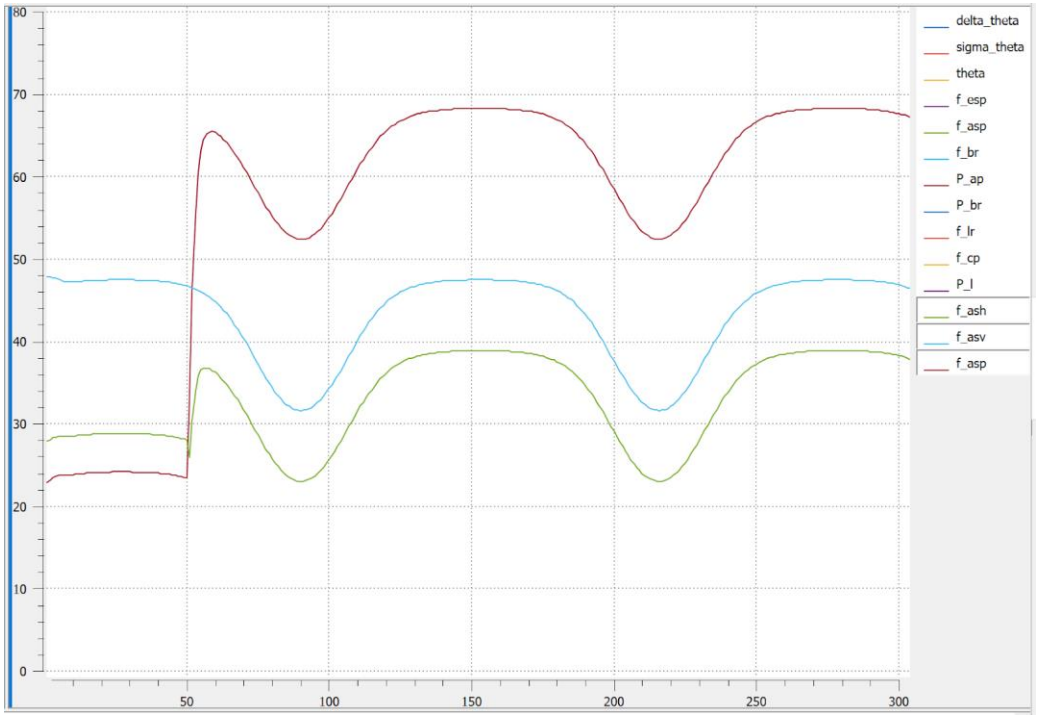

Figure 3.3: Afferent firing frequencies to the heart, peripheral circulation, and unstressed volumes simulated in OpenCOR.

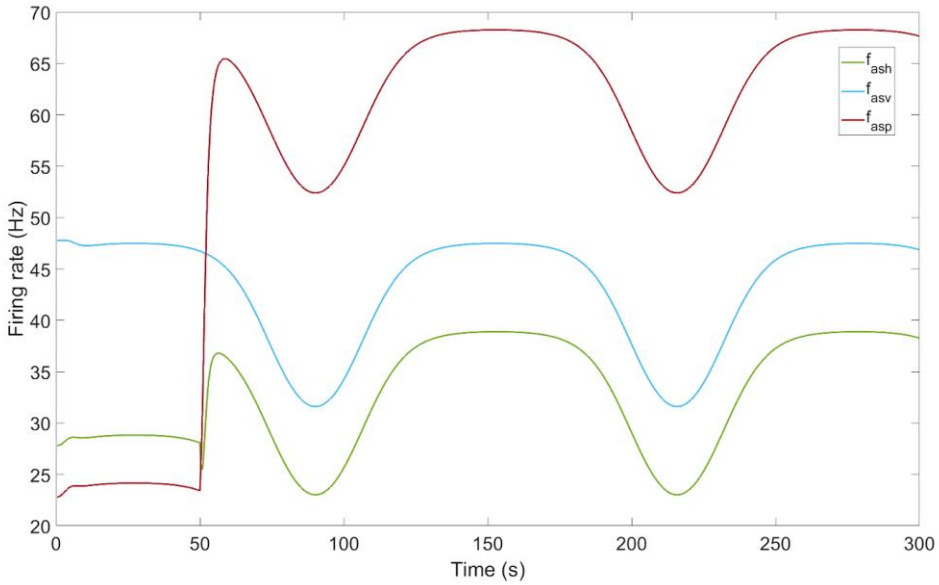

Figure 3.4: Afferent firing frequencies to the heart, peripheral circulation, and unstressed volumes simulated in Simulink.

Firing frequencies based on the initial three receptors and afferent projectionsare sent to the nucleus tractus solitarii (NTS), which livesin the brainstem.[1,17] These are plotted in Figure 3.5 and Figure 3.6 to demonstrate evident replication of the Gee model in OpenCOR (f_NTS_br, f_NTS_ls, f_NTS_cp).

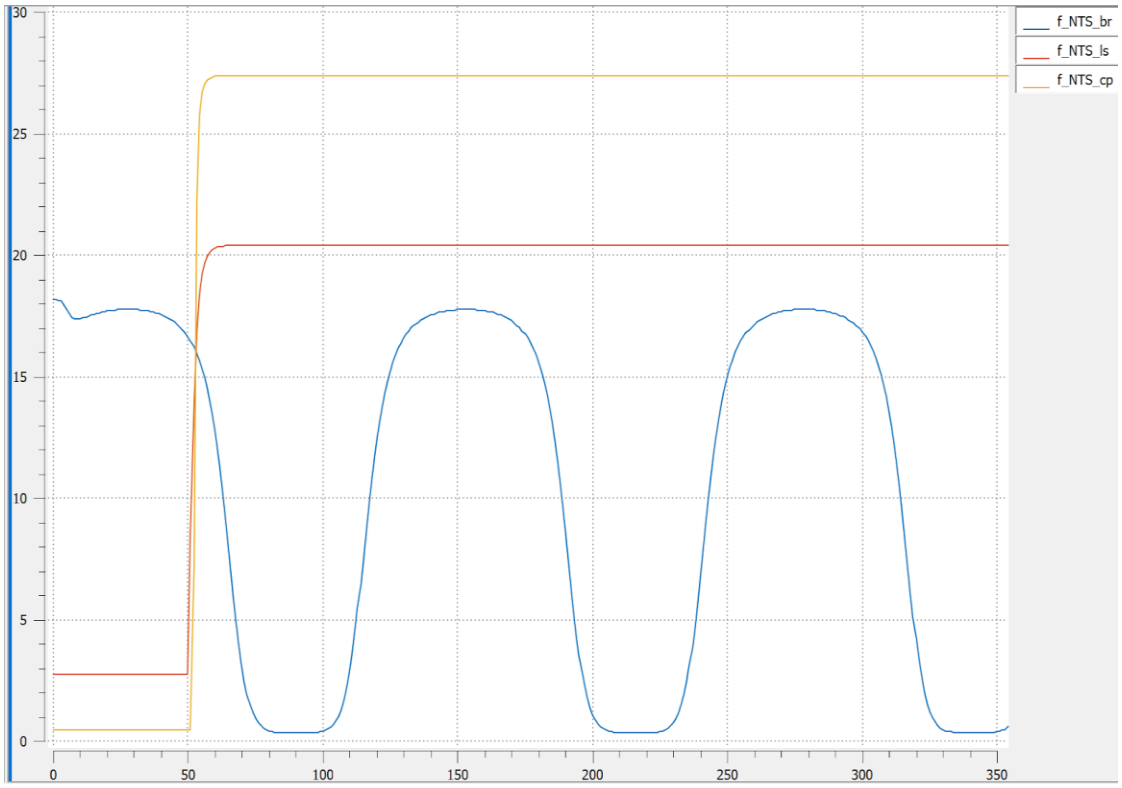

Figure 3.5: NTS firing frequencies from the baroreceptors, lung stretch receptors, and cardiopulmonary receptors simulated in OpenCOR.

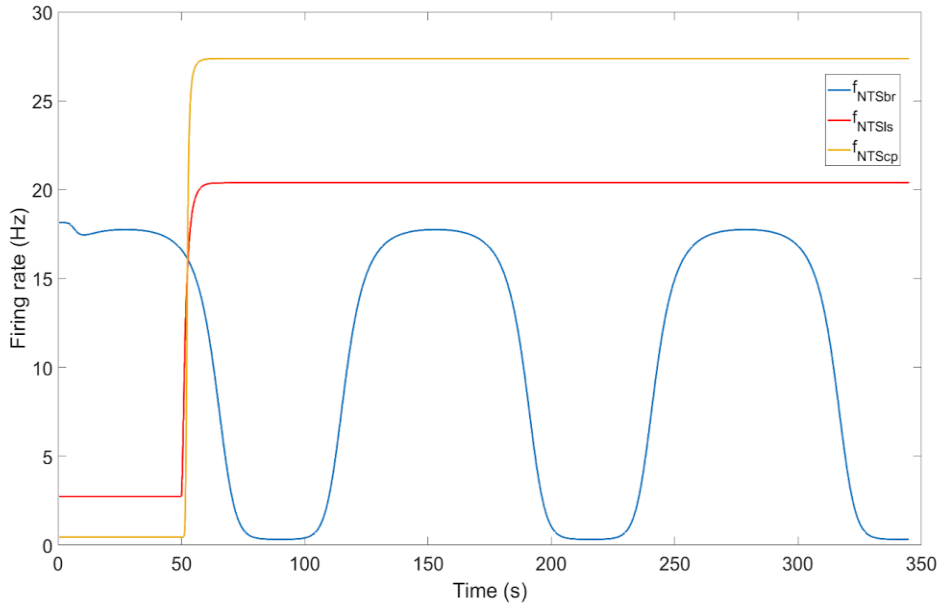

Figure 3.6: NTS firing frequencies from the baroreceptors, lung stretch receptors, and cardiopulmonary receptors simulated in Simulink.

A last set of firing frequencies within the DMV, NA, and NActr (parts described in section 2.1) are plotted (f_DMV, f_NA, f_NActr) to demonstrate accurate translation of the Gee model to OpenCOR.

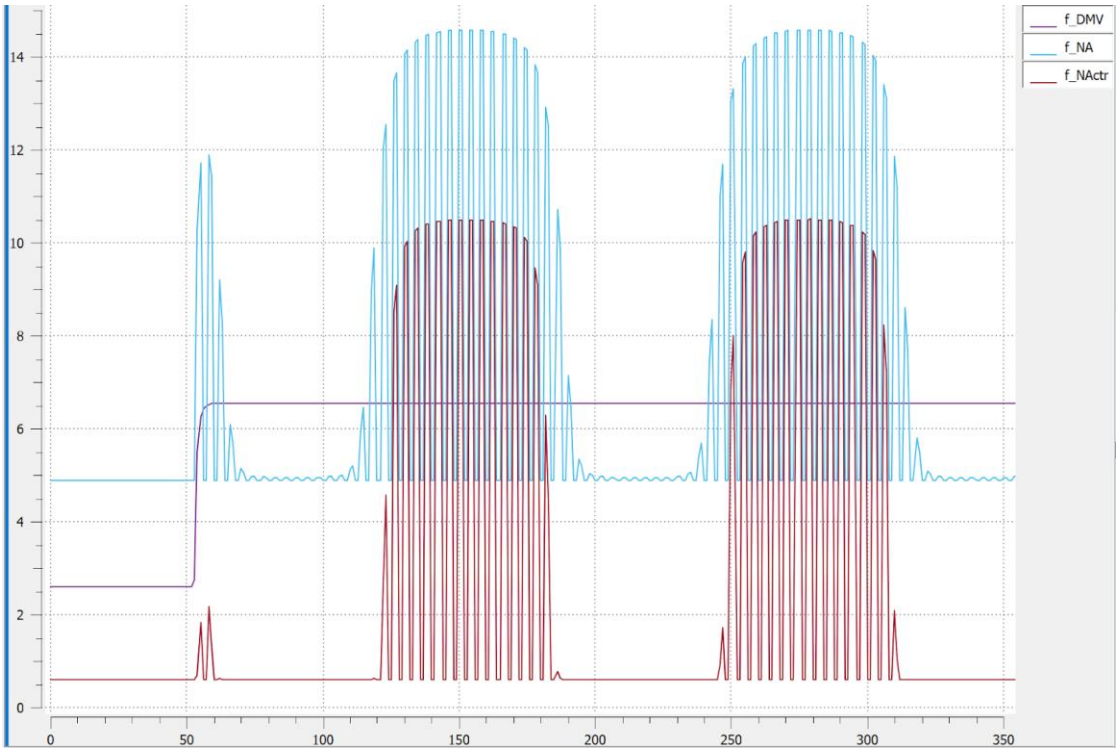

Figure 3.7: Firing frequencies within the DMV, NA, and NActr simulated in OpenCOR.

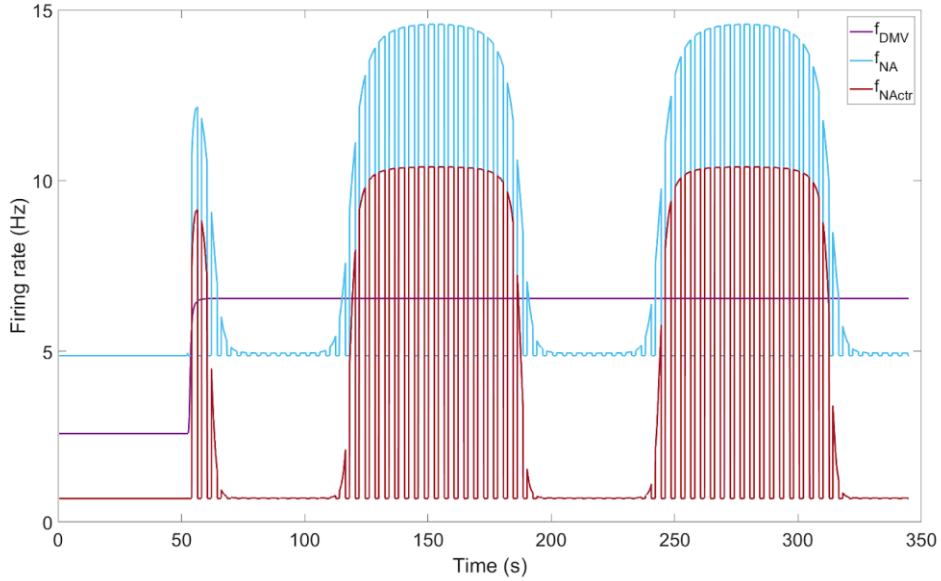

Figure 3.8: Firing frequencies within the DMV, NA, and NActr simulated in Simulink.

As demonstrated with Figures 3.1-3.8, the translation from Simulink to OpenCOR was successfully completed for each of the physiological modules included.

3.2 INTEGRATION OF ARGUS MODEL

As thoroughly described in the Introduction and Methods sections, to create our model, we aimed to combine components of the Gee model–a comprehensive cardiovascular and nervous closed loop system–and the Argus model–an adaptive cardioavascular model with patient-specific capabilities. The integration of the models as described in section 2.4 was completed; however, we are a few lines of code away from linking modules in the model's CSV file and closing the loop. Once closed, the model can be run in OpenCOR and graphs can be generated, allowing more extensive

use of the model to explore actual physiological functions for different patient characteristics. In particular, the integrated model would be suitable for a sensitivity analysis as well as *in-silico* clinical trials.

Chapter 4

DISCUSSION AND CONCLUSIONS

We have created a patient-specific model of the cardiovascular and nervous systems to study the consequences of high blood pressure to address the pressing issue of hypertension. Our approach to developing our model combined equations and frameworks from two different current cardiovascular models, the Gee model and the Argus model. The initial model, which includes the desired nervous system and cardiovascular components, serves as the foundation for our project, with the second model allowing us to integrate our model with a platform that can be used to develop models calibrated to individuals.

Upon translation of the Gee model to CellML and then integration with the Argus model, this model will open a new door for future analysis of hypertension pathophysiology and potential personalized therapies for hypertension through model analysis using patient-specific continuous blood pressure and heart rate data from healthy and hypertensive individuals as depicted in Figure 4.1.

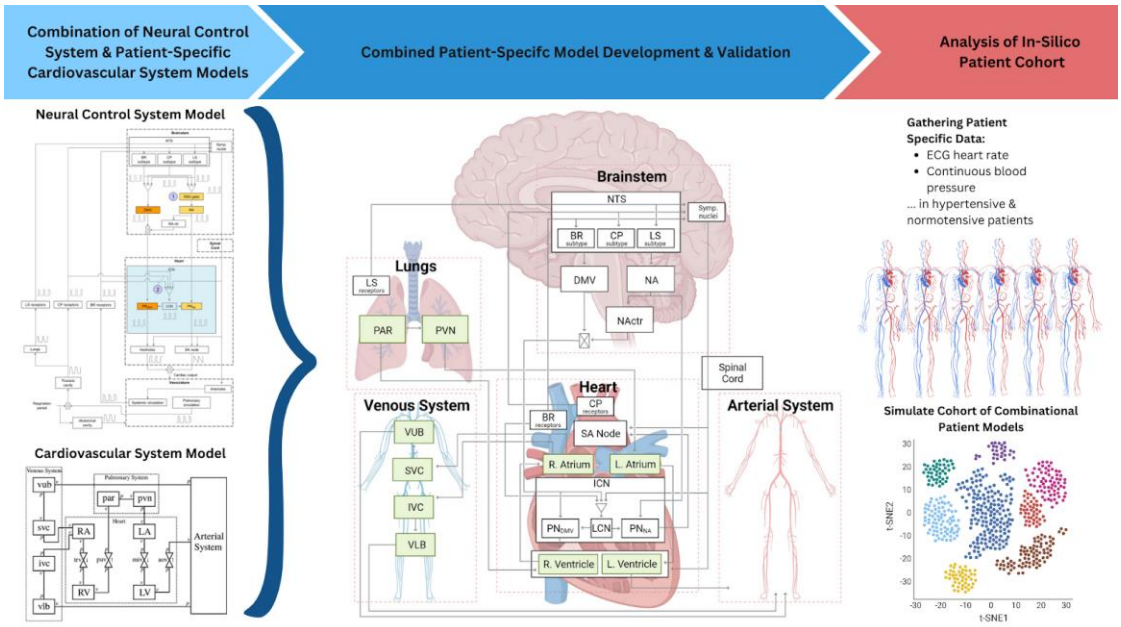

Figure 4.1: Graphical abstract of this project. The left shows the Gee and Argus models, which are translated and integrated into our model. Lastly, the model takes in patient-specic ECG heart rate data and continuous blood pressure data from both hypertensive and normotensive patients to generate normal and disease models, which undergo a cluster analysis.

4.1 BUILDING ON LITERATURE

Traditional cardiovascular models often focus primarily on the mechanical aspects of heart function, like blood flow, heart muscle contractions, and valve operations. While these models provide valuable insights into mechanics and physiology, they oftentimes overlook neural regulation in the ways that our model chooses to incorporate them.

Our integrated model includes both cardiovascular components and neural regulation, which allows it to mathematically characterize the control and coordination of bodily functions through the nervous system, and it has patient-specific capabilities.

By creating such a comprehensive and usable model, this project takes a step towards advancing the field of computational research on physiology. This builds on a substantial body of literature beyond the three models, Gee, Argus, and Ursino, described in the Introduction. By including neural regulation, we can better simulate physiological responses to different stimuli like exercise and disease, which we highlighted in our goal of exploring potential treatments for hypertension. Furthermore, by integrating the model to allow for patient-specific testing, this model can be useful to others in making significant progress in finding optimized treatments based on patients' unique physiology and conditions.

4.2 MODEL LIMITATIONS

There are a few potential limitations to our model. Firstly and most obviously, like all models, this one is a simplification of the real cardiovascular system it aims to represent, so there may be interactions between variables that have been omitted due to lack of knowledge or for computational feasibility that could actually influence results in ways that are unanticipated and not fully capture all the dynamics and behavior of the real-life system. Additionally, our model's equations were drawn from literature that described them based on experimental data and estimates, which could incorporate inaccuracies. The model is also limited to a shorter timestamp, so it cannot be used to evaluate the long-term effects of treatments. There are also potential limitations for usability and scalability of this model, as it is quite complex to fully generate the integrated model, as described in the Methods section. As a result, the required resources to run in-silico simulations can become prohibitive and limit the practical use of the model.

4.3 FUTURE DIRECTIONS

With the fully integrated model, the next step would be to perform model analyses using data representing hypertensive and healthy patients. With hypertensive and normotensive ECG heart rate data and continuous blood pressure data provided by our partners at the University of Auckland, we can perform a parameter sensitivity analysis to identify which parameters have the most significant effects on variables of interest. Additionally, we can perform a cluster analysis using t-distributed scholastic neighbor embedding (t-SNE) plots to cluster models that are most similar to one another and give insights into potential parameters that affect hypertensive and normotensive patients distinctively.

Longer term, we would look into performing in-silico trials for specialized treatment regimens. In-silico clinical trials are virtual clinical trials that simulate various body systems, including the cardiovascular and nervous systems. Virtual trials present a significant advantage over traditional clinical trials; they are faster, more cost-effective, safer, low-risk, well-controlled, reproducible, and can be fine-tuned to achieve optimized results. Through the lens of in-silico trials, the complex interplay between high blood pressure and other physiological conditions can be better understood, paving the way for more effective and individualized treatment plans. With traditional clinical trials and physical patients, the trends or relationships between parameters in the system would not be evident, whereas in a model where the systems are mathematically characterized, the parameters can be plotted, parametric trends can be visualized, and parameter sensitivity analyses can be performed to gain better insight.

Additionally, we may consider incorporating machine learning techniques into this model to enhance its predictive accuracy and personalization capabilities. Machine learning algorithms could be used for parameter estimation, allowing for more precise modeling of individual physiological responses to different treatments. Additionally, machine learning could be employed to analyze patterns in patient-specific data, identifying subtle and complex relationships and predicting accurate outcomes. This could lead to more effective, tailored therapies and result analysis.

This thesis represents a step forward in the modeling of the cardiovascular system and its response to high blood pressure. By developing a comprehensive CellML model and utilizing patient-specific data, we have developed a powerful tool for understanding the dynamics of high blood pressure and exploring potential treatments. Our work highlights the importance of computational modeling in the study of cardiovascular diseases and opens new avenues for in-silico clinical trials and personalized treatment regimens. Future research will focus on further refining the model and expanding its simulation applicability to hypertension models and potentially a broader range of cardiovascular conditions.

REFERENCES

1. Gee, Michelle M., et al. "Closed-loop modeling of central and intrinsic cardiac nervous system circuits underlying cardiovascular control." AIChE Journal, vol. 69, no. 4, 2023, https://aiche.onlinelibrary.wiley.com/doi/10.1002/aic.18033.

2. Argus, Finbar, et al. "Automated model calibration with parallel MCMC: Applications for a cardiovascular system model." Frontiers in Physiology, vol. 13, 2022, https://www.frontiersin.org/articles/10.3389/fphys.2022.1018134/full.

3. Ursino, M., and E. Magosso. "Acute cardiovascular response to isocapnic hypoxia. I. A mathematical model." American Journal of Physiology-Heart and Circulatory Physiology, vol. 279, no. 1, 2000, https://www.ncbi.nlm.nih.gov/pubmed/10899052.

4. Park, James H., et al. "Investigating the Effects of Brainstem Neuronal Adaptation on Cardiovascular Homeostasis." Frontiers in Neuroscience, vol. 14, 2020, https://www.frontiersin.org/articles/10.3389/fnins.2020.00470/full.

5. Gray, Richard A., and Pras Pathmanathan. "Patient-Specific Cardiovascular Computational Modeling: Diversity of Personalization and Challenges." Journal of Cardiovascular Translational Research, vol. 11, no. 2, 2018, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5908828/.

6. Ursino, M. "Interaction between carotid baroregulation and the pulsating heart: a mathematical model." American Journal of Physiology-Heart and Circulatory Physiology, vol. 275, no. 5, 1998, https://pubmed.ncbi.nlm.nih.gov/9815081/.

7. Hadaya, Joseph, and Jeffrey L. Ardell. "Autonomic Modulation for Cardiovascular Disease." Frontiers in Physiology, vol. 11, 2021, https://www.frontiersin.org/articles/10.3389/fphys.2020.617459/full.

8. Fedele, Laura, and Thomas Brand. "The Intrinsic Cardiac Nervous System and Its Role in Cardiac Pacemaking and Conduction." Journal of Cardiovascular Development and Disease, 2021, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7712215/.

9. Pappalardo, Francesco, et al. "In silico clinical trials: concepts and early adoptions." Briefings in Bioinformatics, vol. 20, no. 5, 2019, https://pubmed.ncbi.nlm.nih.gov/29868882/.

10. Filipovic, Nenad, et al. "In Silico Clinical Trials for Cardiovascular Disease." Journal of Visualized Experiments, no. 183, 2022, https://pubmed.ncbi.nlm.nih.gov/35695532/.

11. Niederer, Steven. A., et al. "Creation and application of virtual patient cohorts of heart models." Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences, vol. 378, no. 2173, 2020, https://royalsocietypublishing.org/doi/10.1098/rsta.2019.0558.

12. "Hypertension." World Health Organization (WHO), https://www.who.int/news-room/fact-sheets/detail/hypertension.

13. "Cardiovascular System: Blood Pathways." SEER Training Modules, National Cancer Institute, https://training.seer.cancer.gov/anatomy/cardiovascular/blood/pathways.html#:~:text=The%20systemic%20circulation%20provides%20the,the%20tissues%20of%20the%20body.

14. Park, James H., et al. "Investigating the Effects of Brainstem Neuronal Adaptation on Cardiovascular Homeostasis." Frontiers in Neuroscience, vol. 14, 2020, https://www.frontiersin.org/journals/neuroscience/articles/10.3389/fnins.2020.00470/full.

15. Ursino, M. "Interaction between carotid baroregulation and the pulsating heart: a mathematical model." American Journal of Physiology-Heart and Circulatory Physiology, vol. 275, no. 5, 1998, https://pubmed.ncbi.nlm.nih.gov/9815081/.

16. “Overview of the Autonomic Nervous System." National Institutes of Health, National Library of Medicine, https://www.ncbi.nlm.nih.gov/books/NBK539845/#:~:text=The%20autonomic%20nervous%20system%20is,sympathetic%2C%20parasympathetic%2C%20and%20enteric.

17. "The Nucleus Tractus Solitarii: The Brain's Hub to Regulate Cardiovascular Function." Brazilian Journal of Medical and Biological Research, https://www.scielo.br/j/bjmbr/a/6fGCqW49D4GK5TBWRtk6SkG/#:~:text=The%20nucleus%20tractus%20solitarii%20(NTS,a%20narrow%20range%20of%20variation.