ABSTRACT

GEDDES, JUSTEN ROBERT. Mathematical Modeling and Signal Processing of Postural Orthostatic Tachycardia Syndrome (POTS). (Under the direction of Mette S. Olufsen and Brian E. Carlson.)

Postural Orthostatic Tachycardia Syndrome (POTS) is characterized by orthostatic tachycardia, referring to an increase in heart rate of more than 30 bpm in response to a postural change without a proportional decrease in blood pressure. Diagnosis of POTS requires the use of a postural change, such as the head-up tilt test, to measure a change in heart rates, blood pressure, and experience of symptoms. The symptoms of POTS are wide-ranging, including brain fog, lightheadedness, and shortness of breath. While the singular etiology for POTS is not agreed upon, it is thought to include at least three different causes, known as phenotypes. However, with the pathophysiologies manifesting in similar ways, it is difficult to differentiate the phenotypes and treat the impaired systems.

In the quest for understanding POTS etiology, numerous studies have tried to identify POTS biomarkers, such as the recent observation of autoantibodies in some POTS patients. This study aims to identify features in heart rate and blood pressure data and build mathematical models that can be used to test proposed POTS pathophysiologies. To do so, we use non-stationary signal processing and two novel mathematical models of the cardiovascular system and its control. Using signal processing, we identify characteristics of the heart rate and blood pressure signals. We found that in addition to an increase in heart rate, POTS patients have larger low-frequency (~0.1 Hz) oscillations and smaller average instantaneous phase differences between the low-frequency components. Using mathematical modeling, we explain the emergence and magnification of these signals.

We developed a 0D cardiovascular model with simple controls and a more detailed model that includes a sinoatrial node cell that responds to the presence of adrenergic autoantibodies. For the latter, we use a multiscale approach. At the macroscale level, we predict feedback from the cardiovascular system and its control, and at the microscale level, we predict sinoatrial node membrane potential modulated by predicted neurotransmitter concentration. Results demonstrate that, when combined with the macroscale model, it is possible to predict tachycardia and increased heart rate and blood pressure low-frequency oscillation amplitude.

In summary, the studies presented here present a new way to view POTS - accounting for tachycardia, low-frequency dynamics, and their importance in discerning POTS pathophysiology. Our mathematical models, which are motivated by these aforementioned dynamics, are able to represent the interaction of multiple physiological systems to produce Postural Orthostatic Tachycardia Syndrome.
Mathematical Modeling and Signal Processing of Postural Orthostatic Tachycardia Syndrome (POTS)

by
Justen Robert Geddes

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APPROVED BY:

Mette S. Olufsen
Co-chair of Advisory Committee

Brian E. Carlson
Co-chair of Advisory Committee

Johnny T. Ottesen

Alen Alexanderian

David S. Lalush
DEDICATION

To my parents, Krysten, and Glenn.
Thank you for helping make this dream a shared reality.
BIOGRAPHY

Justen spent his childhood in Dryden, New York. Justen always had many interests, which prompted his mother to tell him, “it’s not a question of what to do for the rest of your life, just what to do next”. Having learned the joys of applying himself during high school, he decided a good next step was to attend the State University of New York (SUNY) at Geneseo.

While at SUNY Geneseo Justen studied mathematics and anthropology but spent much of his time on call as a volunteer emergency medical technician as well as rowing and running. During this time, he solidified his love of mathematics, medicine, service, teaching, and research. At the end of his time at SUNY Geneseo, he knew he wanted a career, and a life, that allowed him to engage in a variety of interests while also serving others. In searching for ways to combine all these aspects into a career path, he visited North Carolina State University and met Dr. Mette Olufsen, who offered a way to do just that. Dr. Olufsen’s lab specializes in interdisciplinary research with an emphasis on the intersection of math and physiology. In other words, a research area that requires one to be interested in – and to have expert knowledge of - a variety of topics with results that can improve people’s lives.

Having found the best research area he could ask for, Justen moved to Raleigh. During his studies at NC State, Justen was able to conduct research, teach classes, mentor undergraduate and high school students, and volunteer. With the help of Dr. Olufsen, Justen was able to travel to Norway, San Diego, and countless other places while doing research he was passionate about, even with a pandemic ruining some of those travel plans. Upon graduating, Justen will be moving to Durham, NC, to join Dr. Amanda Randles’ lab at Duke as a postdoctoral scholar in the Biomedical Engineering Department.
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I’m grateful for such a supportive environment at NCSU in the biomathematics program and math department in general. In particular, thank you to the Cardiovascular Dynamics Group (CDG) for being such great colleagues, and friends, these past 5 years. To my CDG colleagues, Kristen Windoloski, Michelle Bartolo, Alyssa LaPole, Teresa Jones, Mitchel Colebank, Payton Woodall, Chris Schell, Amanda Colunga, Megan Chambers, Umar Qureshi, Atanaska Dobreva, Benjamin Randall, Martin Miranda, I am grateful for your friendship, expertise, and snacks during meetings.

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Lastly, I am incredibly grateful for the support that my family has shown me throughout this journey. It has been a strange journey these past few years, but your love, support, guidance, and grounding have made all the difference. To my parents, thank you for listening to my ramblings and for your support in so many ways. To Krysten, thank you for being the best sister I could have ever asked for - your belief and hope for the future have never gone unnoticed. To Glenn, thank you for being my brother-in-law, part of this family, and an example of the drive to improve the things around us.
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Figure 3.3 Heart rate (HR - left) and blood pressure (BP - right) data for five POTS subjects. The initiation of the head-up tilt (HUT) test is denoted by vertical dashed black lines. Mean heart rate before and after tilt, without analyzing the first 30 seconds of tilt (transition region), are denoted as horizontal red lines. Horizontal lines on blood pressure graphs represent average systolic (green), mean ($\frac{2}{3}$ diastolic + $\frac{1}{3}$ systolic - red), and diastolic blood pressures. Abbreviations: aR - UPEMD low-frequency amplitude at rest, aH - UPEMD low-frequency amplitude during HUT, $\Delta$ - change in HR from rest to HUT.

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Figure 6.9 (a) Importance of computed metrics, including the change in HR between supine and HUT ($\Delta HR$), the mean HR during HUT (Hm), the phase difference between BP and HR at rest (MR), the amplitude of the 0.1 Hz HR oscillations during HUT (HaH), the phase difference between HR and BP during HUT (MH), the amplitude of the 0.1 Hz HR oscillations at rest (HaR), the amplitude of the 0.1 Hz BP oscillations during HUT (PaH), and the amplitude of the 0.1 Hz BP oscillations at rest (PaR). (b) clustering of POTS patients (top) and control subjects (bottom). Three POTS patients were classified as controls and two control subjects as POTS patients.
Hemodynamics is controlled by the baroreflex system, which senses changes in carotid arterial pressure predicted as a function of upper body arterial pressure. Afferent signals from baroreceptor neurons are integrated into the Nucleus Solitary Tract (NTS) and transmitted via sympathetic and parasympathetic neurons regulating HR, peripheral vascular resistance, and ventricular contraction. The systemic circulation is represented by compartments lumping upper (a_u) and lower (a_l) body arteries, upper (v_u) and lower (v_l) body veins, and the left heart (l_h). The upper body compartment contains organs above the lower abdomen, including the abdominal splanchnic vessels, and the lower body compartment contains organs below the lower abdomen. Flow (Q) through the aortic valve (a_v) is transported from the left heart to the upper body arteries. From here, it is transported to the lower body arteries and through the upper body peripheral vasculature (u_p) to the upper body veins. A parallel connection transports flow through the lower body peripheral vasculature (l_p). From the lower body venous flow is transported to the upper body veins and finally via the mitral valve (m_v) back to the left heart. Each compartment representing the heart or a collection of arteries or veins has a pressure (P), volume (V), and elastance (E). Pumping of the heart is achieved by assuming that left heart elastance (E_l_h(t)) is time-varying. Model predictions of heart rate (H (bps), top panel) and upper body arterial pressure (P_a_u (mmHg), lower panel). We analyze upper body arterial pressure for oscillations but use the mean carotid pressure (not shown) as the input to our control equations. 5-second sections of each signal are shown in the overlaid subpanels. Frequency spectra of time-series data (H top, P_a_u bottom) shown in (b). Head-up tilt (HUT) test. Patients are tilted, head up, from 0 to 60° over 7 seconds. The shaded regions illustrate the blood volume distribution. Left panels show the decreasing (a) and increasing (c) Hill functions (light blue, gray, light pink) for characteristic values of k_X and P_2X. Model predictions using these functions are superimposed in (blue, black, pink). Panels (b) and (d) show the time-series predicted from the differential equation 7.11 using the Hill functions in (a) and (c). Process of obtaining amplitude of the ~0.1 Hz component of a heart rate signal, the same process is used for blood pressure. Starting from the left, the solution obtained using a variable step size solver is interpolated at 100 Hz. The last 200 seconds are marked (black trace in (a)). Second, the discrete Fourier transform is applied to obtain the amplitude of the frequencies. We examine the frequency range corresponding to the baroreflex, 0.05 - 0.15 Hz (black spectrum in (b)). Third, we find the maximum of the amplitude in this range (black column in (c)). From left to right: heart rate (H, top) and upper arterial pressure (P_a_u, bottom) predictions for k_H = 10, 20, and 30. Note, the large amplitude oscillations in the right panel are higher than values observed in patient data but are included to illustrate the behavior of the model. From left to right: maximum and minimum values for varying values of k_H, the amplitude of the ~0.1 Hz region response, and frequency of oscillations. Enlarged red dotes show denote measurements corresponding to k_H = 10, 20, 30. This process is used for blood pressure. Starting from the left, the solution obtained using a variable step size solver is interpolated at 100 Hz. The last 200 seconds are marked (black trace in (a)). Second, the discrete Fourier transform is applied to obtain the amplitude of the frequencies. We examine the frequency range corresponding to the baroreflex, 0.05 - 0.15 Hz (black spectrum in (b)). Third, we find the maximum of the amplitude in this range (black column in (c)). From left to right: heart rate (H, top) and upper arterial pressure (P_a_u, bottom) predictions for k_H = 10, 20, and 30. Note, the large amplitude oscillations in the right panel are higher than values observed in patient data but are included to illustrate the behavior of the model. From left to right: maximum and minimum values for varying values of k_H, the amplitude of the ~0.1 Hz region response, and frequency of oscillations. Enlarged red dotes show denote measurements corresponding to k_H = 10, 20, 30.
Figure 7.6 Two-dimensional parameter analysis of $k_R$ vs. $k_H$. (a) Amplitudes of peak heart rate ($HR$) oscillation (left) and peak upper arterial blood pressure ($Pa_u$) oscillation (right) at the $\sim 0.1$ Hz frequency band for values of $k_R$ and $k_H$ at rest (top) and head-up tilt (HUT, bottom). (b) The same information as (a) but with 2% noise. Average measurements from data [Ged20a] are marked for control patients at rest (CR), and POTS patients during head-up tilt (PH). Note that the physiologically possible oscillations correspond to the green regions. (c) Heart rate predictions during HUT for red dots on lower panels of (a); ith panel from top corresponds to ith dot from the left in (a). (d) Similar information as (c) but pertaining to (b).

Figure 7.7 Two-dimensional parameter analysis of blood volume (BV) vs $k_H$. (a) Amplitudes of peak heart rate ($H$) oscillation (left) and peak upper arterial blood pressure ($Pa_u$) oscillation (right) at the $\sim 0.1$ Hz frequency band for values of BV and $k_H$ at rest (top) and head-up tilt (HUT, bottom). (b) The same information as (a) but with 2% noise. Average measurements from data [Ged20a] are marked for control patients at rest (CR), and POTS patients during head-up tilt (PH).

Figure 7.8 Results of simulation with HUT at $t = 75$. Row 1: heart rate, $H$ (bps), left ventricle pressure, $P_{lv}$ (mmHg) row 2: upper arterial pressure, $Pa_u$ (mmHg), lower arterial pressure, $Pa_l$ (mmHg) row 3: upper venous pressure, $P_{vu}$ (mmHg), lower venous pressure, $P_{vl}$ (mmHg).

Figure 7.9 Characteristic data for a control and hyperadrenergic POTS patient (black) and model predictions (red and green) of heart rate ($H$), carotid artery blood pressure ($P_c$), and mean pressure. Simulations with 4,500 mL of blood are in the top row with simulations with 3,500 mL of blood in the bottom row. $Ca_u$ is decreased after HUT for all simulations to represent constriction of vasculature upon HUT. In control $P_{2H}$ is decreased (left), $k_H$ and $P_{2H}$ are increased after HUT to replicate hyperadrenergic POTS (middle) and $k_H$ increased, $R_{lpM}$ and $R_{lpM}$ decreased to replicate neuropathic POTS (right). To compare model predictions $H$ data is scaled such that the baseline is 1 bps and blood pressure vary from 80 to 120 mmHg.
Figure 8.1  Hemodynamics is controlled by the baroreflex system, which senses changes in the carotid sinus baroreceptors. Afferent signals from baroreceptor neurons are integrated into the brain and transmitted via sympathetic and parasympathetic neurons, which influence the concentrations of norepinephrine (NE) and acetylcholine (ACh). Concentrations of NE affect heart contractility and vasculature, and in addition to ACh, affect the concentration of cAMP inside the sinoatrial node (SAN). The membrane potential of the SAN is responsible for the time at which time-varying elastance function contracts, simulating a heartbeat. The systemic circulation is represented by compartments lumping upper (a_u) and lower (a_l) body arteries, upper (v_u) and lower (v_l) body veins, and the left heart (l_h). Flow (Q) through the aortic valve (a_v) is transported from the left heart to the upper body arteries, and from here, it is transported in the arteries (a) to the lower body arteries and through the upper body peripheral vasculature (up) to the upper body veins. A parallel connection transports flow through the lower body peripheral vasculature (l_p). From the lower body, venous flow (v) is transported to the upper body veins and finally via the mitral valve (m_v) back to the left heart. Each compartment representing the heart or a collection of arteries or veins has pressure (P), volume (V), and compliance (C).

Figure 8.2  Nonessential activator reaction scheme. Abbreviations are as follows: R - receptor, N - norepinephrine, A - antibody, G - Gs protein, $k_i$ - rate constants. “Hats” denote the binding of reactants - for example, the binding of N and R is denoted as $\hat{R}N$.

Figure 8.3  Workflow for model simulations. Initial conditions ($g(t), t \leq t_0$), parameters ($\theta$), and final simulation time $t_F$ are set in MATLAB and written to .txt files. .out files are created for the model simulation to be recorded in. The executable is then called from MATLAB while passing the file names in as arguments. The model is then solved and the results are loaded into MATLAB via .out files where they are analyzed.

Figure 8.4  Control (left) and POTS (right) model simulations (blue) of heart rate (HR, top row) and blood pressure (BP, bottom row) before and after tilt (denoted by the dashed black line) plotted with patient data (gray). Patient data is shifted vertically to align with model predictions.

Figure 8.5  Pressure (mmHg) predictions for the left heart (Plh, top), upper body veins (Pvu, middle left), upper body arteries (Pau, middle right), lower body veins (Pvl, bottom left), and lower body arteries (Pal, bottom right) with the initiation of tilt marked by a dashed black line.

Figure 8.6  Volume (mL) predictions for the left heart (Vlh, top), upper body veins (Vvu, middle left), upper body arteries (Vau, middle right), lower body veins (Vvl, bottom left), and lower body arteries (Val, bottom right) with the initiation of tilt marked by a dashed black line.
Figure 8.7  Amplitudes of low-frequency heart rate (HR, top) and blood pressure (BP, bottom) oscillations during rest are depicted by color when parameter $i$ (horizontal axis) is increased or decreased by 5% or 2% (vertical axis) from the POTS parameterization that gives the time series prediction shown in Figure 8.4. Note that the base POTS simulation low-frequency amplitude for HR ($\sim 4$ bpm) and BP ($\sim 20$ mmHg) are shown in the middle row of each panel, denoted by 0% change, and the colors in the surrounding panels denote oscillation amplitude and not the relative change. The model is solved at rest for 10,000 seconds, with oscillations quantified for the last 150 seconds. Parameters are ranked from largest to smallest relative change from POTS simulation low-frequency HR and BP oscillation amplitude, with parameter numbers corresponding to: 1-10: $k_{dL}$, $V_{dl}$, $Na_o$, $K_{mNap}$, $I_{NaK, max}$, $Cao$, $f$, $P_{CaL}$, $\tau_D$, 11-20: $\tau_Z$, $\tau_p$, $\delta_1$, $C_3$, $C_4$, $C_{au}$, $K_{ADC}$, $R_{upM}$, $\tau_S$, $E_mM$, 21-30: $K_{mKp}$, $K_o$, $k_p$, $C_{vu}$, $K_{mFca}$, $K_{c1}$, $Ca_1$, $g_{to}$, $K_{NaCa}$, $K_{ACh}$, 31-40: $R_{pM}$, $g_{Kr}$, $K_{co}$, $K_{2no}$, $K_{3no}$, $K_{1no}$, $V_{Mvl}$, $P_{CaT}$, $K_i$, $E_m$, 41-50: $\tau_{ACh}$, $K_{1ni}$, $K_{s}$, $g_{Kur}$, $g_{Na}$, $K_{2ni}$, $K_{3ni}$, $Q_n$, $m_{vl}$, $R_{apM}$, 51-60: $v_2$, $R_{pM}$, $Q_c$, $g_{KACH}$, $R_{vl}$, $a_{Fca}$, $shift$, $R_{al}$, $k_p$, $K_{cni}$, 61-70: $R_{mv}$, $g$, $E_{mm}$, $d$, $R_{av}$, $g_f$, $K_{mF}$, $a$, $y_{shift}$, $Q_c$, 71-74: $g_{NaL}$, $\delta_m$, $g_{Ks}$, $a_a$ .................................

Figure 8.8  Values of low-frequency heart rate and blood pressure oscillation amplitude ($A_{HR}$, top row, and $A_{BP}$, second row) at rest (blue) and head-up tilt (orange) as well as the change in mean heart rate (bottom row) .................................

Figure 8.9  Results of varying parameters to represent (from left to right) a 1) untreated POTS patient, 2) compression stockings, 3) Midodrine, 4) lower body pressure, 5) increased blood volume, and 6) beta-blockers such as propranolol .................................
Modern medicine is driven by the comparison of healthy physiological and pathophysiological states. However, the pathophysiology of ill health is often not fully understood. The term “syndrome” is used to categorize a set of symptoms and observable physiological markers that manifests a specific type of ill health for which the precise pathophysiology is not known [Cal03]. Syndromes are challenging to treat as they often span multiple physiological systems, and it may not be known how the condition impacts each one. As a result, treating syndromes often require a multi-disciplinary team of medical researchers to understand their effects on the human body.

In this dissertation, we use mathematical techniques to study postural orthostatic tachycardia syndrome (POTS). POTS is characterized by an exaggerated and sustained increase in heart rate in response to a postural change without a substantial decrease in blood pressure. POTS patients can experience many symptoms, including memory problems, shortness of breath, and lightheadedness [Sha19]. POTS is typically diagnosed by measuring blood pressure and the increase in heart rate while a patient undergoes a postural change, such as a head-up tilt or active standing test. The variety of symptoms suggests impairment of multiple physiological systems and that orthostatic tachycardia (the measured biomarker) is likely a symptom, not a cause, of the syndrome. The cause of POTS is not agreed upon, and there is growing consensus that there are multiple different mechanisms that can cause POTS, known as phenotypes, with different pathophysiologies [Mar20; Fed19]. These phenotypes represent excessive sympathetic response, ineffective vascular constriction in the lower body, or low blood volume. In the quest for understanding POTS pathophysiology, some recent studies have found that a subset of POTS patients expresses autoantibodies that bind to receptors in cells controlling heart rate [Li22; GI19; Fed17a; Li14] and smooth muscle tone [GI19; Li14; Fed17a]. The presence of these autoantibodies has prompted the hypothesis that, in some instances, POTS may have an autoimmune
component [Bry19; Gru08b; Mar20; Fed19; GI21].

To improve the understanding and treatment of POTS, the medical community needs to comprehend how the cardiovascular, neural, and immune systems interact to produce the observed symptoms and dynamics, which can identify targets for the treatment of the syndrome [Raj18]. With phenotypes caused by such varying pathophysiologies, treatments will be most effective if the phenotype can be accurately identified in a clinical setting.

These distinct phenotypes suggest that POTS is a multifaceted syndrome, and therefore using a single marker such as postural tachycardia [Fre11; She15; Ste18; Fed19] to characterize the syndrome likely limits the ability to understand the pathophysiology. Heart rate signals include significantly more information than just the quantification of its orthostatic change. In particular, in addition to the increase in heart rate, the heart rate and arterial blood pressure signals exhibit significantly larger ~0.1 Hz oscillations than control subjects [Ged20a]. This observation agrees with other studies [Ste15; Med14] examining continuous data from POTS patients, showing the increased amplitude of low-frequency (0.05-0.15 Hz) heart rate, blood pressure, and cerebral blood flow oscillations when compared to control subjects. Our study [Ged20a] also shows a shorter phase response between heart rate and blood pressure both at rest and during head-up tilt. This finding, not addressed in previous studies, is important as it provides a means to examine patient data without conducting a postural challenge. In summary, quantification of signal dynamics helps describe the syndrome; however, discerning the phenotype of a patient remains challenging. Mathematical modeling motivated by signal processing results can assist in this objective.

Mathematical models of complex systems are built to integrate concurrent states, generating observable measures, such as time courses for blood pressure and heart rate. Models are built by describing healthy physiological responses, and by manipulating parameters or pathways, it is possible to generate hypotheses explaining pathophysiologies. Once the mechanisms are identified, models can also be used to test the efficacy of interventions that seek to assist the body in returning to healthy function. Previous studies have examined the response to orthostatic changes or predicted low-frequency heart rate and blood pressure dynamics. Most studies have modeled orthostatic change using either heart rate or blood pressure as an input [Olu05; Ell08; Kap07; Ott10; Wil14; Mat15]. In addition, some model studies have examined low-frequency oscillations [Hel00; Ham05; Ish20] but have related results to POTS. To our knowledge, prior to the manuscripts presented here, no previous studies have predicted the effects of POTS phenotypes on low-frequency oscillations.

This dissertation presents three primary contributions to the identification and understanding of POTS phenotype pathophysiology, which remains one of the, if not the most, important problems in POTS treatment and research [Raj18]. First, we use state-of-the-art non-stationary signal processing to examine the amplitude of HR and BP oscillations in POTS patients and to derive a novel orthostatic invariant diagnostic metric that represents baroreflex responsiveness. Thus, providing evidence that these oscillations are crucial to the etiology of POTS. Second, we construct a lumped parameter model that can represent the three prominent phenotypes of POTS which displays tachycardia and increased amplitude of low-frequency oscillations and, as a result, suggests physiological attributes that may
be abnormal to cause each phenotype. Third, we construct a multiscale mathematical which shows that the presence of adrenergic agonistic autoantibodies can cause both tachycardia and abnormal low-frequency oscillations, giving merit to the autoimmune hypothesis for POTS in some patients and providing insight into cell-autoantibody dynamics in these patients.

1.1 Summary of this dissertation

This dissertation contains 9 chapters that present background, techniques, and novel findings concerning the mathematical study of POTS outlined above. The results are published in two first-author manuscripts [Ged20a; Ged22], and one first-author manuscript that is in preparation. In addition to this work, Geddes authored an additional first author manuscript [Ged20b] and assisted in four others (one published [Gil21], three in preparation) during his time at North Carolina State University.

The chapters contain the following:

- Chapter 2 provides the physiological background of the cardiovascular system, autonomic nervous system, and electrophysiology required to understand the pathophysiology of POTS.

- Chapter 3 reviews the current understanding of the pathophysiology of POTS and outlines the contributions of this dissertation.

- Chapter 4 gives a brief background of signal processing, in particular non-stationary signal processing.

- Chapter 5 presents modeling methods used in the following chapters with an emphasis on cardiovascular, neurological, and cellular electrophysiology models.

- Chapter 6 includes the published manuscript “Characterization of Blood Pressure and Heart Rate Oscillations in POTS Patients via Uniform Phase Empirical Mode Decomposition” by Geddes, Mehlsen, and Olufsen. This study uses a non-stationary signal processing known as uniform phase empirical mode decomposition to analyze ~ 0.1 Hz heart rate and blood pressure oscillations in POTS and control subjects. Results show larger low-frequency oscillations in POTS patients and a significant difference of a novel orthostatic invariant biomarker, which quantifies the phase interaction of the low-frequency components of the signals. This work serves to underline the importance of low-frequency oscillations to the etiology and diagnosis of POTS.

- Chapter 7 includes the published manuscript “Postural orthostatic tachycardia syndrome explained using a baroreflex response model” by Geddes, Ottesen, Mehlsen, and Olufsen. This study builds a lumped parameter 0D model that is able to represent the three prominent POTS phenotypes. Analysis shows the presence of repeated Hopf bifurcations in the parameter space, as well as parameter effects that represent phenotype pathophysiology.
• Chapter 8 includes the manuscript in preparation “Modeling the role of adrenergic autoantibodies in Postural Orthostatic Tachycardia Syndrome (POTS)” by Geddes, Ottesen, Carlson, and Olufsen. In this manuscript, we derive a multiscale model that combines submodels of the sinoatrial node cell, afferent and efferent baroreceptor nerves, and the cardiovascular system to show the effects of agonistic adrenergic autoantibodies. Results show the ability of autoantibodies to cause POTS dynamics and symptoms, thus providing support to the autoimmune basis for POTS in some patients. This manuscript concludes by testing the efficacy of common POTS interventions on the model.

• Chapter 9 summarizes the content of this dissertation, discusses clinical and mathematical implications, and suggests future work.
This chapter provides an overview of the cardiovascular system, its control, and electrophysiology. We begin our discussion by describing large-scale cardiovascular dynamics (Section 2.1). We then discuss the autonomic nervous system in Section 2.2 with an emphasis on the baroreflex regulation of blood pressure and heart rate. Lastly, we provide an overview of cellular electrophysiology in Section 2.3, with specific attention paid to sinoatrial node cells, which control the pacing of the heart. Unless otherwise stated, information in this chapter is adapted from [Bor12].

2.1 Cardiovascular system

The cardiovascular system is composed of the heart, which is responsible for generating pressure to drive blood flow, and the vasculature, which transports blood carrying oxygen to tissues to drive metabolism and carbon dioxide to the lungs to be expired. The vasculature has two components, the systemic circulation and pulmonary circulation, both consisting of arteries and veins. As shown in Figure 2.1, the systemic arteries transport oxygenated blood from the left heart to the body through progressively smaller vessels. At the smallest vessels, the capillaries, oxygen diffuses into the tissue and carbon dioxide enters the bloodstream. Blood is returned via progressively larger veins to the right heart. The right heart pumps blood to the pulmonary arteries, which, as with the systemic circulation, become gradually smaller. The smallest pulmonary capillaries surround the alveoli facilitating reoxygenation of the blood. The oxygenated blood then returns to the left heart via the pulmonary veins.
Figure 2.1 The journey of blood, starting and ending in the left heart. Blood is ejected from the left ventricle to the aorta and flows through the systemic arteries, then to the capillaries where oxygen and nutrient exchange occurs, and further into the veins until it returns to the right heart. It is then ejected from the right ventricle and is oxygenated in the lungs, then completing its loop by arriving back at the left heart. Reproduced with permission from [Bet13].

2.1.1 Vasculature

To perfuse the body, a healthy adult has approximately 5 liters of blood, but actual blood volume varies primarily as a function of height and weight \([\text{Nad62}]\)

\[
BV = 24.8 \ H^{0.725} \ W^{0.425} - 1954 \quad \text{for women,}
\]

\[
BV = 23.6 \ H^{0.725} \ W^{0.425} - 1229 \quad \text{for men,}
\]

where \(BV\) is blood volume in milliliters, \(H\) is the subject’s height in centimeters, and \(W\) is weight in kilograms. As noted in Table 2.1, the systemic circulation holds most of the blood, and the majority of blood in both circulations is located in the veins.

Blood volume is further differentiated as stressed or unstressed. The unstressed volume is the amount of blood needed to fill a vessel before pressure is developed in the blood by the vessel wall. Additional volume causes the vessel wall to develop pressure in the contained blood and is called the stressed volume \([\text{Spi16}]\). Since the system is always pressurized, this volume is difficult to measure, but it has been shown that total stressed volume in humans is similar to that of animals \((\approx 30\%)\) \([\text{Mag98}]\). Beneken & DeWitt \([\text{Ben67}]\) estimate that \(\approx 30\%\) of the volume in arteries is stressed while only \(\approx 7.5\%\) of
the volume is stressed in veins. They estimated these quantities from a mathematical model relating volume distribution and flows.

The left and right ventricles generate pressure which drives flow first through the arteries, resulting in the highest vascular pressures in each circulation occurring in arteries. Figure 2.2 illustrates the pressure decrease as blood moves from arteries to capillaries, and then to veins, where pressure is the lowest, thus allowing forward flow. Systemic arteries experience pressures between 40-120 mmHg, while systemic venous pressures vary between 3–15 mmHg. Pulmonary artery pressure is approximately 15 mmHg, while pulmonary venous pressure is approximately 5 mmHg. Figure 2.2 also depicts the decrease in pulse pressure (maximum minus minimum pressure) as the journey of blood continues. Mean pressures are shown in Table 2.1.

Figure 2.2 Pressure in the Systemic (A) and Pulmonary (B) circulations as blood travels from arteries to capillaries, and then to veins. Reproduced with permission from [Bor12].

To enable coordinated flow and accurate perfusion, arteries, veins, and capillaries complete different objectives. Arteries maintain high pressure and are efficient at transporting blood to tissues. The sole purpose of capillaries is substance exchange and therefore are only composed of connective tissue and endothelial cells. Veins are responsible for returning blood to the heart under relatively low pressure. In addition, they act as volume reservoirs and hold the majority of blood in the body at any given time. This reservoir can be crucial if blood is lost from the body, if arterial pressure begins to fall, or in response to exercise. In response, the autonomic nervous system can elicit venous constriction, thereby lessening venous volume but increasing arterial volume and maintaining blood pressure [Guy11].

Arteries, veins, and capillaries behave differently as a result of their different compositions. As shown
Table 2.1 Subtable 1: percentage of blood volume in the systemic circulation, pulmonary circulation, and heart at the beginning of heart contraction. Subtable 2: percentage of blood located in arteries, veins and capillaries for the systemic and pulmonary circulation. Subtable 3: mean pressures in the arteries, veins and capillaries for the systemic and pulmonary circulation. Values are from [Bor12].

<table>
<thead>
<tr>
<th></th>
<th>Systemic</th>
<th>Pulmonary</th>
<th>Heart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total volume distribution.</td>
<td>84 %</td>
<td>8.8 %</td>
<td>7.2 %</td>
</tr>
<tr>
<td>Arteries</td>
<td></td>
<td></td>
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<tr>
<td>Veins</td>
<td></td>
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</tr>
<tr>
<td>Capillaries</td>
<td></td>
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</tr>
<tr>
<td>Systemic volume distribution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arteries</td>
<td>17 %</td>
<td>76 %</td>
<td>7 %</td>
</tr>
<tr>
<td>Veins</td>
<td>30 %</td>
<td>45 %</td>
<td>25 %</td>
</tr>
<tr>
<td>Capillaries</td>
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<td></td>
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</tr>
<tr>
<td>Pulmonary volume distribution</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Arteries</td>
<td></td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Veins</td>
<td>15</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Capillaries</td>
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</tbody>
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Arteries have more elastin fibers and have increased activation of vascular smooth muscle cells, while veins are less elastic and can change from a round to an ellipsoidal shape at low pressure. Figure 2.4 shows that these compositional differences cause veins to display a non-linear pressure-volume relationship. Capillaries lack the amount of elastin and vascular smooth muscle cells observed in arteries and do not change shape considerably like veins, thereby allowing them to consistently perfuse tissue. Capillaries have pretty a single epithelial layer and their adventitia is largely connective tissue composed of pericytes.
Figure 2.3 Radius, wall thickness, and relative composition of endothelial cells, elastic fibers, smooth muscle cells, and collagen fibers of the vasculature. Reproduced with permission from [Bor12]

Figure 2.4 Graph of transmural pressure (mmHg) vs relative volume for the aorta (left) and vena cava (right). As volume increases in the aorta, the transmural pressure increase is approximately linear, however, in the vena cava, there is a non-linear pressure-volume relationship as the shape of the vena cava significantly changes as volume increases. Values from [Bor12].

2.1.2 The Heart

The heart acts as a pump that contracts and relaxes rhythmically, increasing pressure to transport blood to the body. This organ is responsible for circulating approximately 5 liters of blood around the body every minute, equivalent to the total blood volume. Cardiac output (mL/min) approximates the amount of blood pumped by measuring how much blood the left ventricle pumps in a minute and is given by multiplying the volume of blood pumped in one contraction (stroke volume - mL) by the number of beats in a minute.

The heart is composed of the left and right atria and left and right ventricles, with valves controlling the flow into and out of each ventricle. A single contraction and relaxation of the heart is referred to
as the cardiac cycle, which has four stages. These are typically depicted for the left ventricle (shown in Figure 2.5). This diagram is referred to as the Wiggers diagram.

The four phases of the cardiac cycle with respect to the left heart are [Sil15],

1. **Isovolumic relaxation**: During this stage, the aortic valve remains closed and both the atrium and ventricle are relaxed. Towards the end of this stage, the ventricle fully relaxes, which allows the mitral valve to open, allowing blood to flow into the ventricle due to the pressure gradient.

2. **Inflow**: With the mitral valve open and the aortic valve closed, the atrium contracts, pushing blood into the ventricle. At the end of the atrial systole, the ventricle has a maximum volume. Therefore the maximum volume is often referred to as the end-diastolic volume.

3. **Isovolumic contraction**: After atrial contraction, the mitral valve closes due to the beginning of ventricular contraction and the aortic valve remains closed. These closed valves cause pressure to build in the ventricle as no volume is being moved out of the chamber. During this stage, the atrial muscles begin to relax, allowing blood to flow into the atrial chambers once the atrial pressure is less than venous pressure.

4. **Ejection**: As the ventricles continue to contract, the mitral valve remains closed and the aortic valve opens, causing blood to be pushed out through the aortic valve and into the aorta. After blood is ejected, the ventricles relax and the cardiac cycle repeats.

### 2.2 Autonomic Nervous System

The human body responds to physiological perturbations to maintain homeostasis. The majority of these responses are unconscious reflexes facilitated by the autonomic nervous system. This system can be conceptualized as having three components: an input signal, a coordinating center, and a response signal. Afferent (visceral) nerves carry signals that reflect physiological conditions or perturbations from normal conditions. These signals are carried to the hypothalamus, which coordinates a response as an unconscious reflex and then sends the response signal via efferent nerves to tissues and organs that can correct the deviation.

There are three branches of the autonomic nervous system - the sympathetic, parasympathetic, and enteric. The enteric nervous system primarily influences the gastrointestinal tract [Fur12] while the sympathetic and parasympathetic have many sites of influence. In this dissertation, we will only be examining the sympathetic and parasympathetic in depth.

Afferent nerves carry signals from a tissue sensor to a coordinating center via visceral sensory fibers [Weh16]. The afferent nerves transport input signals to the hypothalamus, pons, and medulla [Sil15]. These regions then encode an appropriate response and transmit the response to the brain stem and spine, depending on which efferent branch is responsible for transmitting the signal to the target tissue.

The two primary efferent branches of the autonomic nervous system are the sympathetic and parasympathetic branches. The sympathetic branch is sometimes referred to as the “fight or flight"
Figure 2.5 Wiggers diagram of the stages of the cardiac cycle for the left heart. From top to bottom, the graphs show the heart sounds (purple markers), pressure in the aorta (bright red), the left ventricle (dark red), and the left atrium (black). The next graph (black) shows the ventricular volume and the electrocardiogram (blue). To begin, an action potential is fired, causing the R peak in the electrocardiogram as part of the QRS complex. The action potential begins the contraction of the heart and closes the mitral valve, causing pressure to increase as the heart undergoes isovolumic contraction. When the aortic valve opens, blood starts to flow out into the aorta, initiating the ejection phase. Pressure continues to increase and then decrease as this phase continues, and the volume of the ventricle falls until the aortic valve closes, initiating the isovolumic relaxation phase as pressure decreases. With pressure now at the diastolic value, the mitral valve opens, causing the rapid inflow of blood from the left atrium, and the process repeats. Reproduced with permission from [Pol22].

response, however; as pointed out by [Weh16] this is an oversimplification as the sympathetic branch also controls various bodily functions that are not characterized by eminent danger. In addition to the sympathetic branch, the parasympathetic branch also assists in maintaining homeostasis. Targets of sympathetic and parasympathetic nerves are depicted in Figure 2.6 and include the control of heart function and vasculature, which is important to the work presented here.

The brain stem sits above the spine, and the spine is separated into 5 regions: cervical vertebrae (C1-C7), thoracic vertebrae (T1-T12), lumbar vertebrae (L1-L5), sacrum (5 fused vertebrae) and the coccyx (4 fused vertebrae). The sympathetic efferent branch stems from the thoracic and lumbar regions (T1-T12 & L1-L2), while the parasympathetic nerves stem from the brain stem and sacrum. The origins of each system can be seen in Figure 2.6.

The efferent portion of the autonomic nervous system uses two types neurons, a preganglionic and postganglionic, to transmit signals from the spine or brainstem to the target tissue [McC07; Weh16]. Preganglionic neurons are attached to the brain stem or spine and travel to meet postganglionic neurons.
that then innervate the target tissue [McC07]. In this dissertation, we will focus on the innervation of the heart and vasculature to control blood pressure.

### 2.2.1 Neurotransmitters of the autonomic nervous system

Neurotransmitters are signaling molecules excreted to transmit messages to cells or other neurons. There are two primary neurotransmitters of the autonomic nervous system - acetylcholine (ACh) and...
norepinephrine (NE). Epinephrine is also employed by the autonomic nervous system but to a lesser extent. All preganglionic nerve fibers release ACh, regardless of their branch [McC07]. All parasympathetic postganglionic fibers release ACh, while the majority of sympathetic postganglionic fibers release NE.

A neurotransmitter's concentration is modulated by its release, as previously discussed, and its removal. When ACh is released from a nerve fiber, the enzyme acetylcholinesterase removes ACh by hydrolysis, producing choline and acetate [McC07]. The primary removal of NE from the synapse is the reuptake into the nerve that released it [McC07]. In addition to direct innervation, the adrenal medulla releases norepinephrine and epinephrine into the blood in response to danger or exercise. Since the neurotransmitters are released directly into the blood, reuptake is not possible. These neurotransmitters are therefore inactivated by catechol-O-methyltransferase in the liver [McC07].

Once neurotransmitters are released, they can bind to receptors. ACh binds to nicotinic receptors in the postganglionic neurons to stimulate firing and to muscarinic receptors on target tissues. NE binds to adrenergic receptors (α & β). Muscarinic and adrenergic receptors are both G protein-coupled receptors that initiate a cascade of reactions inside the target tissue cells to facilitate a variety of responses depending on cell type, receptor type, and receptor density in the cell membrane.

### 2.2.2 Autoantibody effects on the autonomic nervous system

Autoantibodies react to a subject's own molecules [Elk08]. While these reactions can be neutral or beneficial (i.e., in attacking cancer cells), the effects of autoantibodies can also be harmful, causing disease [Elk08]. There are a plethora of ways autoantibodies may contribute to disease phenotypes, but in this dissertation, we will only examine the effects of autoantibodies on sinoatrial node cells, which receive input from the autonomic nervous system. Numerous studies have shown that it is possible for autoantibodies to modulate the effects of neurotransmitters binding to receptors [SB00; MM13; Li14] or even directly stimulate the receptor [Fed17a]. In these ways, autoantibodies can enhance the effect of a neurotransmitter (agonistic autoantibodies) or prevent the neurotransmitter from causing the intended effect (antagonistic autoantibodies), interfering with the proper function of the autonomic nervous system.

### 2.2.3 The Baroreflex

To effectively perfuse the body during different physiological stressors such as exercise, disease, injury, or simple postural changes, the cardiovascular system relies on the autonomic nervous system. Of the control systems that regulate blood pressure, such as the renin-angiotensin-aldosterone system or the chemoreceptor reflex, the baroreflex is the primary system that controls arterial pressure in the short-term under normal pressure ranges [Wag16].

The baroreceptor control of arterial pressure, also known as the baroreflex, operates as a negative feedback loop to maintain blood pressure. Figure 2.7 illustrates the components of this loop as part of the autonomic nervous system. The baroreflex has 5 components.

1. **Sensors:** The baroreflex has stretch sensors known as baroreceptors located in the aortic arch and
carotid sinuses. These sensors detect stretches of the arterial walls caused by changes in pressure. In response to increased pressure, the walls are stretched, increasing the afferent nerve firing rate. In literature, and in this dissertation, we use the terms “baroreceptors” and “high-pressure baroreceptors” interchangeably. However, there are also low-pressure baroreceptors in various parts of the cardiovascular system, including the systemic veins and atria, that are involved in modulating blood volume. Stimulation of these receptors results in sympathetic signals that reduce renal blood flow and urine output as well as parasympathetic signals that decrease angiotensin, aldosterone, and vasopressin, causing modulations in blood volume and pressure [Thr94; Arm22]. Due to the end results of low-pressure baroreceptor stimulation, these effects occur on longer a time scale than high-pressure baroreceptor regulation. The models presented in this dissertation study the baroreflex effects on the order of seconds to minutes and therefore do not model low-pressure baroreceptor control, which operates on a longer time scale by modulating blood volume.

2. **Afferent nerves**: The stretch of baroreceptors cause modulation in the firing of the attached afferent baroreceptor nerves as illustrated in Figure 2.7. For the aortic arch, these nerves are part of the depressive branch of the vagus nerve, while the afferent nerve for the carotid sinus is the sinus nerve.

3. **Coordinating center**: Afferent nerves then transport the signals to the medullary cardiovascular center. Within this center, most afferent nerves are integrated into the nucleus tractus solitarii (NTS) (shown in Figure 2.7), which encodes messages to correct deviations in blood pressure and sends responses via sympathetic and parasympathetic efferent neurons.

4. **Efferent nerves**: Signals are carried away from the medullary cardiovascular center to effector (target) organs via efferent nerves. The sympathetic efferent nerves used by the baroreflex innervate vasculature and the heart, affecting both heart contraction and heart rate. The parasympathetic efferent nerves innervate the heart via the vagal nerve. Sympathetic efferent nerves transmit signals slower than parasympathetic. This delay is thought to be responsible for the low-frequency (≈0.1 Hz) oscillations found in heart rate and blood pressure data [Jul06; Cev01; DeB87].

5. **Effectors**: Our focus in this dissertation is on the baroreflex effect on the heart and vasculature. The heart takes both sympathetic and parasympathetic signals, while the vasculature only receives the sympathetic signal. If high blood pressure is sensed, the sympathetic input to vasculature results in vasodilation (for low blood pressure, vasoconstriction occurs). In addition to constriction/relaxation of vasculature, sympathetic signals also influence the contractility of the heart and influence heart rate. The parasympathetic nervous system decreases heart rate in response to high blood pressure and vice versa.
Figure 2.7 The baroreflex feedback loop. Baroreceptors sense stretch in both the carotid sinus and aortic arch and transmit signals via afferent nerves to the nucleus tractus solitarii (NTS), which encodes responses via the sympathetic and parasympathetic efferent nerves to control resistance, heart rate, and heart contraction. Adapted from [Ged22].

2.3 Electrophysiology

Physiological actions such as heart contraction and transmission of nervous system information are facilitated by the propagation of electrical signals. The electrical impulses travel by modulating the electrical gradient between the intracellular and extracellular space of cells due to ion concentrations. Understanding how these messages are created and transmitted via electrophysiology will be important to our discussion of POTS.

The dynamics of most cells, including cardiac muscle cells and vascular smooth muscle cells, can be explained using basic cellular electrophysiology. This chapter will introduce basic concepts as well as provide a detailed description of the sinoatrial node (SAN) cell as an example of a pacemaker cell, which controls the pacing of the heart, and discuss how the electrophysiology of a SAN cell, and other pacemaker cells, differ.
2.3.1 Action potentials

An action potential, shown in Figure 2.8, is a rapid increase in membrane potential, which is the difference in electrical potential between the interior and exterior of the cell. The propagation of an action potential allows cells to transmit messages and coordinate actions. The opening and closing of voltage-gated ion channels are the basis for action potentials by allowing potassium, sodium, and calcium to flow in and out of the cell to modulate the membrane potential. A cardiomyocyte action potential has five phases.

- Phase 0 refers to the relatively fast increase in membrane potential due to rapid depolarization of the cell once a threshold membrane potential is reached either by external stimulus or pacemaking activity. Phase 0 occurs by the opening of sodium (as well as calcium in cardiac cells) channels. This allows sodium and calcium to rush into the cell, causing rapid depolarization of the cell and an increase in membrane potential.

- Phase 1 refers to the rapid repolarization of the cell, decreasing membrane potential. This phase, a result of the inactivation of sodium channels and rapid outward potassium current, does not exist in SAN cells and is minor both in time and effect on membrane potential.

- Phase 2 is characterized by the plateau of membrane potential. This plateau is a consequence of the continued entry of calcium and sodium balanced with the outward flux of potassium and a small current generated from the NaCa exchanger (discussed below). Phase 2 is also not present in sinoatrial node cells.

- Phase 3 refers to the primary repolarization of the cell, which causes the largest decrease in membrane potential by closing sodium and calcium channels and opening potassium voltage-gated ion channels and closing which allows the rapid exit of potassium ions.

- Phase 4 is the electrical diastolic phase, where the most negative values of the membrane potential occur. In regular cells, there is a period of hyperpolarization when the membrane potential is more negative than the resting potential. In most cells, all ion channels are closed but there is a small current present in pacemaking cells. The membrane potential reaches the depolarization threshold by external stimulus or pacemaking activity.

A neuron action potential (also depicted in Figure 2.8) consists of a depolarization, repolarization, and hyperpolarization phase, which approximately correspond to phases 0, 3, and 4 in a cardiomyocyte. As noted above, the sinoatrial node cell action potential also only possesses phases 0, 3, and 4, but is shaped differently than a neuron action potential. Additionally, cardiomyocytes do not have a hyperpolarization phase. These differences are caused by different numbers of various ion channels in separate cell types.
Figure 2.8 Membrane voltage ($V_m$) during an action potential for a neuron (left) and ventricular myocyte (right). Phases of an action potential are labeled for the ventricular myocyte action potential. Reproduced with permission from [Sig10].

2.3.2 Ion contributions to membrane potential

The membrane potential is modulated by ions entering and exiting the cell via ion channels, ion transporters, exchangers, and ion pumps.

Ion channels

Ion channels allow ions to pass through when they are open. Voltage-gated channels open and close as a function of membrane potential, while ligand channels are opened (gated) by neurotransmitters binding to the cell. While the dynamics of ligand-gated channels can be intuitively understood as a function of neurotransmitters binding to them, we focus on voltage-gated channels and how their dynamics give rise to action potentials passively as a function of ion concentration gradients and electrostatic potential.

When ion channels open, ions flow through due to a thermodynamic driving force which is the combination of an electrical driving force balanced with an entropy force due to concentration differences inside and outside the cell [Bea12]. $E_X$ is often called the Nernst potential and is the membrane potential at which the thermodynamic driving force for species $X$ is 0, or at equilibrium. For the ion in question, if the membrane potential equals $E_X$ no ions of species $X$ move in or out of the cell, even with open ion channels and differing inner and outer cell concentrations. The Nernst equation states that the thermodynamic force equals zero for ion $X$ when

$$E_X = \frac{RT}{zF} \ln \left( \frac{[X]_o}{[X]_i} \right),$$
where \( X \) is the ion species, \( z \) is the valance of ion species \( X \), \( R = 8314 \text{ J/(kmol K)} \) is the universal gas constant, \( T \) is the temperature in Kelvin for \( (T = 310 \text{ for } 37^\circ \text{C}) \), \( F = 96485 \text{ C/mol} \) is the Faraday constant, \( \ln(s) \) denotes the natural logarithm, \([X]_o\) denotes the outer concentration of ion \( X \), and \([X]_i\) denotes the inner concentration of ion \( X \) [Bea12]. The Nernst potential is crucial to the understanding of electrophysiology as ions will move through open channels in an effort to realize this potential. For example, the Nernst potential for potassium is approximately -88 mV and is closest to the resting membrane potential [Bor12]. Nernst potentials for sodium, potassium, and calcium are shown in Table 2.2. When potassium channels open near the maximum of the action potential, the positively charged potassium ions flow out of the cell in an effort to decrease the voltage of the cell towards the Nernst potential of -88 mV, thereby lowering the membrane potential towards the resting potential. At rest, calcium gates are closed and the resting potential is primarily modulated by sodium and potassium.

**Table 2.2** Values for Nernst potentials of various ions from [Bor12]. Normal ranges for ion concentration \( X \) for outer \(([X]_o)\) and inner \(([X]_i)\) concentrations in millimolar (mM) are as follows: \([K^+]_o = 5 - 10 \text{ mM}, [K^+]_i = 130 - 150 \text{ mM}, [Na^+]_o = 140 - 150 \text{ mM}, [Na^+]_i = 6 - 10 \text{ mM}, [Ca^{2+}]_o = 1.5 - 3 \text{ mM}, [Ca^{2+}]_i = 0.0001 - 0.0003 \text{ mM}.

<table>
<thead>
<tr>
<th>Ion</th>
<th>Nernst potential (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (Na^+)</td>
<td>+72</td>
</tr>
<tr>
<td>Potassium (K^+)</td>
<td>-88</td>
</tr>
<tr>
<td>Calcium (Ca^{2+})</td>
<td>+123</td>
</tr>
</tbody>
</table>

During an action potential, calcium and sodium rapidly enter the cell, and potassium exits due to the desire to reach their respective Nernst potentials, although none of the potentials are ever reached. As a result, at the conclusion of an action potential, there are more calcium and sodium and fewer potassium ions inside the cell than at the pre-action potential state. To facilitate a return to the resting concentrations, the cell relies on ion exchangers and ion pumps.

**Ion Exchangers**

Exchangers facilitate the transport of ions by allowing a certain type of ion out of the cell and allowing another type in. This process is driven by the electrochemical gradient of one ion to enter/exit the cell, which acts to not only force ions in one direction but also to drive out other ions in the opposite direction. Exchangers are an example of cotransporters and are also known as antiporters. The other type of cotransporters is known as symporters, which work in a similar manner but transport the ion against its concentration gradient in the same direction as the ion moving with its gradient.

A prominent example of an exchanger is the sodium-calcium exchanger. The sodium-calcium exchanger seeks to assist sodium in reaching its Nernst potential and allows 3 sodium ions into the cell while expelling 1 calcium ion out. The force of sodium entering the cell causes the passive exclusion of calcium. This results in a net increase in membrane potential.
Ion Pumps

Ion pumps, in contrast to ion exchangers, are a form of active transport, meaning that they require adenosine triphosphate (ATP) to operate. Pumps are essential where ion gradients are either opposing or neutral to the desired flow of ions.

The most important pump in animal cells is the sodium-potassium pump. For each cycle of the sodium-potassium pump, 3 sodium ions are expelled from the cell and 2 potassium ions are introduced. Note that, for physiological values of membrane potential, both of these actions go against the electrochemical gradient for each ion species. This pump is the most important for restoring ion concentrations to a resting value after an action potential is fired.

2.3.3 Sinoatrial Node (SAN) cell

The sinoatrial node (SAN) was first discovered in 1907 by Sir Arthur Keith [Mon10]. The human SAN is a crescent-shaped region on the heart that, as shown in Figure 2.9, is located below the superior vena cava and above the right atrium [Bor12]. While most excitable cardiac cells can only fire an action potential after receiving an external stimulus, a SAN cell generates an action potential spontaneously and is therefore referred to as a pacemaker cell.

In addition to the ion channels, pumps, and exchangers previously discussed, as illustrated in Figure 2.10, pacemaking cells have a leaky sodium and potassium current, known as the “funny” current, $I_f$. The funny current slowly depolarizes (increases) the cell membrane potential during phase 4 of the action potential until the threshold for rapid depolarization is reached. In SAN cells, the rapid
depolarization is primarily a result of the inward current of calcium ions instead of sodium.

![Diagram](image)

**Figure 2.10** Diagram of ion transportation mechanisms in a sinoatrial node cell. Ion fluxes are denoted as $I_i$ for $i = f$ (funny current), $K_{ACh}$ (potassium - ACh mediated), $K_{ur}$ (potassium - rapid), $NaK$ (sodium-potassium pump), $Na$ (sodium), $to$ (potassium - transient outward), $K_s$ (potassium - slow), $Kr$ (potassium - rapid), $NaCa$ (sodium-calcium exchanger), $CaL$ (calcium - long-lasting type), $CaT$ (calcium - transient type). The sarcoplasmic reticulum (SR) is located inside the cell among the cytosol with calcium ions being introduced into the SR via the SERCA pump and released via the RyR. Note that receptors, such as $M_2$ or $\beta$ receptors, are not shown.

There are three pacemaking areas in the heart: the sinoatrial node (SAN), the atrioventricular (AV) node, and the Purkinje fibers. The SAN has the fastest resonance frequency and therefore is the primary pacemaker of the heart as it stimulates the AV node and Purkinje fiber before their own action potential can be produced autonomously. Therefore the atrioventricular node will only autonomously create an action potential if the SAN fails, and Purkinje fibers are only responsible for the origin of an action potential if the SAN and AV node fail.

**Calcium handling within the cell**

The sarco/endoplasmic reticulum $Ca^{2+}$-ATPase (SERCA) pump actively transports calcium from the intracellular space into the sarcoplasmic reticulum, which stores these ions. The sarcoplasmic reticulum then spontaneously releases these ions into the cytoplasm by use of the ryanodine receptor, RyR. However, it has been noted that the role of the SR can act in support of the funny current and that the two mechanisms are interdependent [Jou09].
Modulation of action potential firing

Neurotransmitters modulate the frequency of action potential firing. SAN cells receive input from the sympathetic and parasympathetic branches of the autonomic nervous system. The parasympathetic nervous system releases acetylcholine which binds to $M_2$ receptors, reducing the amount of cyclic adenosine monophosphate (cAMP) in the cell, which slows heart rate. The sympathetic nervous system releases norepinephrine and epinephrine, which bind to $\beta$ receptors, resulting in an increased amount of cAMP in the cell resulting in increased heart rate.

Acetylcholine is released by parasympathetic post-ganglionic neurons and primarily binds to the $M_2$ receptor on the SAN. When acetylcholine binds to the $M_2$ receptor, the coupled $G_i$ protein acts to decrease cAMP and decrease action potential frequency.

Catecholamines (norepinephrine and epinephrine, sympathetic neurotransmitters) bind to both $\beta$ and $\alpha$ adrenergic receptors. However, $\beta_1$ and $\beta_2$ receptors are the most plentiful receptors in the SAN, with $\beta_1$ more so than $\beta_2$. $\beta_1$ receptors are coupled to $G_s$ proteins. When epinephrine or norepinephrine binds to a $\beta_1$ receptor, the $G_s$ proteins activate adenylyl cyclase, facilitating the production of cAMP, which acts on the funny, calcium, potassium, and calcium currents as well as the sodium-potassium exchanger to increase action potential frequency. In addition, cAMP promotes the production of protein kinase A.

Neurotransmitter effects on action potential frequency

To modulate action potential frequency, neurotransmitters affect how quickly the cycle of action potentials occurs in the SAN cell. There are three main ways to increase the frequency of the action potential cycle [Bor12].

1. The slope of the slow depolarization during phase 4 can increase, thus depolarizing the cell to the required threshold for rapid depolarization faster.

2. The lowest negative membrane potential can increase (become more positive). This allows the threshold for rapid depolarization to be reached faster as the cell has to depolarize less during phase 4.

3. The threshold for rapid depolarization can decrease, again allowing for less depolarization to occur during phase 4.

Acetylcholine decreases heart rate by decreasing the amount of cAMP. The decrease in cAMP decreases the steepness of phase 4 depolarization by decreasing the conductance of the funny current. Additionally, acetylcholine allows G protein-coupled inwardly-rectifying potassium channels to open. This allows more potassium to flood in during the repolarization phase, thus decreasing the most negative possible potential, resulting in a larger difference between the diastolic potential and the threshold for rapid depolarization, which increases the duration of phase 4.

Epinephrine and norepinephrine increase heart rate by facilitating the production of cAMP, making phase 4 steeper by increasing the conductance of the funny current. Additionally, cAMP increases
calcium channel conductance, which lowers the threshold of rapid depolarization. The presence of epinephrine and norepinephrine causes the calcium conductance to increase in all myocardial cells, resulting in action potentials to occur faster in all phases [Bor12]. Lastly, cAMP acts on the sodium-potassium exchanger, resulting in faster action potentials.

2.3.4 Propagation of the action potential in the heart

Once an action potential is fired by a SAN cell, the signal first depolarizes the surrounding SAN cells, causing the entire SAN to depolarize. This signal then travels along the SAN fibers directly to the atrial muscle fibers [Guy11], which depolarizes and contracts the atria as the action potential spreads to the atrioventricular node, where it is slowed. This causes a delay that allows the atria to empty the stored blood into the ventricles prior to ventricular contraction [Guy11]. The action potential then travels via the bundle of His, which is positioned between the ventricles, and then continues on to the Purkinje fibers, which rapidly conduct the action potential to the apex (bottom) of the heart. Once at the apex of the heart, the action potential propagates through the ventricular muscle at a relatively slower rate, allowing for a coordinated ventricular contraction that ejects blood through the pulmonary and aortic valves.

In summary, the adequate perfusion of the human body is maintained via a complex and dynamic relationship of multiple systems. Furthermore, when a system fails, it can be difficult to distinguish which part of the interconnected process is the root cause of the compromised components. This results in diseases and syndromes that are difficult to understand, diagnose, and treat.
In this chapter, we will discuss the pathophysiological background of postural orthostatic tachycardia syndrome (POTS). We will first describe general autonomic dysfunction and then present an in-depth study of POTS, focusing on diagnostic protocol, the pathophysiology of phenotypes, and the effect of autoantibodies.

3.1 Dysautonomia

Autonomic dysfunction, known as dysautonomia, is a family of syndromes and diseases that result in the dysfunction of the autonomic nervous system (ANS), usually as a result of toxins, trauma, or use of some medications [Weh16]. The ANS has numerous complex components; therefore, there is a myriad of different ways the ANS can fail, resulting in dysautonomia. Three examples of dysautonomia are reviewed below.

Pure autonomic failure (Bradbury-Eggleston syndrome) patients have difficulties regulating blood pressure and, as a result, present with orthostatic hypotension (low blood pressure upon transitioning to an upright position) and often experience supine hypertension [Gar13]. These patients also experience cerebral hypoperfusion and may experience dizziness, visual disturbances, syncope, and pain in various parts of their body [Mat99].

Pure autonomic failure is caused by the degeneration of preganglionic neurons as well as the malfunction of postganglionic sympathetic neurons, which, among other effects, cause the ineffective
modulation of NE. [Weh16; Gar13].

Parkinson's disease is primarily a result of nerve cell death in the substantia nigra region in the midbrain, which leads to a decrease in the neurotransmitter dopamine [Gol03]. This loss of dopamine is believed to cause the hallmark symptoms associated with Parkinson's, such as tremors, rigidity, and slowness of movement. Additionally, postmortem observations have shown lesions in sympathetic postganglionic neurons which results in loss of cardiac sympathetic innervation [Gol03], thereby causing autonomic dysfunction.

Autonomic-mediated syncope, which includes vasovagal syncope, carotid sinus hypersensitivity, and situational syncope, is caused by either the withdrawal of sympathetic tone, which results in rapid vasodilation, increased parasympathetic tone, which results in bradycardia, or both [Mat13]. This inappropriate ANS response causes the subject to lose consciousness, however; once the subject is supine, the reversal of the effects is usually quite rapid.

### 3.2 POTS

Postural Orthostatic Tachycardia Syndrome (POTS), as the name suggests, is characterized by an increase in heart rate (HR) upon a postural change without orthostatic hypotension (defined as a sustained decrease in blood pressure more than 20 mmHg) [Fre11]. POTS is a phenotype, not a specific disease, and is possibly caused by pathophysiological mechanisms spanning from dehydration to autoantibodies binding to adrenergic receptors [Li14]. While POTS is characterized by the presence of tachycardia upon a postural change, other, often severe, symptoms can significantly lower the quality of life for patients [Ste12; Ste13].

The first attempt to characterize POTS was in 1993 by Schondorf and Low from the Mayo clinic. They identified a syndrome that caused excessive orthostatic tachycardia and mild orthostatic intolerance [Sch93]. However, this was not the first time POTS symptoms were described. There have been reports of similar conditions, including soldier's heart, effort syndrome, DaCosta's syndrome, neurocirculatory asthenia, with the same symptoms and characteristics of POTS spanning back over 100 years before the 1993 paper by Schondorf and Low [Woo76]. The varied descriptions and proposed etiologies reported previously illustrate the complexity of what is likely a multifaceted syndrome with a wide variety of causes.

Of POTS patients, 75% are women aged 20-40 years old [Zal19]. The disease is usually induced by acute stressors such as viral illness [Gru06], pregnancy [Raj06], and injury [Kan10]. In some cases, disease onset occurred after administration of the Human Papillomavirus vaccine, though a causal relationship has not been shown [But17].

Symptoms of POTS are equally widespread. POTS patients may experience [Sha19]

- Cardiovascular symptoms - lightheadedness, chest pain, shortness of breath
- Gastrointestinal symptoms - nausea, stomach pains, diarrhea
- Neurological symptoms (head and brain) - headache, memory problems, difficulty concentrating
• Neurological symptoms (eyes and ears) - Blurred vision, dry mouth, dry eyes

• Neurological symptoms (extremities) - Muscle pains, muscle weakness, tingling, and numbness.

### 3.2.1 Diagnostic protocol

With such a range of symptoms and presentations POTS, clinical diagnostic protocol focuses on the common symptom - postural tachycardia. The two ways that clinicians impose a postural change are (1) by having the patient physically move from a resting to a standing position by actively using their muscles - called the active stand (AS) test, or (2) by placing the patient supine on a head-up tilt (HUT) table and tilting the patient head-up to an angle of 60°, positioning the patient in an upright state without active contraction of their muscles. Schematics of a HUT and AS test are shown in Figure 3.1. During this test, clinicians monitor the patient's continuous heart rate and blood pressure via an electrocardiogram (ECG) and a continuous non-invasive arterial pressure monitor. However, in the absence of this technology, it is possible to perform the standard diagnostic protocol using discrete measurements of heart rate and blood pressure before and after the orthostatic change.

![Figure 3.1 Schematic of a head-up tilt (HUT) (a) and active stand (b) test. During a HUT test, the patient is transferred from a supine position (0°) to a tilted position (60°) to assess tolerance to a postural change. In an AS test, the patient begins in a supine position and then moves to a standing position. Adapted from Ged22.](image)

The current clinical diagnosis protocol requires an increase of HR of more than 30 bpm for an adult, 40 bpm for children less than 19 years old, during HUT or AS tests [Fed19]. Examples of control and POTS subject data from a HUT test are shown in Figures 3.2 and 3.3. In addition to postural tachycardia during these tests, the patient must also not have orthostatic hypotension - a sustained decrease in systolic blood pressure of more than 20 mmHg and must be able to reproduce spontaneous symptoms such as lightheadedness or palpitations. Lastly, there must be a history of POTS symptoms for at least 6 months and an absence of any other conditions that may produce sinus tachycardia [Fre11; She15; Ste18; Fed19].

Even with this criterion, the field has not agreed on the appropriate duration of an AS or HUT test. Additionally, a drawback of this criterion is the reliance on the presence of tachycardia since it can not
solely explain many of the observed symptoms. Healthy humans can have an increase in heart rate of 30 bpm without POTS symptoms, so it is important to understand why a change in posture causes this tachycardia for POTS patients and the precise origin of the various symptoms of POTS. For these reasons, Raj & Robertson have argued that there is a need for a more detailed protocol that examines the pathophysiological causes of the disease [Raj18].

Figure 3.2 Heart rate (HR - left) and blood pressure (BP - right) data for five control subjects. The initiation of the head-up tilt (HUT) test is denoted by vertical dashed black lines. Mean heart rate before and after tilt, without analyzing the first 30 seconds of tilt (transition region), are denoted as horizontal red lines. Horizontal lines on blood pressure graphs represent average systolic (green), mean (\( \frac{2}{3} \) diastolic + \( \frac{1}{3} \) systolic - red), and diastolic blood pressures. Abbreviations: aR - UPEMD low-frequency amplitude at rest, aH - UPEMD low-frequency amplitude during HUT, \( \Delta \) - change in HR from rest to HUT.
3.2.2 Phenotypes of POTS

The etiology of POTS is unclear; there are likely multiple phenotypes, or pathophysiological causes, of POTS that all manifest similarly but have fundamentally different root causes. Understanding POTS pathophysiology is important as it can provide clinicians with more accurate ways to treat the syndrome. To assist in the categorization of the different causes of POTS, several phenotypes of POTS have been set forth [Bry19; Gru08b; Mar20; Fed19]. These phenotypes are explained below, summarized in Table 3.1, and illustrated in Figure 3.4.

**Figure 3.3** Heart rate (HR - left) and blood pressure (BP - right) data for five POTS subjects. The initiation of the head-up tilt (HUT) test is denoted by vertical dashed black lines. Mean heart rate before and after tilt, without analyzing the first 30 seconds of tilt (transition region), are denoted as horizontal red lines. Horizontal lines on blood pressure graphs represent average systolic (green), mean (\( \frac{2}{3} \) diastolic + \( \frac{1}{3} \) systolic - red), and diastolic blood pressures. Abbreviations: aR - UPEMD low-frequency amplitude at rest, aH - UPEMD low-frequency amplitude during HUT, \( \Delta \) - change in HR from rest to HUT.
**Hyperadrenergic POTS** is characterized by increased norepinephrine levels during HUT or AS. Healthy subjects and POTS patients have approximately the same amount of norepinephrine in the supine position [Raj05]. However, upon postural change, the norepinephrine levels double in healthy subjects, whereas in hyperadrenergic POTS patients, levels can more than triple [Jac98]. This increase in norepinephrine, known as a hyperadrenergic state, therefore causes postural tachycardia and is believed to cause the symptoms of POTS. Treatments for hyperadrenergic POTS primarily involve beta-blockers such as propranolol [Mar20].

**Neuropathic POTS** is thought to be caused by partial autonomic neuropathy in the lower body vasculature, resulting in inappropriate relaxation of blood vessels. It has been shown that some POTS patients have impaired sympathetic activity in the lower extremities and that there is decreased norepinephrine release in the lower vasculature in response to controlled stimuli test [Jac00].

This decreased response causes blood to pool in the lower extremities, resulting in increased baroreflex stimulation which increases HR upon a postural change. This increased baroreflex activity results in postural tachycardia, and the symptoms of POTS are thought to result from this excessive autonomic activity to compensate for decreased sympathetic effects in the lower vasculature. Treatments for neuropathic POTS are focused on venous return from the lower body. Interventions include compression stockings, abdominal compression, and maneuvers to facilitate venous blood return from the lower extremities [Mar20].

**Hypovolemic POTS** is caused by consistently low blood volume (hypovolemia). Studies have shown that some POTS patients have as much as 22% less plasma or blood volume compared to controls [Raj05]. The most common hypothesis for this hypovolemic state argues that POTS patients respond differently to angiotensin II than healthy subjects. It is thought that the observed elevated plasma angiotensin II levels in a portion of POTS patients causes a misregulation of fluid, and instead of retaining fluid, POTS patients lose fluid volume as a result of these elevated angiotensin levels - called the renin-aldosterone paradox [Raj05]. Interventions for hypovolemic POTS seek to increase blood volume, for example, by hydration or a high-sodium diet [Mar20].

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Pathophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperadrenergic</td>
<td>Hyperadrenergic state</td>
</tr>
<tr>
<td>Neuropathic</td>
<td>Partial autonomic neuropathy</td>
</tr>
<tr>
<td>Hypovolemic</td>
<td>Decreased blood volume</td>
</tr>
</tbody>
</table>

**Table 3.1** The phenotypes of POTS and their summarized pathophysiology.

**3.2.3 Autoantibody Effects**

In addition to the above three phenotypes, it has been suggested that autoantibodies can aid in causing POTS dynamics and symptoms. Adrenergic autoantibodies have been reported in POTS [Fed17a; Li14;
Figure 3.4 Mechanisms contributing to the pathophysiology of POTS phenotypes. The phenotypes are in gold boxes, immediate pathophysiologies in brown boxes, signs, and symptoms in the gray box, intermediate pathophysiological aspects are in blue boxes, and additional enhancers of various pathophysiologies are in green boxes. Reproduced with permission from [Mar20].

GI19, as well as autoantibodies binding to the $M_4$ receptor [GI19] and angiotensin II type 1 [Yu18] have also been reported. These results are summarized in Table 3.2. These autoantibodies can (1) increase the effects of the transmitter binding to the receptor, (2) illicit the same response as the transmitter binding to the receptor, or (3) bind to the receptor and block transmitters from binding to it. These antibodies, therefore, change the effects of transmitters and can cause the symptoms of POTS by modulating the end effects of the control of blood pressure. For example, agonistic autoantibodies against the $\beta_1$ receptor can cause the increased binding of norepinephrine to sinoatrial node cells, thus increasing the end effects of sympathetic tone and causing increased heart rate. Whether antibodies can have a significant effect on POTS phenotypes, if they can cause POTS dynamics (such as postural tachycardia) on their own, and if they are present as a meaningful part of POTS pathophysiology or as an inconsequential byproduct of the syndrome is still debated among the medical community.

Autoantibodies that bind to $\beta_1$ and $\beta_2$ receptors act as agonists. These autoantibodies bind to the receptors and increase the sensitivity of the receptors to epinephrine and norepinephrine, thereby
increasing the effects of the sympathetic input to the cell. Additionally, Federowski et al. [Fed17a] showed that these autoantibodies also have a direct stimulatory effect on $\beta_1$ and $\beta_2$ receptors, resulting in the autoantibodies activating the receptor in place of epinephrine or norepinephrine. This effect is similar to the hyperadrenergic phenotype but does not have the increased concentration of NE.

Autoantibodies that bind to the $\alpha_1$ receptors in smooth muscle cells act as antagonists [Li14] - reducing the effects of sympathetic neurotransmitters. Most notably, these autoantibodies can affect smooth muscle cells in vasculature, the binding to which results in the inappropriate relaxation of the vasculature. Li et al. [Li14] argue that this relaxation of vasculature could result in a compensatory increase of baroreflex activity, which could cause the postural tachycardia seen in POTS patients. Additionally, the presence of autoantibodies acting on $\beta_1,2$ receptors could further increase this effect. This effect of autoantibodies could present similarly to neuropathic POTS.

Autoantibodies that bind to the $M_4$ receptor can result in the inappropriate expression of the parasympathetic branch of the autonomic nervous system, resulting in inaccurate control of blood pressure via the baroreflex. Additionally, blood pressure and volume are also controlled by the renin-angiotensin-aldosterone system. Thus, autoantibodies that bind to angiotensin II type 1 receptors can cause the inefficient operation of this system, in particular the misregulation of blood volume, thereby causing heart rate to increase upon a postural change to compensate for the lack of blood pressure control by the renin-angiotensin-aldosterone system, which could correspond to hypovolemic POTS.

### 3.3 Contributions of this dissertation to POTS research

This dissertation seeks to (1) examine POTS head-up tilt test data to quantify abnormal oscillation dynamics that could cause POTS symptoms (Chapter 6), (2) increase understanding of etiology by providing a mathematical explanation for the neuropathic, hypovolemic, and hyperadrenergic POTS phenotypes (Chapter 7), and (3) show, via a multiscale mathematical model, that the presence of adrenergic autoantibodies can contribute to POTS heart rate and blood pressure dynamics (Chapter 8). Background information for these chapters is discussed in Chapter 4, which overviews signal processing, and Chapter 5, which presents modeling methods. In combination, this dissertation shows that low-
frequency (~0.1 Hz) oscillatory dynamics provide insight into the health of POTS patients, with two novel mathematical models illustrating how these oscillations can be caused.
The pursuit of finding meaning in data has given rise to many fields of statistics and mathematics. If data exhibits patterns, then we can start to infer what is causing those patterns. A popular pattern is the periodic repetition of data with respect to time, called oscillations. In this chapter, we will discuss signal processing methods, which seek to quantify the contribution of each frequency within a signal. Identifying the contribution (power and phase) of each frequency can provide insight into the dynamics of the process creating that portion of the signal. This is crucial to understanding how multiple simultaneous processes are creating one observed signal. The objective of this study is to determine if heart rate and blood pressure data from patients with postural orthostatic tachycardia syndrome exhibit abnormal low-frequency (≈ 0.1 Hz) oscillations compared to healthy controls.

The human body is a complicated system that has a plethora of different mechanisms to ensure its healthy functioning. Examples of cyclic behavior include the heartbeat (≈1 s), menstrual cycle (≈28 days), circadian (24 hours), and others [Bra15; Nak98; DR09; DeB87; RA06]. In this dissertation, we are examining heart rate (HR) and blood pressure (BP) time-series recordings to quantify the contribution of the baroreflex (0.05-0.15, ≈0.1Hz) to each signal, measured for up to 30 minutes, typically in response to a postural challenge (head-up tilt).

To motivate the signal processing techniques used in this dissertation, this Chapter provides an overview of signal processing. Section 4.1 discusses stationary signal processing by presenting theoretical and practical conditions and methods for treating a signal as stationary. We then discuss non-stationary signal processing methods in Section 4.2.
4.1 Stationary Signal Processing

A signal is stationary if the process generating the signal is not changing. However, often information about the generating process is not known and we must assess stationarity via the observed data. A signal, $y_t$, is denoted as stationary if it satisfies the following criteria [Hua98].

\[ E(y_t) = E(y_{t-1}) = \mu, \quad (4.1) \]
\[ \text{Var}(y_t) = \gamma < \infty, \quad (4.2) \]
\[ \text{Cov}(y_t, y_{t-k}) = \text{Cov}(y_{t+\tau}, y_{t-k+\tau}), \quad (4.3) \]

where $\text{Cov}(\cdot)$ denotes covariance, $\text{Var}(\cdot)$ denotes the variance, and $E(\cdot)$ denotes the ensemble average, which is analogous to the expected value. An example of a stationary and non-stationary signal is shown in Figure 4.1. In some applications, it is known that the underlying processes generating the signal are non-stationary, but stationary methods can be applied if the requirements in equations (4.1) - (4.3) are approximately satisfied.

![Figure 4.1](image.png)

**Figure 4.1** Examples of a stationary (left) and non-stationary (right) signal. The non-stationary signal violates the condition set forth by equation 4.1. Abbreviations: A.U. - arbitrary units.

In this dissertation, we examine physiological signals that are known to be a result of a non-stationary process and do not satisfy equations (4.1) - (4.3). Namely, the heart rate and blood pressure of humans are constantly changing due to the autonomic nervous system control, and the heart rate increase seen in postural orthostatic tachycardia syndrome patients upon an orthostatic change violates the requirement set forth by equation 4.1.

Stationary signal processing methods are well-studied and highly effective. When the requirements
set forth by equations (4.1) - (4.3) are reasonably satisfied, the application of stationary methods is often a proper first attempt. Numerous stationary techniques, such as certain filters, stem from the application of the Fourier transform. A review of common methods can be found in [Byr14].

The premise of the Fourier transform is to separate a signal into the complex sinusoids that form it to quantify the power and phase at each frequency. An example of the Fourier transform applied to a stationary signal to extract the amplitude of the sinusoids it is composed of is illustrated in Figure 4.2. Many filtering methods apply the Fourier transform and then limit what frequencies are inverted to create the filtered signal.

![Figure 4.2 A stationary signal (left) and its power in the frequency domain via the application of the Fourier transform. Abbreviations: A.U. - arbitrary units.](image)

### 4.2 Non-stationary Signal Processing

Non-stationary signals are produced by a process changing with respect to time. Non-stationary signal processing methods seek to accomplish similar aims as stationary methods but differ mathematically so that they can be applied to non-stationary signals. Wavelet analysis and Empirical Mode Decomposition (EMD) are the two most popular methods to analyze such signals, though other techniques, such as splitting the domain into quasi-stationary intervals, exist.
Wavelets

Wavelet analysis is the favored method for transforming a signal into the frequency/time domain; however, there are applications that favor the extraction of components of the signal without transforming it into the frequency domain. Wavelet analysis seeks to obtain similar information as the Fourier transform while acknowledging the complexities of the signal with respect to time. Instead of displaying the 1-D output of the power or phase of a signal, wavelet analysis outputs a 2-D representation of the power at each frequency at each time point, known as a scalogram [Rhi19]. An example of a scalogram of a non-stationary heart rate signal from a postural orthostatic tachycardia syndrome patient is shown in Figure 4.3.

Figure 4.3 A non-stationary heart rate (HR) signal (left) and its corresponding Wavelet scalogram with magnitude (HR) is depicted by the color bar (right). The scalogram shows the power of the signal (value depicted by the color bar) at each frequency (vertical axis) at each time point (horizontal axis), thereby showing how the contributions of each frequency to the signal change with respect to time.

Wavelets analyze signals by convolution of a “mother wavelet” with the signal. The convolution produces larger values if the signal is similar to the scaled (amplitude in codomain) and shifted (translation in the domain) mother wavelet, hence expressing the power of the signal at a particular frequency in the time domain. The mother wavelet ($\psi$) is shifted and scaled by

$$
\psi_{a,b}(t) = \frac{1}{\sqrt{a}} \psi\left(\frac{t-b}{a}\right)
$$

for $a > 0$ and $-\infty < b < \infty$ [Rhi19]. The most common mother wavelet, the Morlet wavelet, is shown in
Figure 4.4. The continuous wavelet transform of a signal $f(t)$ is given by

$$W_f(a,b) = \int_{-\infty}^{\infty} f(t) \psi_{a,b}^*(t) dt$$

where $\psi_{a,b}^*$ denotes the conjugate of the mother wavelet.

![Morlet Wavelet](image)

**Figure 4.4** The Morlet Wavelet, given by the equation $\psi(t) = e^{-t^2/2} \cos(5t)$. Abbreviations: A.U. - Arbitrary units.

---

**Empirical Mode Decomposition (EMD)**

Empirical Mode Decomposition (EMD) [Hua98] iteratively sifts out stationary components of a non-stationary signal. This method is the basis for Uniform Phase Empirical Mode Decomposition (UPEMD), which is used in the manuscript presented in Chapter 6 and is further explained there. The benefit of this method is that the algorithm is applied in the time domain, thereby allowing results to be inherent to signal behavior and not a result of a choice of frequency cut-offs. The result of EMD is a collection of stationary signals called intrinsic mode functions (IMFs) that show the different contributions of various frequencies. Mathematically, EMD produces $n$ IMFs ($c_i$) and a residual ($r_{n+1}$) that equal the original signal, $f(t)$. Hence, we have

$$f(t) = \sum_{i=1}^{n} c_i + r_{n+1}.$$  

A limitation of EMD is the phenomena of “mode-mixing”, meaning that two IMFs may have overlapping frequency content. To remedy this, methods such as Ensemble Empirical Mode Decomposition (EEMD) were introduced but have their own drawbacks, such as introducing noise to the signal. Uniform Phase Empirical Mode Decomposition (UPEMD) [Wan18] was created to remedy mode mixing and other limitations without introducing additional noise.
UPEMD accomplishes this by applying EMD on a collection of signals perturbed by cosine waves with uniformly distributed phases across $[0, 2\pi)$. Once the IMFs are calculated, they are averaged together, thereby canceling out the cosine wave perturbations. This allows UPEMD to have the benefits of a noise-assisted algorithm, such as a reduction in mode-mixing, without the presence of introduced noise in the output. The UPEMD method is presented in detail in Chapter 4. An example of the application of UPEMD applied to a non-stationary heart rate signal (the same signal in Figure 4.3) is shown in Figure 4.5.

![Figure 4.5](image)

*Figure 4.5* A non-stationary heart rate (HR) signal (left) and the last three IMFs of the UPEMD algorithm (right). The last IMF ($p$) represents the targeted $\sim 0.1$ frequency.

UPEMD is useful if one wishes to obtain a stationary time domain representation of a non-stationary signal at a specific frequency and has been used broadly. For example, Li et al. [Li23] used UPEMD to denoise underwater acoustic signals, and Yadan et al. [Yad22] employed UPEMD to assist in solving inverse problems related to electrocardiograms. As seen in Chapter 6, a time-domain representation of a specific frequency is crucial to the computation of an orthostatic-invariant diagnostic metric for postural orthostatic tachycardia syndrome.
This Chapter reviews modeling methodologies employed to represent the cardiovascular system and its control. Section 5.1 describes the compartment electrical circuit analogy used to model the cardiovascular system dynamics, and Section 5.2 provides an overview of models used to predict cardiovascular control. We focus on models of increasing complexity that predict baroreflex control, which regulates heart rate, vascular resistance, vascular compliance, and cardiac contractility as functions of changes in blood pressure. We start by considering simple first-order equations predicting the effects of the control as a function of blood pressure and continue by exploring models that also predict the afferent neural firing rate. We then review the Hodgkin-Huxley formulation for cellular electrophysiology and discuss the difference between neurons and cardiomyocytes, which are modeled in Chapter 8. Lastly, we derive the Michaelis-Menten equation in Section 5.3, which we utilize in multiple models presented in this dissertation.

### 5.1 Cardiovascular model

The quantity of interest that a modeler wishes to observe is central to the cardiovascular blood flow model choice. For the foremost detail, such as fluid behavior at valves or the fluid-structure interaction, the Navier-Stokes or Lattice Boltzmann equations should be employed [Ran15; Baz09; VC10]. These equations predict the velocity and pressure accounting for time and three spatial dimensions (3D), which is ideal for studies requiring full-dimensional representation of the fluid flow. However, 3D models are computationally expensive and are, therefore, primarily used to study hemodynamics in local regions. Moving in the direction of less complexity, the next level of models includes 1D (more common) [Gam15] and 2D models [Lag21]. 1D models are used to analyze questions examining the
propagation of pulse waves [Shi11], while 2D models are used in studies with axisymmetric domains. The most computationally efficient representation of hemodynamics is 0D models, typically formulated as a transmission line [He12] or a compartment electrical circuit analogy [Sec16]. 0D compartment models are well suited for systems-level analysis over long time scales. This type of model is also referred to as a compartment model, where compartments represent organs (e.g., the liver) or parts of the arterial or venous network, such as the large arteries or veins. A modeler chooses the number and location of compartments to provide detail only where needed [Shi11]. A limitation of 0D models is their inability to resolve waveform shape or describe the effects of wave-propagation. 0D cardiovascular models originated with the windkessel model, first put forth by Stephen Hales in 1733 [Hal33], and later improved by Otto Frank in 1899 [Fra99]. The windkessel model represents arterial blood flow by assuming compartments to be compliant, meaning that they can expand but exert inward force to return to the original volume, and flow is resisted between compartments. 0D models can also use inductors to represent the inertia of blood flow between compartments, generating more realistic looking waveforms [Bur11].

This dissertation aims to analyze POTS dynamics during a postural change from supine to head-up tilt, i.e., we seek to study hemodynamics at the systems level over minutes to an hour. We do not intend to describe flow waveforms; therefore, we use 0D cardiovascular models formulated via the RC-circuit analogy shown in Figure 5.1. These models have compartments representing flow (Q, mL/min) analogous to current, pressure (P, mmHg) to voltage, compliance (C, mmHg/mL) to capacitance, and resistance (R, mmHg s/mL), which is the same in both formulations (summarized in Table 5.1).

Table 5.1 Electrical circuit analogy for 0D cardiovascular models. Abbreviations: mL - milliliter, A - ampere, mmHg - millimeters of mercury, V - volts, C - coulomb, s - seconds, Ω - ohms, F - Farad, H - Henry.

<table>
<thead>
<tr>
<th>Cardiovascular parameter</th>
<th>Electrical Circuit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood flow (mL/s)</td>
<td>Current (A)</td>
</tr>
<tr>
<td>Pressure (mmHg)</td>
<td>Voltage (V)</td>
</tr>
<tr>
<td>Volume (mL)</td>
<td>Charge (C)</td>
</tr>
<tr>
<td>Resistance (mmHg s/mL)</td>
<td>Resistance (Ω)</td>
</tr>
<tr>
<td>Compliance (mL/mmHg)</td>
<td>Capacitance (F)</td>
</tr>
<tr>
<td>Inertance (mmHg s²/ml)</td>
<td>Inductance (H)</td>
</tr>
</tbody>
</table>

For each compartment, i, volume (V, mL) is conserved, i.e., the change in volume equals the flow into (Q_{in}, mL/s) minus the flow out of (Q_{out}, mL/s) of the compartment,

\[
d\frac{V_i}{dt} = Q_{in} - Q_{out}
\]

Flow and pressure are related via Ohm's law

\[
Q_i = \frac{P_{i-1} - P_i}{R_i},
\]

(5.1)
Figure 5.1 (a) 5-compartment hemodynamic model representing flow, volume, and pressure in the left heart (lh), upper body arteries (au), lower body arteries (al), lower body veins (vl), and upper body veins (vu). (b) Each compartment $i$ is associated with a pressure $p_i$, a volume $V_i$. Compartments are compliant (represented by a capacitor $C$) and are separated by resistors $R_i$. Flow $Q_i$ moves between compartments from higher $p_i$ to lower $p_{i-1}$ pressure.

where $R_i$ (mmHg s/mL) is the resistance between compartments $i$ and $i - 1$. If compliance is assumed to be constant, the pressure-volume relationship is given by

$$P_i - P_{ui} = \frac{V_i - V_{ui}}{C_i},$$

(5.2)

where $C_i$ (mL/mmHg) is the compliance, $V_i$ (mL) is the volume, $V_{ui}$ (mL) is the unstressed volume, $P_i$ (mmHg) is the pressure, and $P_{ui}$ (mmHg) is the unstressed pressure. However, as shown in Figure 2.4 in Chapter 2, veins exhibit a nonlinear pressure-volume relationship if the volume is varied significantly, for example, the increase in lower body volume from supine to standing. In this case, the traditional circuit analogy which assumes a constant compliance to relate the pressure to volume, is not appropriate. Instead, a nonlinear pressure-volume formulation is required. For example, the commonly used model proposed by Hardy et al. [Har82], assumes the rate of change in pressure is proportional to the difference.
between the maximal volume and the current value, which has the solution

\[ P_i - P_{ui} = \frac{1}{m_i} \log \left( \frac{V_{M_i} - V_{ui}}{V_{M_i} - V_i} \right), \]  

(5.3)

where \( V_{ui} \) (mL) is the unstressed volume, \( V_{M_i} \) (mL) is the maximal volume, and \( m_i \) (1/mmHg) is a parameter that relates nominal pressure, volume, and maximal volume so that the point \((P_i, V_i) = (P_{i0}, V_{i0})\) where \( P_{i0} \) is the pressure expected in the compartment at a volume \( V_{i0} \) (mL).

The pumping of the heart is often modeled by a time-varying elastance function. An example is the Gaussian activation function used in [Col20]. This model assumes that cardiac contractility and relaxation take the same time, i.e., it uses a symmetric activation function. Another example is the work by Danielsen and Ottesen [Dan01], which provides an accurate representation of the heart as a pressure source using an elastance function that allows prediction of isovolumic and ejection phase dynamics. However, this formulation has many parameters, and its accurate predictions of pressure are not crucial for heart pumping coupled to a basic RC circuit model primarily concerned with volume distribution.

An asymmetric time-varying elastance function includes different contraction and relaxation times, providing a simple but adequate approximation as

\[
E_{lh}(\hat{t}) = \begin{cases} 
\frac{E_S - E_D}{2} \left( 1 - \cos\left( \frac{\pi \hat{t}}{T_S} \right) \right) + E_D & 0 \leq \hat{t} \leq T_S \\
\frac{E_S - E_D}{2} \left( \cos\left( \frac{\pi(\hat{t}-T_S)}{T_D} \right) + 1 \right) + E_D & T_S \leq \hat{t} \leq T_S + T_D \\
E_D & T_S + T_D \leq \hat{t} \leq T,
\end{cases}
\]  

(5.4)

where \( E_S \) (mmHg/mL) is the end-systolic elastance, \( E_D \) (mmHg/mL) the end-diastolic elastance, \( T_S \) (s) the time for end-systole, and \( T_D \) (s) the time for end-diastole. This model is advantageous as it has only two elastance parameters, two timing equations, and it is smooth.

To facilitate the pumping of the heart, valves that are positioned at ventricular inlets and outlets open and close. As described in Chapter 2, the opening and closing of valves are facilitated by changes in pressure. The most common technique to model valve dynamics in a 0D framework is using diodes, i.e., the valves open or close depending on pressure differences,

\[
Q_i = \begin{cases} 
\frac{P_{i-1} - P_i}{R_i} & P_{i-1} > P_i, \text{ (valve is open)} \\
0 & P_{i-1} \leq P_i, \text{ (valve is closed)}
\end{cases}
\]  

(5.5)

Other valve formulations include the addition of drag coefficients to represent valve closure [Žáč96], the use of varying resistances dependent on pressure [Olu05], or the use of differential equations with values inferred from 3D studies that are able to represent vortex flow near the valves [Kor06].

To simulate head-up tilt, we allow gravity to apply a force on the flows from the upper to lower body arteries and veins \((Q_a, Q_v, \text{mL/s})\) similar to [Wil14]. Hence, these flows are given by

\[
Q_a = \frac{P_{au} - P_{ai} + P_{i\, tilt}}{R_a}, \quad Q_v = \frac{P_{v\, u} - P_{v\, i} - P_{i\, tilt}}{R_v}
\]  

(5.6)
with
\[ P_{\text{tilt}} = \rho g h \sin \left( \frac{\theta \pi}{180} \right), \quad \theta \in [0^\circ, \ldots, 60^\circ], \tag{5.7} \]

where \( g = 982 \text{ (cm/s}^2\text{)} \) is the gravitational constant, \( \rho = 1.06 \text{ (g/cm}^3\text{)} \) the density of blood, \( \theta \) is the tilt angle, and \( h \text{ (cm)} \) is the height between the assumed centers of the upper and lower body, which is dependent how the body is represented via compartments. Additionally, we assume a valve, formulated according to Equation (5.5), exists between the upper and lower body veins to prevent reverse blood flow.

5.2 Baroreflex control models

The baroreflex control system, part of the autonomic nervous system (described in detail in Chapter 2), senses changes in pressure and modulates effectors, including vascular resistance, vascular compliance, cardiac contractility, and heart rate. Cardiovascular control is complex, and therefore modeling it can be challenging. In our quest to understand the origin of low-frequency oscillations observed in POTS patients, we start by employing a simple formulation of the control.

Baroreflex control, discussed in-depth in Chapter 2, follows the flow depicted in Figure 5.2. Baroreceptors in the aortic arch and carotid sinuses sense blood pressure and modulate the afferent firing rate to the nucleus tractus solitarius (NTS). Sympathetic and parasympathetic efferent signals emanate from this location via different pathways enabling modulation of effector organs by releasing norepinephrine and acetylcholine. The sympathetic pathways modulate peripheral vascular resistance, vascular compliance, cardiac contractility, and heart rate, while the parasympathetic nerves primarily influence heart rate. We start by presenting a modeling pipeline that begins with blood pressure and, following the steps depicted in Figure 5.2, ends with effector organ response. We then discuss modifications to the pipeline to include cell-level models (the latter discussed in detail in Chapter 8) to understand the role of the sinoatrial node cell in regulating heart rate.

5.2.1 Blood pressure (\( \tilde{P} \))

As described in Chapter 2, baroreceptors sense changes in blood pressure via stretch receptors in the aortic arch and carotid sinus. A range of models has been proposed for this step. The simplest models [Ish20; Ott04] assume an algebraic relation to pressure, i.e., \( \tilde{P} = P \) or \( \tilde{P} = a P + b \frac{dP}{dt} + c \). Other models, such as the one presented in Chapter 7, assume that sensors respond to mean pressure, computed as
\[
\frac{d\tilde{P}}{dt} = -\tilde{P} + \frac{P}{\tau_p},
\]

where \( \tau_p \text{ (s)} \) is a time scale. This gives the closed-form solution
\[
\tilde{P} = e^{-t/\tau_p} \left( \frac{1}{\tau_p} \int e^{\xi/\tau_p} P(\xi) d\xi + C \right).
\]
Figure 5.2 Baroreflex control. Blood pressure is sensed by baroreceptors (\(\hat{P}\)), which modulate afferent neural firing rate (\(f\)). These signals are integrated in the brain generating efferent sympathetic (\(T_S\)) and parasympathetic (\(T_P\)) signals modeled as non-dimensional “tones”. Effector responses include heart rate (\(HR\)), cardiac contractility (\(E_D\)), peripheral vasculature resistance (\(R\)), and vascular compliance (\(C\)). Simple models modulate heart rate directly as a function of sympathetic and parasympathetic tones (red arrows). To study the effects of autoantibodies, we add a micro-scale model predicting heart rate as a function of sinoatrial node cell stimulation (purple arrows).

More detailed models account for the fact that the firing rate of baroreceptor afferent nerves sense blood pressure and the rate of change of blood pressure [Guy11], which motivates the formulation put forth by Ursino et al. [Urs96],

\[
\frac{d\hat{P}}{dt} = \frac{1}{\tau_p} \left( -\hat{P} + P + \tau_Z \frac{dP}{dt} \right),
\]

where \(\tau_Z\) (s) is a timescale. This gives the closed-form solution

\[
\hat{P} = e^{-t/\tau_p} \left( \frac{1}{\tau_p} \right) \left( \frac{\tau_Z}{\tau_p^2} \right) \int e^{\xi/\tau_p} P(\xi) d\xi + \frac{\tau_Z}{\tau_p} e^{t/\tau_p} P(t) + \frac{\tau_Z}{\tau_p} C.
\]

In addition to simply predicting the change in pressure, some models include an additional step, predicting the change in vascular wall stretch, [Bug10; Mah13; VJ11] and then predicting the firing rate. Given the complexity of other model components, the studies here do not add this extra layer of detail.

5.2.2 Firing rate (\(f\))

The afferent nerve firing rate (\(f\), Hz), the second box from the left in Figure 5.2, is modulated by changes in \(\hat{P}\). The first of two models discussed here is the simple amplifier model (reviewed by [Mah13]), which assumes neural firing can be predicted as a function of a gain and shift of sensed pressure \(\hat{P}\), as

\[f = s_1 \hat{P} - s_2\]

where \(f\) is the firing rate, \(s_1\) is the gain (Hz/mmHg), and \(s_2\) is the shift (Hz).
**Leaky integrate-and-fire**

The leaky integrate and fire model can be used in conjunction with the simple amplifier model to provide a more physiologically accurate representation of neuron dynamics. This model relates cell membrane potential to an electrical circuit. This model, first proposed by Lapicque [Lap07], relates neuron firing to a simple RC circuit (illustrated in Figure 5.3) with an input source, a leakage current, and a capacitor in parallel. This formulation gives the differential equation

\[
C_m \frac{dV_m}{dt} = I_{ne} - g_{\text{leak}} V_m,
\]

where \(V_m\) (mV) is the membrane potential, \(C_m\) (nF) the membrane capacitance, \(g_{\text{leak}}\) (µS) the leakage conductance, and \(I_{ne}\) (pA) the input, which is a function of sensed blood pressure in baroreflex modeling (e.g., \(I_{ne} = s_1 \tilde{P} + s_2\)), as summarized in [Mah13]. This model is useful for predicting neuron firing when multiple signals must be received before firing. If we assume that a certain threshold needs to be reached before the neuron fires, \(V_{th}\) (mV), and that there is a refractory period after the neuron fires, \(t_{\text{ref}}\) (s), then

\[
f = \begin{cases} 
\frac{C_m}{g_{\text{leak}}} \left[ \ln \left( \frac{I_{ne} - g_{\text{leak}} V_{th}}{I_{ne}} \right) \right] + t_{\text{ref}} \right]^{-1} & I_{ne} > g_{\text{leak}} V_{th} \\
0 & \text{otherwise.}
\end{cases}
\]

### 5.2.3 Sympathetic and parasympathetic tones

Afferent firing rate \((f)\) is integrated into the nucleus tractus solitarius (NTS), from which it is distributed to the organs controlled. A non-dimensional efferent sympathetic \((T_S)\) and parasympathetic \((T_P)\) tone is often predicted as

\[
\frac{dT_i}{dt} = -\frac{T_i + \tilde{T}(f)}{\tau_i},
\]
where $f$ (Hz) is the afferent neuron firing rate and $\tilde{T}$ an algebraic equation that the response follows at a time scale $\tau_i$ (s). To accommodate the saturation of tones at high and low values of $f$, the function $\tilde{T}$ is often modeled as either a non-dimensional (varying between 0 and 1) exponential sigmoid or Hill functions [Bug10; Olu05]. In the following work, we use increasing (parasympathetic)

$$\tilde{T}(f) = \frac{f^k_i}{f^k_i + f_{2i}^k_i}$$

(5.8)

or a decreasing (sympathetic)

$$\tilde{T}(f) = \frac{f_{2i}^k_i}{f^k_i + f_{2i}^k_i}$$

(5.9)

Hill functions where $f_2$ (Hz) is the half-saturation value and $k_i$ is the Hill coefficient which governs how steep the transition between minimal and maximal responses is. Increasing and decreasing Hill functions with varying values of $k_i$ are illustrated in Figure 5.4. The transmission speed of the efferent nerve branches can be represented by allowing

$$\tau_p \ll \tau_s,$$

where $\tau_p$ (s) is the time scale for parasympathetic effects and $\tau_s$ (s) is the time scale for sympathetic effects [Ged22]. While parasympathetic signaling is almost instantaneous, sympathetic signaling is slower. To account for this effect, the sympathetic signal is often predicted by introducing an explicit delay, i.e., $T_s(t - \tau_D)$ [Ish20; Ran19; Ott97].

![Figure 5.4 Increasing (left, Equation (5.8)) and decreasing (right, Equation (5.9)) Hill functions as functions of firing rate ($f$, Hz) for varying Hill coefficient values ($k_i$). In this illustration, the half-saturation point is denoted as $f_{2i}$.](image-url)
Organ response

The effect on the organ, including peripheral vascular resistance, compliance, cardiac contractility, and heart rate, is modulated in response to sympathetic and/or parasympathetic signaling. Most existing models (e.g., [Bug10; Ran19]) assume that the organ effect, $E_i$, with units $E_u$, directly relates to the sympathetic or parasympathetic tone, assuming

$$
\frac{d E_i}{dt} = -E_i + w_i(T_i) / \tau_i,
$$

(5.10)

where $w_i (E_u)$ is a function that scales neural tone, often predicted as

$$
w_i = w_{i,1} T_i + w_{i,2}
$$

with $w_{i,1} (E_u)$ denoting the scale of the response, $w_{i,2}$ denoting the shift $(E_u)$, and $T_i$ is either sympathetic ($T_S$) or parasympathetic ($T_P$) tone. Controls primarily modulated by the sympathetic system are typically modeled using Equation (5.10). The exception is the modulation of heart rate, which often is modeled as a function of both $T_S$ and $T_P$. For example, Randall et al. [Ran19] use a linear combination of efferent responses, while others, such as Ottesen [Ott97], employ nonlinear combinations of the tones.

One proposed pathophysiology of POTS is the presence of autoantibodies which bind to the sinoatrial node cell and vasculature. In order to incorporate the effects of these autoantibodies binding, we derive a sinoatrial node cell model that is able to predict action potential firing in response to adrenergic autoantibodies as well as norepinephrine and acetylcholine, which are functions of sympathetic and parasympathetic tone. To predict neurotransmitter concentration, the equations of tone ($T_i$) can modulate neurotransmitter concentration ($c_i, \text{mM}$) which binds to cells. This dynamic is often represented via first-order kinetics, with time-scale $\tau_{c_i} (s)$, as

$$
\frac{d c_i}{dt} = -c_i + w_i(T_i) / \tau_{c_i},
$$

(5.11)

where $w_i(T_i) (\text{mM})$ is a function that relates tone to neurotransmitter concentration. These neurotransmitter concentrations then modulate cell dynamics which affect organ response.

5.2.4 Cell-based models

During the 1940s and early 1950s, Alan Hodgkin and Andrew Huxley conducted now famous research on the electrophysiology of a giant squid nerve axon to formulate equations that govern ion currents, which earned them the Noble prize in Physiology or Medicine. Their model is still relevant today as the framework continues to be a popular method to represent the electrophysiology of ion channels, such as to predict neuron firing rates [Stu17] or the generation of action potentials in sinoatrial node cells, as described in Chapter 8. To understand the basic concepts behind the sinoatrial cell model, we review the Hodgkin-Huxley experiments and model derivation.

The work of Hodgkin and Huxley is based on a few key observations. First, as illustrated in Figure 5.5,
they noted that the varying conductances of sodium and potassium are primarily responsible for the neuron action potential. Secondly, as shown in Figure 5.6, they modeled the flux of sodium, potassium, and a “leakage” current that was made of “chloride and other ions” [Hod52], which predicts membrane potential \( v \) (mV) as

\[
C \frac{d v}{d t} = I_K + I_{Na} + I_L
\]

where \( C \) (pF/cm\(^2\)) is the cell capacitance and \( I_i \) (\( \mu \)A/cm\(^2\)) is the ion current for potassium (K), sodium (Na), and the leakage current (L). Third, they assumed that ions only travel through specific ion channels, i.e., potassium cannot go through a sodium channel [Hod52]. Fourth, their work used the concept of the Nernst potential, which is the value of the membrane potential that ion species will flow into or out of a cell to achieve [Bea12]. In summary, their work depended on predicting when cellular ion gates were open and closed.

**Figure 5.5** The action potential of a neuron (red) and the relative conductance of sodium and potassium. Sodium conductance increases at the beginning of the action potential to cause rapid depolarization and decreases while potassium conductance increases, allowing potassium out of the cell, thereby repolarizing the neuron. Reproduced with permission from [Gaw17].

**Potassium channel**

Hodgkin and Huxley denoted the flux of potassium, \( I_K \) (\( \mu \)A/cm\(^2\)), in their original model as

\[
I_K = -g_K (v - v_K),
\]

where \( g_K (v) \) (\( \mu \)S/cm\(^2\)) is the conductance of potassium, \( v \) (mV) is the membrane potential, and \( v_K \) (mV) is the Nernst potential for potassium. The variable \( v = V - V_0 \), where \( V \) (mV) is the measured voltage and \( V_0 \) (mV) is the voltage observed when no external current is applied. This equation can
be interpreted as a varying conductance that, when non-zero, allows the movement of ions until the conductance goes to zero or the membrane potential reaches the Nernst potential.

Hodgkin and Huxley observed that conductance, $g_K$, depends on voltage. To account for this variation, they introduced a gating variable ($n$) representing the probability of the gate being open ($0 < n < 1$). The gating variable is predicted by

$$\frac{dn}{dt} = \alpha_n (1 - n) - \beta_n n,$$

where $\alpha$ and $\beta$ are rate constants denoting the opening and closing of the gate. Note that if $\alpha_n \approx 1, \beta_n \approx 0$ then $n$ converges to 1 as the stable fixed point of the equation

$$\frac{dn}{dt} = \alpha_n (1 - n).$$

If $\alpha_n \approx 0, \beta_n \approx 1$, then $n$ converges to 0 as the stable fixed point of the equation

$$\frac{dn}{dt} = -\beta_n n.$$

Given this formulation of gating variable $n$, $g_K$ is given by

$$g_K = n^4 \bar{g}_K,$$

where $\bar{g}_K$ is the maximum conductance. $n$ is raised to the fourth power to represent the presence of four identical gates. Hodgkin and Huxley chose the fourth power because it was the smallest value of $n$ that supplied a good fit to the giant squid nerve axon data [Hod52].

To formulate equations for $\alpha_n$ and $\beta_n$ as functions of voltage, Hodgkin and Huxley fit data for $\alpha_n$ and $\beta_n$ while applying a constant voltage to the axon via a voltage clamp experiment to measure the resulting ion flow. Having quantified the flow of potassium in response to constant membrane potentials,
they estimated $\alpha_n$ and $\beta_n$ for each applied voltage and then derived equations for both variables that reproduced these fits as a function of voltage. Using data from experiments and noting that the opening gate, $\alpha_n$, should increase with applied voltage while the closing rate, $\beta_n$, decreases, they found that the following equations fit the data well:

$$
\alpha_n = 0.01 \frac{10 - \nu}{\exp\left(\frac{10 - \nu}{10}\right) - 1}
$$

$$
\beta_n = 0.125 \exp\left(-\frac{\nu}{80}\right).
$$

The parameter values used in expressions for $\alpha_n$ and $\beta_n$ depend on experimental conditions and the type of neuron. These values were calculated in a bath of seawater at 8°C. A graph of $\alpha_n$ and $\beta_n$ can be seen in Figure 5.7 for varying voltages. To agree with previous voltage conventions, voltage is negated in these equations [Bea12; Hod52].

![Figure 5.7 Values of Hodgkin-Huxley potassium gating variables $\alpha_n$ (blue line) and $\beta_n$ (red line) (1/s) predicted as a function of membrane potential ($\nu$, mV).](image)

**Sodium channel**

When Hodgkin and Huxley conducted their experiments, they noticed that sodium displays different behavior than potassium data. In particular, they observed that when the cell depolarizes, the sodium conductance increases, reaching a maximum quickly, and then decays to zero [Bea12]. In their paper, Hodgkin and Huxley argue that sodium requires two gating variables that represent activating and inactivating molecules. Sodium may pass through a channel if a single site is occupied by 3 activating molecules and is not occupied by an inactivating molecule. Given this, they formulated their sodium
channel equation as

\[ g_{Na} = m^3 h g_{Na} \]
\[ \frac{dm}{dt} = \alpha_m (1 - m) - \beta_m m \]
\[ \frac{dh}{dt} = \alpha_h (1 - h) - \beta_h h, \]

where \( m \) is the activating molecule and \( h \) is the inactivating molecule. Using these equations, Hodgkin and Huxley fit the data (largely by visual inspection) and found values for the rate constants via voltage clamp experiments (similar to the \( n \) gating variable for the potassium channel). The equations they found were

\[ \alpha_m = 0.1 \frac{25 - v}{\exp\left(\frac{25-v}{10}\right) - 1} \]
\[ \beta_m = 4 \exp\left(-\frac{v}{18}\right) \]
\[ \alpha_h = 0.07 \exp\left(-\frac{v}{20}\right) \]
\[ \beta_h = \frac{1}{\exp\left(\frac{30-v}{10}\right) + 1}. \]

Finally, the membrane potential is a function of the ion fluxes

\[ \frac{dv}{dt} = \frac{1}{C} \sum I_i, \]

where \( v \) is the membrane potential (mV), \( C \) is the cell capacitance (pF/cm²), and \( I_i \) denotes the \( i \)th ion flux.

**Sinoatrial node cell model**

Hodgkin and Huxley put forth the model above to specifically quantify neuron action potential. However, this methodology can be applied to a wide variety of cells, including predicting afferent and efferent neuron firing rates. In this work, we employ the Hodgkin-Huxley formulation to predict membrane potential in sinoatrial node cells. Human cardiomyocyte action potentials, as depicted in Figure 5.8, have a different shape than that of neurons; for example, cardiomyocytes do not hyperpolarize. In particular, the SAN cell is able to depolarize autonomously and the depolarization is primarily a result of calcium, not sodium. Hence the model studied in Chapter 8 has additional channels, pumps, and exchangers that are not present in the Hodgkin-Huxley formulation. However, many ion channels are still formulated in a similar manner to the original formulation put forth by Hodgkin and Huxley [Dem99; Fab17].
Figure 5.8 Depictions of action potentials from a neuron (left) and a ventricular myocyte (right). Note that, while the neuron rapidly spikes and recovers, the ventricular myocyte has 5 distinct phases. Reproduced with permission from [Sig10].

5.3 Michaelis-Menten Kinetics

Another important component of the models in this dissertation is the use of reaction schemes to describe receptor dynamics. We will employ these techniques to represent neurotransmitter and autoantibody binding to the sinoatrial node cell in Chapter 8. These kinetics also motivate our use of Hill functions in both Chapters 7 and 8.

A common assumption in cellular modeling is that reactions can be described using the Michaelis-Menten kinetic equation. In this section, we will review the derivation of the Michaelis-Menten equation originally presented in their 1913 paper [Mic13] and later summarized in [Bea12]. First, consider a simple reaction where a substrate, $A$, interacts with an enzyme, $E$, and undergoes a reversible reaction forming the complex $EA$. Furthermore, assume that $EA$ undergoes an irreversible transformation to produce $B$ and $E$, i.e.,

$$A + E \rightleftharpoons EA \rightarrow E + B.$$ 

Assume that the reversible reaction from $A + E$ to $EA$ occurs with the forward rate of $k_{+1}$ and reversible rate of $k_{-1}$, and that the reaction from $EA$ to $E + B$ occurs at rate $k_2$. Using mass action, we assume that the rate at which a reaction occurs is the product of the rate constant and the concentrations of the reactants. Thus, these reactions can be represented as a system of ordinary differential equations,
\[
\begin{align*}
\frac{da}{dt} &= -k_{+1}e a + k_{-1} c, \\
\frac{de}{dt} &= k_{-1} c + k_2 c - k_{+1} e a, \\
\frac{dc}{dt} &= -k_{-1} c - k_2 c + k_{+1} e a, \\
\frac{db}{dt} &= k_2 c,
\end{align*}
\]

where \(a = A\), \(e = E\), \(b = B\), and \(c = AE\). Doing so gives us the following equations. Note that \(\frac{de}{dt} = -\frac{dc}{dt}\).

Conservation of mass implies that \(e + c\) remains constant, which results in two of the equations being dependent; therefore, we can reduce the dimension by one. Additionally, note that \(b\) does not appear on the right-hand side of any equation. Therefore, we consider the equations for \(\frac{da}{dt}\) and \(\frac{dc}{dt}\) which make up an independent system. If we assume that the first reaction, \(A + E \rightleftharpoons AE\) occurs quickly relative to the other reactions, we can argue that \(a\) is in a quasi-steady state, i.e.,

\[
\frac{da}{dt} = 0 = -k_{+1}e a + k_{-1} c \\
\Rightarrow \frac{c}{e a} = \frac{k_{+1}}{k_{-1}} = \frac{1}{k_1},
\]

where \(k_1 = \frac{k_{-1}}{k_{+1}}\). Given this formulation, note that

\[
c = \frac{e a}{k_1} = \frac{a(E_0 - c)}{k_1} \quad E_0 = e + c \\
\Rightarrow c(k_1 + a) = aE_0 \\
\Rightarrow c = \frac{aE_0}{k_1 + a}.
\]

Hence, we have an analytical expression for \(c\) given a quasi-steady state assumption. Recall that \(\frac{db}{dt}\) only depends on \(c\). Given this, we can an equation for the flux of \(b\) as a function of \(a\) of the form

\[
\frac{db}{dt} = k_2 c = k_2 \frac{aE_0}{k_1 + a} = \frac{ak_2 E_0}{k_1 + a}.
\]

Let the maximum value of the flux as \(V_{\text{max}} = k_2 E_0\) and the Michaelis-Menten constant \(K_m = k_1 = \frac{k_{-1}}{k_{+1}}\), giving
\[
\frac{db}{dt} = V_{\text{max}} \frac{a}{K_m + a}.
\]

Exchanging this equation, we see that as \(a \to \infty\), \(\frac{db}{dt} \to V_{\text{max}}\). Also note that when \(a = K_m\), \(\frac{db}{dt} = \frac{1}{2} V_{\text{max}}\).

Lastly, as \(a \to 0^+\), \(\frac{db}{dt} \to 0\).

We use the Michaelis-Menten formulation to represent both intracellular interactions and macro-scale effects of cardiovascular control. In addition, we will also use an extension of the Michaelis-Menten formulation known as the Hill equation, which is similar to the Michaelis-Menten equation except both \(a\) and \(K_m\) are raised to a power \((k)\) that modulates the steepness of the transition between 0 and \(V_{\text{max}}\),

\[
H(a) = V_{\text{max}} \frac{a^k}{K_m^k + a^k}.
\]

Note that the Hill equation was used in our discussion of first-order control models in Section 5.2.
The study “Characterization of blood pressure and heart rate oscillations of POTS patients via uniform phase empirical mode decomposition” was published in *IEEE Transactions on Biomedical Engineering*, volume 67, issue 11, in 2020. Contributions included implementation of the UPEMD algorithm, data processing, derivation of the $M_h$ metric, statistical and machine learning analysis, and writing the manuscript.

### 6.1 Abstract

*Objective:* Postural Orthostatic Tachycardia Syndrome (POTS) is associated with the onset of tachycardia upon postural change. The current diagnosis involves the measurement of heart rate (HR) and blood pressure (BP) during head-up tilt (HUT) or active standing test. A positive diagnosis is made if HR changes with more than 30 bpm (40 bpm in patients aged 12-19 years), ignoring all of the BP and most of the HR signals. This study examines 0.1 Hz oscillations in systolic arterial blood pressure (SBP) and HR
signals providing additional metrics characterizing the dynamics of the baroreflex. **Methods:** We analyze data from 28 control subjects and 28 POTS patients who underwent HUT. We extract beat-to-beat HR and SBP during a 10 min interval including 5 minutes of baseline and 5 minutes of HUT. We employ Uniform Phase Empirical Mode Decomposition (UPEMD) to extract 0.1 Hz stationary modes from both signals and use random forest machine learning and k-means clustering to analyze the outcomes. **Results** show that the amplitude of the 0.1 Hz oscillations is higher in POTS patients and that the phase response between the two signals is shorter ($p < 0.005$). **Conclusion:** POTS is associated with an increase in the amplitude of SBP and HR 0.1 Hz oscillation and shortening of the phase between the two signals. **Significance:** The 0.1 Hz phase response and oscillation amplitude metrics provide new markers that can improve POTS diagnostic augmenting the existing diagnosis protocol only analyzing the change in HR.

### 6.2 Introduction

Postural Orthostatic Tachycardia Syndrome (POTS) is associated with the presence of chronic (more than six months) tachycardia measured during head-up tilt (HUT) or active standing combined with a history of orthostatic intolerance [Fre11]. POTS is a phenotype and not a specific disease, the symptoms likely can be caused by several pathophysiological mechanisms spanning from tachycardia caused by dehydration to hyperadrenergic mechanisms due to agonistic antibodies to specific adrenergic receptors [Li14]. Symptoms associated with POTS include dizziness, nausea, palpitations, visual blurring, and/or brain fog appearing during the transition from sitting or supine to upright position [Ste12]. These symptoms may be mild, but they can lead to severe incapacitation [Ste13]. Positive diagnosis for an adult (20 years or older) is defined as an increase in heart rate (HR) of more than 30 bpm within 10 minutes after onset of the HUT, whereas for children and young adults (aged 12 to 19 years) positive diagnoses is associated with a HR increase of more than 40 bpm [Raj]. Postural tachycardia is the current approach to identify POTS but as pointed by Raj and Robertson there is a need for more detailed diagnostic approaches to differentiate POTS patients with respect to pathophysiological mechanisms [Raj18].

A first step is to determine if blood pressure (BP) and HR signals contain other characteristics that further describe the patients. The purpose of our study is to use signal processing to explore this approach.

An exact definition of the interval over which HR should be monitored does not exist. The American College of Cardiologists recommends diagnosing patients with POTS if tachycardia is observed within the first 10 minutes of postural change. This criteria was used by Wang et al. [Cev01], who found that POTS patients exhibit tachycardia 5-10 min following postural change, while Kirbis et al. [Kir13] argue that it is adequate to measure HR for 3 minutes following the postural change. These differences likely occur due to the simple one-value measure used in diagnostic criteria, highlighting the need for a more detailed protocol to analyze HR and BP signals.

Approximately 75% of patients experiencing POTS are young women aged 20 to 40 years old [Zal19], and the disease onset is typically induced by acute stressors, including viral illness [Gru06], pregnancy [Raj06], and injury [Kan10]. For some patients, the disease onset has been observed after the adminis-
tration of the Human Papillomavirus vaccine; however, a causal relationship has not been established [But17]. The current diagnosis only targets the increase in HR, yet visual inspection of both the HR and BP signals suggest that POTS patients experience increased oscillatory behavior at the 0.1 Hz frequency associated with modulation of the baroreceptor reflex [Cev01]. This study provides a more detailed analysis of these signals, which potentially can lead to better classification and understanding of the disease.

In healthy controls, physiological systems operate via negative feedback keeping the system at homeostasis. A wide range of normal physiological processes oscillates at specific mean frequencies. For example, for females, the slowest frequency is the menstrual (infradian) cycle ~28 days [Bra15], followed by circadian (~24 h) [Nak98] and ultradian (< 24 h) cycles. Other prominent frequency responses include the baroreflex response (~0.1 Hz), respiration (~0.25 Hz), and HR (~1 Hz) [DeB87; DR09].

This study examines HR and BP oscillations caused by the baroreflex feedback, which operates at a mean frequency of approximately 0.1 Hz [Cev01]. The baroreflex is a negative feedback system increasing HR, vascular resistance, and cardiac contractility in response to a decrease in BP sensed by the baroreceptors located in the aortic arch and carotid sinuses. In healthy adults this reflex operates along the parasympathetic and sympathetic pathways keeping HR and BP at homeostasis [Bor12]. Upon HUT, an immediate increase in HR is the first response to gravity causing an increase in flow to the lower extremities. Within 5-10 sec the resistance vessels contract due to stimulation of the adrenergic alpha-1-receptors [Gun19]. The presence of agonistic antibodies directed at one or more parts of the baroreflex arc or changes in the elimination of transmitters in the autonomic nervous system would likely cause oscillations by enhancing the negative baroreflex feed-back loop at its resonance frequency of 0.1 Hz, while low cardiac filling (dehydration) would produce static changes.

In the data analyzed, we observed that in addition to tachycardia in upright position there are significant BP and HR oscillations at ~0.1 Hz. We hypothesize that these oscillations are more prominent (with higher amplitude) in POTS patients compared to control subjects and that the phase between the HR and BP 0.1 Hz oscillations is shorter for POTS patients. To show this, we extract beat-to-beat HR and SBP values over 6-10 min from 28 control and 28 POTS patients undergoing a HUT test. The signals include at least 3 minutes of data before and during HUT. To test our hypothesis, we use Uniform Phase Empirical Mode Decomposition (UPEMD) to analyze the signals [Wan18].

Most studies analyzing HR and BP data from POTS patients focus on characterizing the discrete change in HR measured in the transition from supine to HUT position [Gar19; Wis17]. Although this analysis is simple, it ignores all of the BP signal and only analyzes the discrete change in HR between the supine and HUT position ignoring all features within the signal. The analysis performed in this study was motivated by visual inspection of data, revealing that compared to control subjects, POTS patients display a higher amplitude of 0.1 Hz oscillations.

To our knowledge, only a few previous studies have analyzed the oscillatory behavior of data from POTS patients. One study by Stewart et al. [Ste15] describes oscillations in POTS patients using measurements of HR, SBP, and transcranial doppler measurements of cerebral blood flow velocity. Results from this study using autospectra techniques concluded that cerebral blood flow velocity in POTS patients, all
experiencing orthostatic intolerance, oscillated with a larger amplitude as compared to control subjects. Another study by Medow et al. [Med14] investigated the oscillatory dynamics of neurocognition in POTS patients using similar methods as Stewart et al. [Ste15]. These studies were able to quantify the amplitude of the 0.1 Hz frequency band but were unable to examine the 0.1 Hz frequency signal with respect to time.

The baroreflex changes the power and instantaneous frequency of both HR and SBP with respect to time in response to physiological changes. Therefore, to analyze the data, it is essential to use methods that can analyze non-stationary and noisy signals, e.g., [RA06; Cha14; Lo08]. One popular method for analysis of non-stationary signals is EMD, which has successfully been used to analyze similar data during exercise and HUT [Cha14; Mag09]. These studies applied EMD to quantify how a change in physiological state (HUT, exercise, or the Valsalva maneuver) affects oscillations in RR intervals and arterial BP. In the present study, we use a similar methodology to quantify the effects of a HUT test in control subjects and POTS patients. By using Uniform Phase Empirical Mode Decomposition (UPEMD), which essentially filters the non-stationary data extracting the 0.1 Hz component of the signal, we can analyze how this portion of the signal changes in time and use stationary methods to analyze the power of the oscillations. Obtaining a signal in the time domain is advantageous as it can be used to characterize the phase response of the signals both at rest and during HUT.

We use random forest machine learning to calculate the importance of each metric to the correct classification of patients but do not present a classification model for future data due to the limited number of subjects in this study [Bre01]. We compute predictor association and use \( k \)-means clustering to categorize data based on the developed metrics and traditional diagnostic criteria. We then compare the cluster groupings with the diagnosis of by physicians.

**Figure 6.1** Example HR (bpm) and BP (mmHg) data from a POTS patient (top) and a control subject (bottom). The solid vertical lines indicate the start and end of the data segment analyzed. The dashed vertical line denotes the onset of HUT. For the POTS patient, the resting HR is higher (75 bpm) compared to the control subject (50 bpm) and it is increased by 31 bpm. For the control subject HR is increased by only 9 bpm.
6.3 Methods

To characterize oscillations in POTS patients and control subjects, we analyze non-stationary electrocardiogram (ECG) signals and BP data from HUT studies. Using these data, we extract HR and SBP. This study uses SBP as it is associated with dysfunction of autonomic BP control to a larger degree than the diastolic signal [Fed17b]. To determine the frequency content of the signals, we use UPEMD to extract stationary signals, known as Intrinsic Mode Functions (IMFs). To study baroreflex regulation, we target the 0.1 Hz frequency range and examine the frequency spectra of the IMFs using Fast Fourier Transformation (FFT). We then fit a Gaussian curve to the transformation of the 0.1 Hz IMF to compare the power of the signal across groups. We characterize the 0.1 Hz IMF phase response by calculating the average instantaneous phase difference between the 0.1 Hz HR and SBP IMFs. We then compute the spontaneous baroreflex sensitivity (BRS) for every patient to compare against our phase difference metric. Finally, we use machine learning and clustering to determine what metrics best characterize the two groups (POTS patients vs. control subjects).

6.3.1 Experimental Protocol

Data summarized in Table 6.1 are extracted from clinical examinations at Frederiksberg and Bispebjerg Hospitals, Denmark. All data are collected with approval from the Frederiksberg and Bispebjerg Hospitals ethics committee, and all subjects gave written consent to participate in research studies. Data analyzed include ECG and BP measurements from 28 women with a positive POTS diagnosis and 28 female control subjects. This patient group was chosen as POTS primarily affects women [Zal19]. Patients with severe arrhythmia, who experienced syncope, or were diagnosed with other cardiovascular or neurological diseases were excluded from this study.

Patients were given a POTS diagnosis if they experienced orthostatic intolerance episodes and exhibited a HR increase of more than 30 bpm (40 bpm if aged 12-19 years), or if they maintained a HR ≥ 120 bpm in upright position [Abe12].

For all patients, ECG readings were obtained from a precordial ECG-lead, while BP was measured using photoplethysmography in the index finger on the non-dominant hand (Finapres Medical Systems BV, Amsterdam, The Netherlands). The Finometer signal was calibrated against sphygmomanometer measurements. Both signals were sampled at a frequency of 1000 Hz. Deidentified data were stored in LabChart (LabChart, AD Instruments Inc., Colorado Springs, CO, USA).

Patients begin the procedure resting in the supine position for at least three minutes before being tilted head-up to 60° at a speed of 15° per second measured by way of an electronic marker. Subjects remained tilted head-up for at least three minutes. For this study, we extract 6-10 minutes of data, including, up to 5 minutes before the HUT and 5 minutes during the HUT. This produces up to 600 seconds of data for each patient, as illustrated in Figure 6.1 depicting the raw HR (bpm) and BP (mmHg) signals for a POTS patient and a control subject, respectively. For all data sets, the HUT maneuver was one of several tests performed to assess the autonomic control system. For all data sets we aimed at including five minutes of data before and during the tilt, as longer data-segments allow for more reliable
signal processing results. The study performed here is a retrospective analysis, therefore we were not able to extract five minutes before or during the HUT for all subjects. Shorter supine segments were caused by a delay in initiation of the recording device – meaning the patient was resting but data were not recorded until later in their resting period. Shorter HUT segments were because some other test was performed (e.g. sublingual nitroglycerine, carotid massage). For these patients we included as much data as possible. The supine segment was reduced for 7 patients (for 4 patients we extracted 4-5 minutes segments and for 3 patients we extracted 3-4 minutes segments). The HUT segment was reduced for 5 patients (for 4 patients we extracted 4-5 minutes segments and for 1 patient we extracted 3-4 minutes segments). To ensure that the analysis meet criteria suggested by [Kir13], for all data sets we analyzed a least 3 minutes of data before and during the HUT.

Table 6.1 Standard Patient Characteristics. Standard patient characteristics presented as mean ± standard deviation for both POTS and control subjects. All subjects were female.

<table>
<thead>
<tr>
<th>Subject Group</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>∆ HR (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POTS</td>
<td>25.6 ± 10.0</td>
<td>172 ± 6</td>
<td>66 ± 14</td>
<td>31.2 ± 11.7</td>
</tr>
<tr>
<td>Control</td>
<td>40.4 ± 17.0</td>
<td>162 ± 6</td>
<td>67 ± 13</td>
<td>7.7 ± 6.3</td>
</tr>
</tbody>
</table>

The patient data were separated into two parts representing rest and HUT. The rest period is defined as the up to 300 seconds before the marker noting the onset of HUT. The HUT segment begins at the marker, denoting the HUT onset and ends up to 300 seconds after the procedure starts. HR and SBP are then extracted from the ECG and continuous BP time series data.

6.3.1.1 Heart Rate

Heart rate (shown in Figure 6.2a) is calculated from the ECG signal as the inverse of the RR interval for each cardiac cycle. Since the time-series signal is non-stationary, we filtered the ECG signal using the medfilt1 median filter algorithm in MATLAB twice with a 200 and a 600 ms window storing the stationary components of the QRS complex and the P-waves [Sch13]. Additional drift in the signal was identified and removed using a Savitsky-Golay filter with 150 milliseconds (ms) and an order 5 polynomial. To identify the peaks in the filtered signal, we used MATLAB’s peak detection algorithm find-peaks with the minimum distance between peaks set to 200 ms. To ensure the identification of the R peaks, the mean of these peaks is used as a minimum peak height for the findpeaks algorithm. Next, we compute the distance between the R peaks and use these to calculate the RR (ms) intervals and $HR_i = 60/RR_i$ (bpm), where $RR_i$ is the length of the $i^{th}$ RR interval. This calculation gives HR at $n - 1$ points, where $n$ is the number of time points. RR intervals and HR are depicted in Figure 6.2. The smooth HR signal (shown in Figure 6.2b) is obtained by interpolating over these points using a piecewise cubic Hermite interpolating polynomial (PCHIP) and then subsampling the signal to 250 Hz.
6.3.1.2 Systolic blood pressure

Blood pressure (shown in Figure 6.2c) is measured continuously using the FinaPres. From this signal, we use the function `findpeaks` in MATLAB with a minimum peak prominence of 25 mmHg and a minimum peak distance of 0.25 seconds to extract SBP within each cardiac cycle. Similar to HR, we obtain a continuous signal (shown in Figure 6.3) by interpolating the discrete signal using PCHIP and then subsampling to 250 Hz.

6.3.2 Uniform Phase Empirical Mode Decomposition

We use UPEMD (an extension of EMD) to analyze the 0.1 Hz frequency response in non-stationary HR and SBP time series. We chose this method over other methods such as Ensemble EMD (EEMD) [Wan14] since UPEMD has the unique advantage of explicitly targeting a frequency band to be examined [Wan18]. This feature is essential for the analysis of the HR and BP data, which have significant frequency signatures in bands close to the 0.1 Hz band, in particular from respiration (∼0.25 Hz). This allows us to examine the contribution of the baroreflex (0.1 Hz) with minimal input from other frequencies.

![](image.png)

**Figure 6.2** Snapshot of (a) ECG (mV), (b) HR (bpm), and (c) BP (mmHg) signals at rest, depicted over a 3-second interval. Beat-to-beat HR (bpm) (a) and SBP values (red) (c) values are predicted using a peak detection algorithm (red and blue circles). Continuous signals are obtained using PCHIP interpolation.

6.3.2.1 Empirical Mode Decomposition

EMD [Hua98], decomposes a non-stationary oscillatory signal into a number of stationary IMFs and a residual. The EMD analysis (Table 6.2) relies on an iterative method, which sifts out the non-stationary
portion of the signal, resulting in a stationary oscillatory signal, the intrinsic mode function (IMF). As outlined in Table 6.2, we find the maxima and minima in the signal, and use these to construct an upper and lower envelope, which we subtract from the data. We repeat this process until it is not possible to obtain more IMFs.

The IMFs are stationary decompositions of the signal. They have an equal number of maxima and minima, and the number of peaks and troughs differ by at most one. The upper and lower envelopes of the filtered signal defined by the maxima and minima must average to zero at all points [Hua98]. In this study, IMFs are computed using the `emd` function in MATLAB’s signal processing toolbox. This algorithm, described in detail by Huang et al. [Hua98] uses a Cauchy type criterion, that represents the standard deviation (SD) of two consecutive siftings, defined as

\[
SD = \sum_{t=0}^{T} \left[ \frac{|h_{i,k}(t) - h_{i,k-1}(t)|^2}{h_{i,k-1}(t)} \right] < 0.2. \tag{6.1}
\]

As suggested in [Hua98], we impose SD < 0.2. Therefore, we restrict SD to 0.2 for two consecutive siftings, that is, if SD < 0.2. Then \( h_{i,k} \) is labeled as the next IMF \( c_i \).

We repeat the sifting until either the residual signal \( r_i(t) = x(t) - \sum_{i=0}^{i-1} c_i \) is monotonic and therefore cannot produce more IMFs, or if the energy ratio

\[
ER = 10 \log_{10} \left( \frac{||x(t)||^2}{||r_i(t)||^2} \right) > \gamma
\]

where \( x(t) \) denotes the original signal and \( \gamma = 20 \) denotes the default energy ratio (ER) threshold. Intuitively, the ER compares the energy of the signal at the beginning of the sifting with the average envelope energy.

Finally, by combining the IMFs and the final residual, it is possible to reconstruct the original signal as

\[
x(t) = \sum_{i=1}^{p} c_i + r_{p+1}. \tag{6.2}
\]

### 6.3.2.2 Uniform Phase Empirical Mode Decomposition

A limitation of the EMD method is a phenomenon known as mode mixing referring to IMFs that overlap in the frequency domain or encode vastly different portions of the frequency spectra [Aga13]. To minimize mode mixing, we use the Uniform Phase EMD (UPEMD) [Wan18].

UPEMD (Table 6.3) averages the IMFs computed with the EMD on a series of perturbed signals. These perturbations are sinusoidal functions that are uniformly distributed on the interval \([0, 2\pi]\). Perturbing the original signal in this way reduces the effects of noise and allows for a more accurate representation of a target frequency free from mode mixing. As suggested in the literature [Wan18], we assume that the number of perturbations \( n_p = 16 \), the number of IMFs, \( \text{n}_{\text{imf}} = \log_2 n \approx 16 \), where \( n \) is the number of observation points for a data set, and the target frequency \( f_W = 0.1 \) Hz.
6.3.2.3 Analyzing the Power of Intrinsic Mode Functions

The output of the targeted UPEMD is a collection of IMFs that represent unique frequencies of the original signal in the time domain. Note that, by definition, the IMFs are stationary, and therefore we can compute the one-sided power spectrum of the 0.1 Hz IMF; we use MATLAB’s FFT algorithm.

The IMF FFTs with mean frequencies 0.05-0.5 Hz are shown in Figure 6.5 for two characteristic data sets. To determine the power of the 0.1 Hz frequency response across the population, we fit a Gaussian distribution \( f(\omega) \) to the data of the form

\[
f(\omega) = a e^{-\left(\frac{\omega - b}{c}\right)^2},
\]

where \( a \) is the maximum amplitude of the Gaussian function, \( b \) is the value at which the function achieves its’ maxima, and \( c \) characterizes the curve width. Figure 6.6 shows the FFT and Gaussian fits for the characteristic subjects. To determine differences between position and disease (POTS), we compare values of \( a \), the amplitude of the Gaussian for the 0.1 Hz spectra of the IMF.
Table 6.2 EMD (Adapted from [Hua98; Mat])

<table>
<thead>
<tr>
<th>Input: Signal $x(t)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Output: IMFs</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>1 $r_0(t) \leftarrow x(t)$</td>
</tr>
<tr>
<td>2 $i \leftarrow 0$</td>
</tr>
<tr>
<td>3 while $r_i(t)$ does not meet stopping criterion</td>
</tr>
<tr>
<td>4 $h_{i,0}(t) \leftarrow r_i(t)$</td>
</tr>
<tr>
<td>5 $j \leftarrow 0$</td>
</tr>
<tr>
<td>6 while $h_{i,j}$ does not meet the numerical IMF criterion</td>
</tr>
<tr>
<td>7 Compute upper and lower envelope of $h_{i,j}$, $u_{i,j}$, and $l_{i,j}$ (using cubic splines)</td>
</tr>
<tr>
<td>8 $m_{i,j} = (u_{i,j} + l_{i,j})/2$</td>
</tr>
<tr>
<td>9 $h_{i,j+1} = h_{i,j} - m_{i,j}$</td>
</tr>
<tr>
<td>10 $j \leftarrow j + 1$</td>
</tr>
<tr>
<td>11 end</td>
</tr>
<tr>
<td>12 $c_i \leftarrow h_{i,j}$ ($c_i$ is an IMF)</td>
</tr>
<tr>
<td>13 $r_{i+1} = r_i - c_i$</td>
</tr>
<tr>
<td>14 $i \leftarrow i + 1$</td>
</tr>
<tr>
<td>15 end</td>
</tr>
<tr>
<td>16 Return Matrix with column $n$ equal to IMF $c_n$</td>
</tr>
</tbody>
</table>

Table 6.3 UPEMD (Adapted from [Wan18])

<table>
<thead>
<tr>
<th>Input: Signal $x(t)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Output: $n_{imf}$ IMFs</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>1 $r_0(t) \leftarrow x(t)$</td>
</tr>
<tr>
<td>2 for $n = 1$ to $n_{imf}$</td>
</tr>
<tr>
<td>3 $\epsilon_n = \text{std}(r_{n-1}(t))$</td>
</tr>
<tr>
<td>4 for $k = 1$ to $n_p$</td>
</tr>
<tr>
<td>5 $y_k(t) = r_{m-1} + \epsilon_n \cos\left(2\pi\left(f_w t + \frac{k-1}{n_p}\right)\right)$</td>
</tr>
<tr>
<td>6 $c_{n,k}(t) =$ first column of EMD($y_k(t)$)</td>
</tr>
<tr>
<td>7 end</td>
</tr>
<tr>
<td>8 $c_n(t) = \frac{1}{n_p} \sum_{k=1}^{n_p} c_{n,k}(t)$</td>
</tr>
<tr>
<td>9 $r_n(t) = r_{n-1}(t) - c_n(t)$</td>
</tr>
<tr>
<td>10 end</td>
</tr>
<tr>
<td>11 Return Matrix with column $n$ equal to $c_n$</td>
</tr>
</tbody>
</table>

6.3.2.4 Quantification of Phase Dependence

The afferent baroreceptor nerves sense changes in BP. The signal is transmitted to the brain via negative feedback, mediating changes in HR, vascular resistance, compliance, and cardiac contractility. Hence, the analysis of the interaction between the two signals gives additional insight into the baroreflex function. To quantify the responsiveness of the baroreflex, we examine the interaction of the phases of the 0.1 Hz IMF for the HR and BP signals at every time point. The baroreflex responds to an increase in
BP by decreasing HR, and a decrease in BP by increasing HR [Hal16]. This implies that the baroreflex is a negative feedback loop, and therefore, a phase difference of $\pi$ implies that the reflex is instantaneous. To quantify the responsiveness of the baroreflex, we calculate the relative difference between $\pi$ and the instantaneous phase difference between the two 0.1 Hz signals. To do so, we utilize that the properties of IMFs allowing the application of the Hilbert Transform to calculate the instantaneous phase [Hua98].

Let $Z(t)$ denote the IMF, $\text{HT}[Z(t)]$ the Hilbert Transform of $Z(t)$, the instantaneous phase $\hat{\phi}(t)$ is then given by

$$\hat{\phi}(t) = \tan^{-1}\left(\frac{\text{HT}[Z(t)]}{Z(t)}\right)$$

(Fel11). We compute a continuous version of the instantaneous phase by using the unwrap command in MATLAB, denoted here by $U(X(t))$. This gives a continuous instantaneous phase, $\phi(t)$, defined as

$$\phi(t) = U\left(\frac{\text{HT}[Z(t)]}{Z(t)}\right).$$

For each data set, we denote the instantaneous phase of the 0.1 Hz HR IMF by $\phi_{HR}(t)$, and the instantaneous phase of the 0.1 Hz SBP IMF as $\phi_{SBP}(t)$. Defining $T$ as the length of the signal in seconds, we quantify the interaction of the two signals by

$$M_h = \frac{1}{T} \int_0^T \mod_{2\pi}(\phi_{HR}(t) - \phi_{SBP}(t)) - \pi \, dt.$$  

(6.6)

This equation quantifies the average distance of the instantaneous phase difference from $\pi$, the instantaneous baroreflex. A value of $M_h = 0$ implies that as SBP increases/decreases, HR compensates by decreasing/increasingly instantaneously. Hence, a smaller value of $M_h$ ($0 < M_h < \pi$) represents a more responsive, baroreflex. Our assumption that the period of these oscillations is approximately 10 seconds implying that $M_h = \pi$ corresponds to a response time of 5 seconds [Hal03]. The bounds of $M_h$ therefore agree with the current understanding of the baroreflex [Bor83b]. We calculate the relative difference between $\pi$ and the instantaneous phase difference between the 0.1 Hz frequency component of the signals.

### 6.3.2.5 Spontaneous Baroreflex Sensitivity (BRS)

The spontaneous baroreflex sensitivity (BRS) quantifies the change in HR due to the change in BP. To calculate BRS, we determine the mean slope of a regression line through three or more consecutive SBP peaks that are either increasing or decreasing when plotted against the RR interval of the beat following the SBP peak [Par88].

### 6.3.2.6 Statistical Analysis

To compare the power of the 0.1 Hz frequency in our data, and the phase responses, we use the one-way Analysis of the Variance function ANOVA1 in MATLAB.
6.3.2.7 Random Forest and Clustering Analysis

Given the eight metrics identified in this study, we seek to cluster the data to quantify the importance of each metric to correct grouping and how patients are grouped based on multiple diagnostic metrics. We first find the most important metrics by classifying patients using random forest machine learning. We use the MATLAB function `fitcensemble` to create an ensemble of 100 trees and compute the k-fold loss ($k=10$) for different maximum branching numbers to prevent overfitting. We then compute the predictor importance using the function `oobPermutedPredictorImportance`. We then employ $k$-means clustering to classify the data, including new metrics as well as the change in HR from supine to HUT and average HR during HUT [Has09].

6.4 Results

For each patient, our analysis produces an IMF that represents the 0.1 Hz frequency of the signal with respect to time for HR and SBP at both rest and HUT, totaling 4 IMFs per patient. The 0.1 Hz IMFs for one POTS patient and one control subject are shown in Figure 6.4. We compare the power and phase difference of the signals across groups and use random forests and clustering to determine the importance of metrics.

![Figure 6.4](image)

Figure 6.4 SBP (mmHg - red) and HR (bpm - black) IMF's containing 0.1 Hz oscillations at rest (left) and during HUT (right) for a representative POTS patient (top) and control subject (bottom).

6.4.1 Signal Power

Each group contains predictions from 28 subjects. The results of IMF FFTs are shown in Figure 6.5 for a representative control subject and POTS patient. This figure shows that frequencies cluster at 0.1 Hz characterizing the power of the baroreflex response [DR09]; 0.25 Hz characterizing respiration and the
response of the RSA reflex [Cev01], and a broad distribution at higher frequencies (~0.3–0.5 Hz); the last frequency distribution (yellow) is wide and nearly uniform, and most likely shows noise in the original signal. The results of a Gaussian fit of the FFT of the 0.1 Hz IMF are shown in Figure 6.6 for 2 subjects. For each subject, the amplitude $a$ (reported in Table 6.4) of the 0.1 Hz frequency response is computed as the max of the Gaussian distribution.

![Figure 6.5 Amplitude of oscillations of the frequency bands detected by UPEMD. The amplitude was computed from FFT of the IMFs. The blue spectra show the FFT of the 0.1 Hz IMF; orange spectra show the FFT of the respiratory frequency (~0.2 Hz) IMF; the broad yellow spectra show the FFT of the high-frequency IMF.](image)

Table 6.4 Signal characteristics. Numbers are reported as the mean ± standard deviation. ΔHR report the change in HR from rest to HUT. A * marking denotes that the marker is used in the random forest and clustering analysis.

<table>
<thead>
<tr>
<th></th>
<th>Ctrl Rest</th>
<th>Ctrl HUT</th>
<th>POTS Rest</th>
<th>POTS HUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>$a_{HR}$</td>
<td>0.55 ± 0.31*</td>
<td>0.52 ± 0.31*</td>
<td>0.82 ± 0.27*</td>
<td>1.03 ± 0.43*</td>
</tr>
<tr>
<td>$a_{SBP}$</td>
<td>0.71 ± 0.22*</td>
<td>0.86 ± 0.36*</td>
<td>0.68 ± 0.20*</td>
<td>1.22 ± 0.49*</td>
</tr>
<tr>
<td>$M_h$</td>
<td>1.29 ± 0.24*</td>
<td>1.31 ± 0.30*</td>
<td>0.95 ± 0.25*</td>
<td>0.90 ± 0.31*</td>
</tr>
<tr>
<td>HR</td>
<td>72 ± 12</td>
<td>78 ± 12*</td>
<td>74 ± 13</td>
<td>104 ± 16*</td>
</tr>
<tr>
<td>SBP</td>
<td>117 ± 21</td>
<td>124 ± 22</td>
<td>110 ± 16</td>
<td>112 ± 16</td>
</tr>
<tr>
<td>Δ HR</td>
<td>7.6 ± 5.8*</td>
<td></td>
<td>32.0 ± 11.7*</td>
<td></td>
</tr>
<tr>
<td>BRS</td>
<td>6.36 ± 4.7</td>
<td>3.81 ± 2.35</td>
<td>8.09 ± 4.61</td>
<td>3.17 ± 1.92</td>
</tr>
</tbody>
</table>

Results show that in POTS patients, the amplitude of SBP 0.1 Hz oscillations is significantly larger during HUT than at rest, but we fail to reject the null hypothesis for the same comparison in the control subjects for both HR and SBP, and for HR in POTS patients. The amplitude of the HR oscillations is larger
Table 6.5 One-way ANOVA comparing the amplitude of the 0.1 Hz IMF oscillations. ANOVA compressions of amplitude of 0.1 Hz component of various signals. We use 0.005 as our threshold for statistical significance.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest vs HUT</td>
<td></td>
</tr>
<tr>
<td>Control HR</td>
<td>0.69</td>
</tr>
<tr>
<td>SBP</td>
<td>0.06</td>
</tr>
<tr>
<td>POTS HR</td>
<td>0.03</td>
</tr>
<tr>
<td>SBP</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Control vs POTS</td>
<td></td>
</tr>
<tr>
<td>Rest HR</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>SBP</td>
<td>0.57</td>
</tr>
<tr>
<td>HUT HR</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>SBP</td>
<td>&lt; 0.005</td>
</tr>
</tbody>
</table>

in POTS patients compared to control subjects both at rest and during HUT, and the amplitude of the SBP oscillations is only larger between control subjects and POTS patients during HUT. These results indicate that at rest, the sympathetic branch can maintain BP at homeostasis, while the parasympathetic branch is impaired both at rest and during HUT.

Figure 6.7 shows box plots comparing the 0.1 Hz amplitude for each group. ANOVA tests, summarized in Table 6.5, compare predictions of $a$ (maxima of the Gaussian fit of the 0.1 Hz Fourier spectra) between the four groups: Rest (control subjects and POTS patients) and HUT (control subjects and POTS patients). Overall, the results presented here indicate that the POTS patients exhibit an abnormally sensitive baroreflex when compared to the control subjects.

6.4.2 Phase Response

To compare the instantaneous phase difference $M_h$ across groups, we performed an ANOVA analysis, including predictions from 28 subjects per group. Calculated values of $M_h$ are reported in Table 6.4 and illustrated in Figure 6.8. The ANOVA analysis (summarized in Table 6.6) compare predictions between groups show that $M_h$ is significantly smaller in POTS patients compared to controls, both at rest and during HUT, but it does not change significantly between rest and HUT within control subjects or POTS patients. The decreased $M_h$ value in POTS patients implies that they have a faster baroreflex response than the control subjects regardless of their orthostatic position.

We conduct the same comparisons for the action (BRS) calculated with a 1 heartbeat delay, as is traditionally done. Results of BRS are reported in Table 6.4, and ANOVA of BRS are presented in Table 6.5. The only significant difference for BRS is in POTS patients between rest and HUT. We observe that the coefficient of variation (Standard deviation divided by mean) of BRS is greater than 50% for all groups, whereas the coefficient of variation of $M_h$ is below 25%.

6.4.3 Clustering Analysis

We used random forest machine learning to determine what factors provided better predictors for POTS. We compared eight predictors given in Table 6.4, including the amplitude of the 0.1 Hz oscillations of
Figure 6.6 Gaussian fit to 0.1 Hz HR (top) and SBP (bottom) spectra for a representative POTS patient (left) and control subject (right). The power amplitude is summarized in Table 6.5 averages the response for all subjects in each group.

Figure 6.7 Box and whisker plots, comparing the amplitude of the 0.1 Hz IMFs for each patient group: controls at rest (CR), POTS at rest (PR), controls during HUT (CH), and POTS during HUT (PH). A red + denotes an outlier.
Table 6.6 One-way ANOVA Comparisons for \( M_h \). \( p \)-values from a one-way ANOVA comparing \( M_h \). We use 0.005 as our threshold for statistical significance.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>( M_h ) ( p )-value</th>
<th>BRS ( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control rest vs. Control HUT</td>
<td>0.82</td>
<td>0.01</td>
</tr>
<tr>
<td>POTS rest vs. POTS HUT</td>
<td>0.59 &lt; 0.005</td>
<td></td>
</tr>
<tr>
<td>Control rest vs. POTS Rest</td>
<td>&lt; 0.005 0.17</td>
<td></td>
</tr>
<tr>
<td>Control HUT vs. POTS HUT</td>
<td>&lt; 0.005 0.27</td>
<td></td>
</tr>
</tbody>
</table>

Figure 6.8 Box and whisker plots comparing the instantaneous phase difference (\( M_h \)) for each patient group: controls at rest (CR), controls during HUT (CH), POTS at rest (PR), and POTS at HUT (PH). A red + denotes an outlier.

HR during rest/HUT, SBP during rest/HUT, the change in HR during HUT, and the average HR during HUT. Note, that average HR during HUT is calculated over the entire extracted HUT segment. The value of k-fold loss for different maximum branching numbers varies from 0.04 – 0.08, with a value of 0.07 with a maximum branching number of 8 (number of predictors used). Results in Figure 6.9a shows that the four most important metrics to detect POTS include: (1) the change in HR (\( \Delta H \)) between rest and HUT, (2) the average HR during HUT (Hm) (3) the phase difference \( M_h \) at rest (MR), and (4) the amplitude of HR oscillations during HUT (HaH). Subsequently, we used clustering with \( k \)-means to cluster with all eight metrics. Figure 6.9b shows the silhouette plot of the predicted clusters. This plot shows how similar a member of a cluster is to other members of the same cluster. The silhouettes have an average length of 0.47. The clustering labeled three patients previously diagnosed POTS patients as control, and two controls as POTS patients.

The machine learning analysis assumes that the medical diagnosis is accurate, which may be true. All
patients underwent a series of tests, including a Valsalva maneuver, a head-up tilt test, a deep breathing test, and an active standing test. In principle, all tests should result in a POTS type response, but in practice, some tests may fail to do so.

In summary, our results show that the amplitude of the 0.1 Hz frequency component of the HR and SBP is larger in POTS patients during HUT and that the phase response between HR and SBP is shorter in POTS patients. Machine learning and clustering analysis show that the phase difference at rest is an effective metric that can be calculated at without subjecting the patients to HUT.

6.5 Discussion

Our study has shown that postural orthostatic tachycardia (POTS) patients have a more pronounced 0.1 Hz frequency response compared to controls both during rest and head-up-tilt (HUT). This frequency response is associated with the baroreflex [Par88]. Therefore, our results indicate, as hypothesized, that POTS patients have an oversensitive baroreflex causing significant and rapid changes in both SBP and HR.

POTS is currently diagnosed by the presence of tachycardia without syncope upon postural change from supine to standing or with HUT. Positive diagnosis requires a change in HR of more than 30 bpm in adults (40 bpm in children/young adults aged 12 to 19 years old). The patient data analyzed here were categorized as POTS if they experienced orthostatic intolerance and a significant increase in HR or a sustained high HR (above 120 bpm) during HUT or an active standing test. The analysis performed
here focuses on identifying markers that correlate with the baroreflex response (∼0.1 Hz), enabling us to generate physiological hypotheses explaining the observed oscillations in HR and BP [Wis17], i.e., the ΔHR response was not included in the analysis. The overactive system could correlate to findings by us (not published) and others [Dah16], noting that most POTS subjects express agonistic antibodies that bind to cardiac pacemaker cells and smooth muscle cells within the arterial wall. While the presence of specific autoantibodies does not confirm disease causality, and results are difficult to translate to system-level BP and HR observations, the correlation between these observations suggests that the baroreflex system may be compromised in this patient subgroup.

By using UPEMD [Wan18], we can represent the nonstationary signals as a series of stationary components that can be analyzed using stationary methods in both the time and frequency domain. Our results show that POTS patients exhibit larger 0.1 Hz oscillations in both HR and SBP both at rest and during HUT. This result agrees with previous studies, e.g., the study by Stewart et al. [Ste15], which quantified the amplitude of cerebral blood flow and BP oscillations. Results from that study suggested that these oscillations may be responsible for decreased neurocognition “brain fogginess” in POTS patients.

This study analyzed data from a HUT, but other tests could be used including the Valsalva maneuver and active standing. The HUT test is a common diagnostic procedure for patients with syncope [Alv00] but is here used for analysis of patients with POTS, where pathological changes occur immediately upon assumption of the upright posture, in contrast to syncope that develops over longer period of time. The use of 6-10 min of data for the analysis agrees with [Kir13].

The advantage of UPEMD is that we can treat the signals as non-stationary, which is motivated by our understanding of the baroreflex and cardiovascular system. Previous studies of these signals have used stationary techniques as approximations; however, to agree with the theory, we elected to use UPEMD. Using UPEMD, we also study the frequency response in time (as shown in Figure 6.8). This allows us to quantify the phase relationship (via $M_h$) between the signals, a novel result that to our knowledge, has not been reported previously.

Our analysis compared eight metrics: the amplitude of 0.1 Hz oscillations at rest and HUT for both HR and BP; the phase difference between HR and BP at rest and during HUT; the change in HR during HUT, and the magnitude of HR during HUT. Results of the random forest analysis revealed that in addition to the change in HR, the phase difference (our new marker) between the two signals provides the most significant markers. By using a maximum branching number of 8 (number of predictors) we obtained a k-fold loss of $\sim 0.07$. We view this as acceptable for our purpose of ranking importance of metrics. The instantaneous phase difference is of importance as it provides a new way to quantify baroreflex sensitivity other than the spontaneous baroreflex (BRS) method.

The new marker, $M_h$, quantifies the response time of the baroreflex, whereas BRS measures the magnitude of the baroreflex response. We see from our analysis that BRS changes in POTS patients when transitioned from rest to HUT. This implies that BRS can only detect abnormal baroreflex activity in POTS patients with a HUT, whereas $M_h$ can detect an abnormal baroreflex during rest and HUT. Furthermore, since $M_h$ does not change from rest to HUT, and BRS does for POTS patients, we argue
that $M_h$ is better at detecting abnormal responses.

A potential problem with BRS is the assumption that the response of a change of pressure can be fully quantified by the RR interval of the next heartbeat. In reality, this response time is likely not equal to the next RR interval time. Our metric, $M_h$, represents this response time, and is calculated in a continuous fashion. Hence, future work could calculate a continuous version of BRS using a patient specific response time ($M_h$).

The new marker, $M_h$, is calculated using the Hilbert Transform to find the instantaneous phase of this signal. It should be noted that one could calculate the instantaneous amplitude of the signal via the Hilbert Transform to characterize the amplitude of the $\sim0.1$ Hz oscillations and obtain similar results as using the FFT method presented above.

A diagnosis of POTS is made using a number of criteria: that patients showed signs of orthostatic intolerance (a metric not directly quantifiable by the data analyzed), that they exhibited an increase in HR upon standing, in response to a Valsalva maneuver (data not analyzed), a HUT (analyzed here), or that they had a sustained HR at or above 120 bpm. Clustering analysis characterizing POTS by a $\Delta HR > 30$ or a sustained HR of more than 120 bpm resulted in 6 POTS patients classified as control subjects. Neither of these patients had a $\Delta HR > 30$ bpm. Nevertheless, an inspection of data from Valsalva maneuvers and active standing tests showed that tests were associated with a HR increase $\Delta HR > 30$ bpm. In comparison, classification, including the 0.1 Hz frequency response metric, identified only three POTS patients as controls (also labeled control if only $\Delta HR$ was considered). These patients did not experience a change in HR at or above 30 bpm, but they all exhibited a fairly high HR response to active standing ($\Delta HR \approx 30$). It should be noted that one of the three miscategorized patients had a very high resting HR, and almost no oscillations. We hypothesize that this patient may have POTS combined with inappropriate sinus tachycardia.

The clustering analysis performed in this study placed all POTS patients in one group, even though the phenotype likely are caused by different mechanisms [Raj18]. The lack of differentiation within the POTS group could be because all POTS patients analyzed had the same genotype, that the sample size was too small, or that the HUT tilt is not able to differentiate the subgroups. The approach used here can easily be expanded by including a larger sample size and by comparing markers identified by the HUT test to other tests, e.g. the Valsalva maneuver or active standing.

In addition, two control patients were categorized as POTS. These patients could have been misdiagnosed. Most of our data from control subjects are from people contacting the autonomic clinic because they experienced orthostatic intolerance but were classified as healthy since their HR response did not display abnormal features according to existing protocols. Overall, our results are promising, and they motivate future work. In particular, it would be beneficial to include data from other tests including active standing and the Valsalva maneuver.

This study is limited as we only analyze data from 56 patients (28 POTS patients and 28 control subjects). Due to this limitation, we were not able to match patients based on demographics. Future studies should include more datasets, potentially including more measurements per patient, including demographics and orthostatic intolerance markers.
Another disadvantage of this limited sample size is the inability to validate the model produced by Random Forest Machine Learning on an independent cohort of patients. For this reason, the Random Forest approach is only used to calculate the importance of the metrics presented in this paper and cannot be used as a diagnostic tool. Future studies, with more data sets, should use machine learning to create, and validate, models that can assist with clinical diagnosis.

In summary, we present evidence that HR and BP oscillations are essential to understanding the underlying dynamics of POTS and provide a way to incorporate the detection of oscillations into the diagnosis protocol. We argue that by quantifying both the oscillations and an increase in HR, clinicians will be able to provide a more accurate patient diagnosis. We showed that in addition to changes in HR, POTS diagnosis should include metrics computing the amplitude of the HR and SBP 0.1 Hz frequency response and the phase difference between the HR and BP signals. These metrics all agree with our hypothesis that the baroreflex is enhanced in POTS patients. The addition of our new metrics comparing the heart and BP response opens an avenue providing more insight into the pathophysiology of POTS. POTS is typically a comorbidity in a number of conditions, including visceral pain, chronic fatigue [Wis17], migraine, joint hypermobility [CG19], and chronic anxiety [Dah16]. Including the specific comorbidity, and our new POTS markers may allow us to differentiate between the POTS patients, essential to generate better treatment protocols.

6.5.1 Conclusion

This study demonstrates that the amplitudes (power) of HR and BP oscillations are increased and that the instantaneous phase difference between HR and BP is smaller in POTS patients compared to controls. The amplitude of the 0.1 Hz response of HR during HUT and the instantaneous phase difference both at rest and HUT are the most significant markers for POTS. This result indicates that POTS patients have a hypersensitive baroreflex even at rest, indicating that it may be possible to diagnose POTS without invoking the HUT test. We speculate that these oscillations may be responsible for symptoms of the disease, in particular, fatigue as the body uses excessive energy to keep BP at homeostasis. Based on our findings, we suggest that POTS diagnosis protocols should characterize oscillations at 0.1 Hz, providing a more detailed insight into the disease pathophysiology, e.g., by differentiating between tachycardia caused by a reduced central blood volume as opposed to increased baroreceptor sensitivity.

ACKNOWLEDGEMENTS

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CHAPTER 7

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME (POTS) EXPLAINED USING A BAROREFLEX RESPONSE MODEL

The study "Postural orthostatic tachycardia syndrome explained using a baroreflex response model" was published in the Journal of the Royal Society Interface, volume 19, issue 193, in 2022. Contributions included formulating aspects of the model, design and implementation of the simulation to signal processing pipeline, parameter space exploration techniques and phenotype effects, as well as general design of code, and writing the manuscript.

Abstract

Patients with Postural Orthostatic Tachycardia Syndrome (POTS) experience an excessive increase in heart rate and low-frequency (∼0.1 Hz) blood pressure and heart rate oscillations upon head-up tilt. These responses are attributed to increased baroreflex responses modulating sympathetic and parasympathetic signaling. This study uses a closed-loop cardiovascular compartment model controlled by the baroreflex to predict blood pressure and heart rate dynamics in response to head-up tilt. The cardiovascular model predicts these quantities in the left ventricle, upper and lower body arteries, and veins. Head-up tilt is simulated by letting gravity shift blood volume from the upper to the lower body compartments, and the baroreflex control is modeled using set-point functions modulating peripheral vascular resistance, compliance, and cardiac contractility in response to changes in mean carotid blood
pressure. We demonstrate that modulation of parameters characterizing baroreflex sensitivity allows us to predict the persistent increase in heart rate and the low-frequency blood pressure and heart rate oscillations observed in POTS patients. Moreover, by increasing baroreflex sensitivity, inhibiting baroreflex control of the lower body vasculature, and decreasing central blood volume, we demonstrate that it is possible to simulate patients with neuropathic and hyperadrenergic POTS.

7.1 Introduction

Postural Orthostatic Tachycardia Syndrome (POTS) is a form of autonomic dysfunction characterized by an excessive increase in heart rate (tachycardia) upon transitioning from a supine to an upright position in the absence of orthostatic hypotension and other conditions provoking sinus tachycardia. A positive diagnosis also requires a history of persistent (at least six months) symptoms, including brain fog, palpitations, visual blurring, or dizziness, [Fed19; Fre11; Mar20]. Since POTS is a phenotype of autonomic dysfunction and not a specific disease, it is difficult to identify the compromised mechanisms. This is partly due to POTS’ numerous potential pathologies, including neuropathy or the presence of agonistic antibodies binding to specific adrenergic receptors [Mar20; Li14]. POTS is typically diagnosed by examining beat-to-beat heart rate (HR), and blood pressure (BP) signals measured during a postural challenge, such as head-up tilt (HUT) or active standing [Raj06]. These signals, measured continuously, are reported along with a description of symptoms, yet diagnosis primarily relies on a single quantity - tachycardia (heart rate increase \( \geq 30 \text{ bpm}, \geq 40 \text{ bpm for adolescents} \)) [Raj06; Sin12].

Diagnosis of POTS from postural tachycardia is problematic as the single measure does not provide adequate insight into the syndrome’s underlying causes. Recent studies [Ged20a; Ste15; Med14] have reported that POTS patients exhibit tachycardia (increasing HR more than normal) in response to postural change. They also experience increased \( \sim 0.1 \text{ Hz} \) HR and BP oscillations. In our previous study [Ged20a] examining data from 28 controls and 28 POTS patients, we found that \( \sim 0.1 \text{ Hz} \) oscillations had a higher amplitude during head-up tilt and that phase difference is smaller in POTS patients at rest and during HUT. These observations agree with Stewart et al. [Ste15; Med14] reporting increased \( \sim 0.1 \text{ Hz} \) oscillations in cerebral blood flow during HUT. Adding a marker characterizing low-frequency oscillation may improve diagnoses, but it should be accompanied by better characteristics describing what causes this feature to change.

Moreover, POTS has several phenotypes [Fed19; Mar20; Gru08b; Bry19] including (1) neuropathic POTS caused by neuropathy in the vascular beds, particularly in the lower body; (2) hypovolemic POTS attributed to low fluid volume, and (3) hyperadrenergic POTS characterized by high levels of circulating norepinephrine during postural change inducing an exaggerated sympathetic response.

It is known that POTS is associated with modulation of the baroreflex function [Mar20; Ged20a]. Several hypotheses have been put forward suggesting what parts of the system are compromised, though it is difficult to determine how each factor impacts dynamics. As a result, patients receive a series of tests to examine their dynamic response, but more methods are needed to examine the output. This study uses mathematical modeling to investigate how the system responds when parameters associated
with baroreflex sensitivity are varied and if modulation can differentiate POTS phenotypes. Results provide new insight, which has the potential to be incorporated into diagnostic criteria providing a more elaborate diagnosis.

For healthy people, the baroreflex system operates via negative feedback modulating sympathetic and parasympathetic nerve activity, mitigating BP changes. During head-up tilt, stretch receptors in the carotid sinus detect changes in BP modulating firing rate in the glossopharyngeal nerve, which sends signals to the nucleus tractus solitarius (NTS). From here, the signals are transmitted via the efferent sympathetic and parasympathetic nerves. HR is modulated by changes in the firing of both sympathetic and parasympathetic nerves, while the sympathetic nervous system primarily modulates peripheral vascular resistance and cardiac contractility. At rest, sympathetic activity is low (~20% of its maximum), while the parasympathetic activity is high (~80% of its maximum) [Kor76]. In response to a decrease in BP, the afferent signaling is inhibited, leading to parasympathetic withdrawal and sympathetic stimulation, which increase HR, cardiac contractility, and peripheral resistance [Bor12]. Numerous studies have examined baroreflex signaling [Med14; Cev01; DeB87], and it has been established that BP and HR are controlled by negative feedback with a resonance frequency of approximately ~0.1 Hz. This response is easily distinguished from HR (with a frequency of ~1 Hz) and respiration (which oscillates with a frequency of 0.2 – 0.3 Hz) [DeB87].

Several recent studies have examined the magnitude and phase of the low-frequency (~0.1 Hz) BP and HR oscillations in POTS patients [Ged20a; Ste15; Med14]. The studies by Stewart et al. [Ste15], and Medow et al. [Med14] used Transcranial Doppler measurements of cerebral blood flow and finger arterial plethysmography to analyze blood flow and HR oscillations in response to a postural challenge. Using auto-spectral and transfer function analysis, they reported that increased low-frequency oscillations in arterial pressure lead to increased oscillations in cerebral blood flow, which they suggest may be responsible for the “brain fog” experienced by many POTS patients. These results agree with our empirical mode decomposition findings to examine BP and HR signals measured during HUT from females diagnosed with POTS. However, as noted in our previous study [Ged20a] not distinguishing POTS phenotypes, low-frequency oscillations are increased after HUT in all POTS patients, but there is significant variation among individuals. This suggests that oscillation amplitude and phase difference may differ among the POTS phenotypes. In summary, from previous work [Ged20a] and other previous studies [Fed19; Mar20; Bry19] it is clear that the baroreflex is compromised. Still, more work is needed to explain how specific pathophysiology impact HR and BP dynamics.

To model the baroreflex response to HUT, additional considerations are needed. First, the cardiovascular model must be adapted to account for the gravitational pooling of blood in the lower extremities. Second, the baroreflex model must be adjusted to account for the orthostatic stress challenge. Several studies have examined this phenomenon, e.g., [Hel00; Olu05; Ell08; Kap07; Ott10; Wil14; Mat15]. The model by Olufsen et al. [Olu06b] used HR as an input to predict BP during active standing for a healthy young adult, estimating patient-specific parameters modulating peripheral vascular resistance and vascular compliance. Williams et al. [Wil14] adapted this approach to study the response to HUT. Matzuka et al. [Mat15] used Kalman filtering and Williams et al. [Wil19] used optimal control to estimate model
While these studies captured variations in response to a postural change, to our knowledge, only a few studies have attempted to test if dynamical systems models display ∼0.1 Hz oscillations. The study by Heldt et al. [Hel00] built a model predicting low-frequency oscillations in astronauts undergoing an active standing test using a baroreflex control model. They found that the low-frequency oscillations emerge but do not persist after the transition from sit-to-stand. Another attempt was made by Hammer and Saul [Ham05], who used an open- and closed-loop baroreflex model to predict postural change. This model uses arterial BP as an input to predict HR. While this model examines the ∼0.1 Hz oscillations, it does not study how the response changes in time; instead, it quantifies stability at fixed operating points responsible for low-frequency oscillations. More recently, Ishbulatov et al. [Ish20] used a closed-loop baroreflex model to replicate low-frequency aspects of patient data during a passive HUT test. This study analyzes how a healthy human body adapts to an orthostatic challenge. However, this model is complex and does not study the response in POTS patients.

To our knowledge, no previous studies have combined a mechanistic model with signal analysis to explain the emergence and modulation of the low-frequency oscillations for POTS patients. To remedy the shortcomings of these previous studies, we use a simple differential equations model without delays to examine temporal and frequency baroreflex response to HUT for POTS patients. We use simulations to encode the three POTS phenotypes identified by Mar and Raj [Mar20] to study how they affect BP and HR dynamics. Our model is formulated using a simple closed-loop 0D cardiovascular model, with first-order set-point control equations representing the baroreflex regulation. We analyze our model output using signal processing techniques and study the effects of critical model parameters that correspond to the physiological abnormalities that cause each POTS phenotype. Results indicate that changes in clinically relevant parameters can generate low-frequency oscillations with amplitude equal to that observed in POTS patient data from our previous study [Ged20a]. Discussion of our results focuses on clinical implications and motivation for future studies.

### 7.2 Methods

This study develops a closed-loop 0D model describing the emergence and amplification of low-frequency (∼0.1 Hz) oscillations observed in POTS patients during head-up tilt. The model is parameterized to fit average BP and HR signals measured in control and POTS patients, and simulation results are depicted along with characteristic data. Model results are predicted at rest and during HUT, and by varying characteristic parameters, we demonstrate how to differentiate POTS phenotypes suggested by Mar and Raj [Mar20].

Similar to our previous studies [Wil14; Ott13], we predict blood flow and pressure in the systemic circulation using an electrical circuit model with five compartments, including the upper and lower body arteries and veins, and the left heart (see Figure 7.1(a)). The baroreflex is incorporated via negative feedback control equations predicting the effector response (HR, vascular resistance, and cardiac contractility) as functions of mean carotid pressure. The magnitude and phase of the low-frequency
oscillations generated by the baroreflex are determined using discrete Fourier transform, analyzing computed HR and BP signals.

Computations are first conducted in the supine position, followed by HUT simulated by accounting for gravity shifting blood from the upper to the lower body. We demonstrate the importance of incorporating HR variability by adding uniformly distributed white noise to predictions of HR and discuss how phenotypes suggested by Mar and Raj [Mar20] can be simulated.

7.2.1 Data
In this study, model simulations are qualitative and meant to illustrate how changing system properties impact dynamics. To test if the outcome of our simulations is realistic in terms of physiological behavior, we included BP and HR measurements (extracted from [Ged20a]) from two representative subjects: a control subject and a POTS patient.

Measurements from these subjects include continuous ECG and upper arterial BP measurements extracted at rest for 5 minutes and then for 5 additional minutes after the HUT onset. HR is extracted from the high-resolution 3-lead ECG measurements as the inverse distance between consecutive RR intervals and continuous BP measurements are obtained using a Finapress device (Finapress Medical Systems BV, Amsterdam, Netherlands). BP and ECG signals are sampled at 1000 Hz. BP and HR signals are sub-sampled to 250 Hz, after which the Uniform Phase Empirical Mode Decomposition [Ged20a] is used to extract the magnitude and phase of ~0.1 Hz oscillations. Data are scaled to literature values in the supine position (at rest) for a healthy subject setting HR to 60 bpm = 1 bps and BP varying between 80 and 120 mmHg. In addition, to illustrate severe tachycardia characteristic of hyperadrenergic POTS, during HUT, HR is set and maintained at 1.5 bps, an increase of 30 bpm = 0.5 bps.

The afferent input to the baroreflex control model assumes that BP is measured at the level of the carotid baroreceptors (above the center of gravity). Therefore BP data, measured at the level of the heart, is adjusted by subtracting the effect of gravity as described in our previous study [Wil14].

7.2.2 Cardiovascular model
We employ an electrical circuit analogy to predict blood flow (analogous to current), pressure (analogous to voltage), and volume (analogous to charge) in the systemic circulation represented by five compartments, including the upper (u) and lower (l) body arteries (a) and veins (v), and the left heart (lh). Each compartment is quantified by its volume (Vi(t) mL) and pressure (Pi(t) mmHg), while flow Qi(t) (mL/s) exists between compartments. The lower body contains organs below the lower abdomen while the upper body compartments contain organs above the lower abdomen including the abdominal-splanchnic vessels. Figure 7.1 depicts the model and Table 7.1 lists the dependent cardiovascular variables.

To ensure flow conservation, for each compartment (i = lh, au, al, vl, vu), the change in volume is computed as the difference between flow into and out of the compartment,

\[ \frac{dV_i}{dt} = Q_{in} - Q_{out}, \]  

(7.1)
Figure 7.1 (a) Hemodynamics is controlled by the baroreflex system, which senses changes in carotid arterial pressure predicted as a function of upper body arterial pressure. Afferent signals from baroreceptor neurons are integrated into the Nucleus Solitary Tract (NTS) and transmitted via sympathetic and parasympathetic neurons regulating HR, peripheral vascular resistance, and ventricular contraction. The systemic circulation is represented by compartments lumping upper (a_u) and lower (a_l) body arteries, upper (v_u) and lower (v_l) body veins, and the left heart (l_h). The upper body compartment contains organs above the lower abdomen, including the abdominal splanchnic vessels, and the lower body compartment contains organs below the lower abdomen. Flow (Q) through the aortic valve (a_v) is transported from the left heart to the upper body arteries. From here, it is transported to the lower body arteries and through the upper body peripheral vasculature (u_p) to the upper body veins. A parallel connection transports flow through the lower body peripheral vasculature (l_p). From the lower body venous flow is transported to the upper body veins and finally via the mitral valve (m_v) back to the left heart. Each compartment representing the heart or a collection of arteries or veins has a pressure (P), volume (V), and elastance (E). Pumping of the heart is achieved by assuming that left heart elastance (E_{l_h}(t)) is time-varying. (b) Model predictions of heart rate (H (bps), top panel) and upper body arterial pressure (P_{a_u} (mmHg), lower panel). We analyze upper body arterial pressure for oscillations but use the mean carotid pressure (not shown) as the input to our control equations. 5-second sections of each signal are shown in the overlaid subpanels. (c) Frequency spectra of time-series data (H top, P_{a_u} bottom) shown in (b)

where Q_{in} denotes the flow into, and Q_{out} denotes the flow out, of compartment i. Ohm’s law relates flow to pressure and the resistance (R, mmHg s/mL) between compartments (i − 1) and (i),

\[ Q_i = \frac{P_{i-1} - P_i}{R_i}. \]  

(7.2)

For each arterial compartment and upper venous compartment i, pressure and volume are related
using the linear relation

\[ P_i - P_{ui} = E_i(V_i - V_{ui}), \quad (7.3) \]

where \( V_{ui} \) is the unstressed volume, \( E_i \) is the elastance (reciprocal of compliance, analogous to capacitance), and \( P_{ui} = 0 \) is the unstressed pressure.

Given that pressure changes significantly on the venous side, in particular in the lower venous compartment during HUT, as suggested by Hardy et al. [Har82] we employ a nonlinear relation between lower venous pressure and volume given by

\[ P_{vl} = \frac{1}{m_{vl}} \log \left( \frac{V_{Mvl}}{V_{Mvl} - V_{vl}} \right), \quad (7.4) \]

where \( m_{vl} \) is a parameter that relates nominal pressure, volume \( V_{vl} \) and maximal volume \( V_{Mvl} \) [Pst17].

The pumping of the heart is achieved by introducing a time-varying elastance function of the form

\[
E_{lh}(t) = \begin{cases} 
\frac{E_S - E_D}{2} \left( 1 - \cos \left( \frac{\pi t}{T_S} \right) \right) + E_D & 0 \leq t \leq T_S \\
\frac{E_S - E_D}{2} \cos \left( \frac{\pi (t - T_S)}{T_D} \right) + E_D & T_S \leq t \leq T_S + T_D \\
E_D & T_S + T_D \leq t \leq T,
\end{cases} \quad (7.5)
\]

where \( E_S, E_D, T_S, \) and \( T_D \) denote the end systolic and end diastolic elastance, and the time for end systole and diastole, respectively. This function is used to model cardiac contraction determined by \( E_M - E_m \).

The timing parameters \( T_S \) and \( T_D \) are determined as functions of the length of the current cardiac cycle (\( T \), the RR interval). By combining the prediction of the length of the QT interval from [Akh81; KJ85] and the ratio of cardiac mechanical contraction to relaxation from [Jan10], we get

\[ T_S = 0.45 \left( c_1 + \frac{c_2}{T} \right), \quad T_D = 0.55 \left( c_1 + \frac{c_2}{T} \right), \quad (7.6) \]

where \( c_1 = 0.52 \text{ s} \) and \( c_2 = -0.11 \text{ s}^2 \) from [Akh81].

Similar to arterial compartments, the left heart pressure \( P_{lh} \) and volume \( V_{lh} \) are related by

\[ P_{lh} - P_{lh,u} = E_{lh}(t)(V_{lh} - V_{un}), \quad (7.7) \]

where \( P_{lh,u} = 0 \) and \( V_{lh,u} = 10 \) are the unstressed pressure and volume in the left heart, and \( E_{lh}(t) \) is the time-varying elastance.

### 7.2.3 Head-up tilt (HUT)

During HUT, gravity pools blood from the upper to the lower body affecting the flow between the upper and lower body (\( Q_a \) and \( Q_v \)). This maneuver is depicted in Figure 7.2. We model this effect by adding a tilt term accounting for the additional force caused by gravitational pooling [Wil14], i.e.,

\[
Q_a = \frac{P_{au} - P_{a1} + P_{tilt}}{R_a}, \quad Q_v = \frac{P_{vu} - P_{v1} - P_{tilt}}{R_v}, \quad (7.8)
\]
Table 7.1 Dependent variables (volume $V$ (mL), pressure $P$ (mmHg), and flow $Q$ (mL/s)) for the cardiovascular system and baroreflex control system. The latter includes peripheral vascular resistance $R_{up}$ and $R_{lp}$, left ventricular elastance $E_{lv}$, and heart rate $H$.

<table>
<thead>
<tr>
<th>State variables</th>
<th>Symbol</th>
<th>Description</th>
<th>States</th>
<th>Units</th>
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<td>Resistance</td>
<td>$R$</td>
<td>Upper peripheral ($up$)</td>
<td>mmHg·s/mL</td>
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<td></td>
<td></td>
<td>Lower peripheral ($lp$)</td>
<td>mmHg·s/mL</td>
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<tr>
<td>Elastance</td>
<td>$E$</td>
<td>Left heart ($lh$)</td>
<td>mmHg/mL</td>
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<td>$P$</td>
<td>Left heart ($lh$)</td>
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<td>Volume</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Arteries ($a$)</td>
<td>mL/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper peripheral ($up$)</td>
<td>mL/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower peripheral ($lp$)</td>
<td>mL/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Veins ($v$)</td>
<td>mL/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mitral valve ($mv$)</td>
<td>mL/s</td>
<td></td>
</tr>
</tbody>
</table>

with

$$P_{tilt} = \rho g h \sin \left( \frac{\theta \pi}{180} \right), \quad \theta \in [0^\circ, \ldots, 60^\circ],$$

(7.9)

where $\rho = 1.06$ [g/cm$^3$] is the density of blood, $g = 982$ [cm/s$^2$] is the gravitational constant, $h = 25$ [cm] is the height between the upper and lower body compartments, and $\theta$ is the angle of tilt. We determine the value of $h$ by estimating the distance between the center of mass for the upper body (the lower chest) and lower body (the pelvis) compartments.

### 7.2.4 Baroreflex model

The baroreflex (BR) control system maintains homeostasis. Afferent baroreceptor nerves sense changes in the aortic arch and carotid sinus BP. Signaling in afferent baroreceptor neurons stimulated by BP are integrated into the medulla, from which efferent neurons are activated, modulating signaling along sympathetic and parasympathetic neurons. We do not compute sympathetic and parasympathetic outflow directly but instead predict controlled quantities as a function of pressure, i.e., afferent and efferent signaling lumps contributions from afferent and efferent (sympathetic and parasympathetic)
nerves. Quantities controlled include heart rate ($H$), peripheral vascular resistance ($R_{up}, R_{lp}$), and cardiac contractility ($E_D$).

As discussed in previous studies [Bor12; Wil14], during HUT, afferent baroreflex firing is modulated by changes in mean carotid pressure. The cardiovascular model described above, predicts upper body arterial pressure at the level of the heart. Using analysis from Williams et al. [Wil14], we compute carotid pressure from upper body arterial pressure as

$$P_c = P_{au} - \rho g \tilde{h} \sin(\theta)$$

and mean carotid pressure as

$$\bar{P}_c = \frac{\bar{P}_c - P_c}{\tau_p},$$  \hspace{1cm} (7.10)

where $\tilde{h} = 20$ [cm] is the height between the carotid and aortic baroreceptors.

Equations for the baroreflex control regulating effectors $X \in \{R_{up}, R_{lp}, E_D, H\}$ (listed with units in Table 7.2) as functions of mean carotid pressure $\bar{P}_c$ are derived under the assumption that each response has a saturation point and a minimum value. This assumption motivates the use of first-order kinetic control equations given by

$$\frac{dX}{dt} = -X + \bar{X}(\bar{P}_c) \frac{\tau_X}{\tau_X},$$  \hspace{1cm} (7.11)

where $\tau_X$ is the time-constant for the response $X$ (shorter for effectors primarily modulated by the parasympathetic neurons than those primarily modulated by sympathetic neurons). For the control of heart rate $H$ and vascular resistance $R_{up}, R_{lp}$ the set-point function $\bar{X}$ is represented by a decreasing Hill function of the form

$$\bar{X} = (X_M - X_m) \frac{P_{kX}^{kX}}{P_c^{kX} + P_{2X}^{kX}} + X_m,$$  \hspace{1cm} (7.12)

while ventricular contractility is controlled by changing the minimum end diastolic elastance $E_D$. For this control, the set-point function $\bar{X}$ is represented by a decreasing Hill function of the form

$$\bar{X} = (X_M - X_m) \frac{P_{2X}^{kX}}{P_c^{kX} + P_{2X}^{kX}} + X_m,$$  \hspace{1cm} (7.13)
where $X_M$ is the maximum value of $\tilde{X}$, $X_m$ is the minimum value, $P_{2X}$ is the half-saturation value, and $k_X$ is the Hill coefficient. Graphs depicting the increasing and decreasing Hill functions, varying the steepness $k_X$ and the half-saturation value $P_{2X}$, and how these impact predictions of effectors are shown in Figure 7.3.

It should be noted (as shown in Figure 7.3) that the controls are not initiated at half the maximum value but at values ensuring that the controlled effectors can increase and decrease as expected from physiological considerations. Additionally, we see that while the response curve, $\tilde{X}$, may take on these saturated values, the actual response does not. This can be seen in Figure 7.3 where pressure changes from 85 to 100 mmHg which causes $\tilde{X}$ to vary between the lower ($\approx X_m$) and upper ($\approx X_M$) bounds. Figure 7.3 shows this for varying values of $k_X$ and $P_{2X}$.

The equations listed above provide continuous estimates for the effector variables, which modulate the equations relating the dependent cardiovascular variables. The peripheral resistances ($R_{up}, R_{lp}$) are used in equation (7.1) relating flow to pressure. End diastolic elastance $E_D$ is used in equation (7.5) predicting the heart’s pumping, and heart rate $H$ is used to determine the length of the cardiac cycle $T = 1/H_b$.

Note that $T$ is a discrete quantity only updated at the end of each heart beat, while $H$ is a continuous variable. To ensure that $T$ remains discrete we introduce a discrete heart rate $H_b$ that remains constant between cycles. For the first cardiac cycle ($i = 1$, at time $t = 0$) $H_b^1 = H(0)$ and $T_1 = 1/H_b^1$. For subsequent cardiac cycles $i > 1$, $H_b^i = H(t_{\text{end}}^{i-1})$, where $t_{\text{end}}^{i-1}$ is the time at the end of the previous cycle and $T^i = 1/H_b^i$.

<table>
<thead>
<tr>
<th>Quantity being controlled</th>
<th>Symbol</th>
<th>Increasing/Decreasing</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance, upper peripheral</td>
<td>$R_{up}$</td>
<td>Decreasing</td>
<td>mmHg · s/mL</td>
</tr>
<tr>
<td>Resistance, lower peripheral</td>
<td>$R_{lp}$</td>
<td>Decreasing</td>
<td>mmHg · s/mL</td>
</tr>
<tr>
<td>Elastance at end diastole</td>
<td>$E_D$</td>
<td>Increasing</td>
<td>mmHg/mL</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>$\dot{H}$</td>
<td>Decreasing</td>
<td>bps</td>
</tr>
</tbody>
</table>

### 7.2.5 Heart rate variability (HRV)

In addition to changes in BP mediated by the baroreflex control system, heart rate data exhibit spontaneous variation, referred to as heart rate variability (HRV) [Mal96] likely caused by fluctuations in vagal firing. These oscillations have physiological relevance and have proven to be essential for cardiovascular dynamics. Typically healthy young people have a high HRV, while the elderly and people with autonomic dysfunction have low HRV. However, setting up a mechanistic model predicting HRV is challenging. Most studies accounting for HRV refer to the phenomena as mathematical chaos [Gol91; Sha17], and while it is believed to most closely resemble "pink noise" [Gol02], as suggested by others, we use "white noise" to predict HRV.
As noted above, we solve the differential equation (7.12) continuously and update $H_b$ and the length of each cardiac cycle $T = 1/H_b$ at the end of each cycle. HRV is accounted for by adding white noise to $T$ sampled from a uniform distribution, i.e., we let

$$T \bigg|_{t_{H0}} \leftarrow \frac{1}{H_b \bigg|_{t_{H0}}} \left( 1 + \frac{U[-1,1]}{50} \right), \quad (7.14)$$

where $U[-1,1]$ is a uniform random distribution from -1 to 1, and $t_{H0}$ denotes the starting time for each heartbeat. We choose to scale the noise by 2% to approximately match patient data.

### 7.2.6 Model parameters and initial conditions

Nominal parameter values and initial conditions are deduced from literature and physiological data representing a healthy young female. Below we describe *a priori* calculation of the parameters, which are detailed with units in Appendix A.
7.2.6.1 Cardiovascular parameters

Blood volume

is calculated using height and Body Mass Index (BMI). Combining the classic formula for BMI [WHO20] by which weight is given by \( W = \text{BMI} \left( \frac{h}{100} \right)^2 \), with Nadler’s equation for blood volume (BV) [Nad62], to estimate blood volume (mL) as

\[
BV = \begin{cases} 
0.4948 \text{BMI}^{0.425} h^{1.575} - 1954, & \text{female}, \\
0.4709 \text{BMI}^{0.425} h^{1.575} - 1229, & \text{male},
\end{cases}
\] (7.15)

where \( h \) is the height in cm. For our baseline patient we use the average height of women in Denmark, 167.2 cm [Col16], and a “healthy” BMI of 22 kg/m\(^2\) [WHO20].

The total blood volume (BV) is distributed between the systemic (≈ 85%) and pulmonary (≈ 15%) circulations [Bor12]. Within the systemic circulation, at rest, we assume that approximately 15% is in the arteries and 85% is in the veins. We assume that half the adipose tissue, one-fourth of the gastrointestinal tract, half of the muscle, half of the skin, and half of the skeleton are in the lower body while the rest of the organs (heart, half of muscle, brain, etc.) are located in the upper body. In the supine position, we assume that 80% of the blood is in the upper body, [Bor12]. To predict circulating blood volume, we differentiate the volume between stressed (circulating) and unstressed volume. Following Beneken and DeWitt [Ben67], in the arteries, we assume that 30% of the volume is stressed, while in the veins, we assume that 7.5% of the total volume is stressed.

Blood pressure:

The model is parameterized to represent dynamics in a healthy young female with a systolic arterial pressure of 120 mmHg and diastolic arterial pressure of 80 mmHg [Lap18]. Using standard clinical index [DeM20], we compute the mean pressure as \( P_m = \left( \frac{2}{3} P_{dia} + \frac{1}{3} P_{sys} \right) \approx 93 \text{ mmHg} \) [Mea00]. As BP is typically measured in the arm, which is included in the upper body arteries, we assign these values to the upper arterial compartment. To allow blood flow from the upper to the lower body arteries, we set the lower body artery pressure to 0.98 times the values in the upper body. Since the venous circulation’s pulse pressure is small, we only determine mean values in venous compartments. Using standard literature values [Bor12] we assume that the upper body venous pressure is 3 mmHg; again, to ensure flow in the correct direction, the lower body venous pressure is \( P_{vl} = 1.1 P_{vu} \).

Parameters for the lower body venous pressure-volume equation (7.4) are calculated as

\[
V_{Mvl} = 4 V_{vll}
\]
\[
m_{vl} = \frac{1}{P_{vll}} \log \left( \frac{V_{Mvl}}{V_{Mvl} - V_{vll}} \right),
\]

where \( V_{vll}, P_{vll} \) and \( V_{Mvl} \) is the nominal volume, pressure and maximal volume for the lower venous compartment \((v'l)\) respectively. \( V_{Mvl} \) is set such that the volume does not saturate at HUT, and \( m_{vl} \) is
set such that at rest, blood flows from the lower to the upper body veins.

**Elastance:**

To calculate the nominal elastance parameters for the arterial compartments and the upper body veins, we use equation (7.3), assuming that the unstressed pressure $P_{un} = 0$ and using the stressed volume fractions given above. The non-linear venous pressure-volume equation (7.4) was used to predict the lower venous elastance. This parameter is adjusted following the HUT onset to capture the effect of the changing pulse pressure during HUT.

*Left heart end-diastolic and end-systolic elastance:* At the end of diastole, the left heart pressure is approximately equal to the venous pressure, and the ventricular volume is maximal, i.e., the nominal (minimal) elastance at diastole can be approximated by $E_D = P_{vu} / \max(V_{lh})$. Similarly, at the end of systole, the left ventricular pressure is approximately equal to the arterial pressure, and the volume is minimal. Hence, the the nominal (maximal) elastance at systole is given by $E_S = P_{au} / \min(V_{lh})$.

**Blood flow:**

In a healthy human cardiac output (CO) is approximately 5 L/min [Bor12]. We assume that the total blood volume is circulated in approximately 60 seconds, i.e., the cardiac output $CO \approx BV / 60 \text{ mL/s}$ [Wil14]. With our previously assumed distribution of blood, we estimate that 80% of cardiac output travels through the upper peripheral, perfusing the upper body, while 20% perfuse the lower body [Wil89]. Hence we obtain nominal values of $Q_{up} = 0.8 \text{ CO}$, and $Q_a = Q_{lp} = Q_v = 0.2 \text{ CO}$.

**Resistance:**

The atrial and mitral valve resistance are both set to 0.0001, as we assume the valves do not have significant resistance compared to resistance generated by flow through the vasculature. Therefore, the remaining nominal resistances are calculated using Ohm’s law, $R = (P_{i-1} - P_i) / Q$, where $P_{i-1}$ is the pressure in the previous compartment, $P_i$ is the pressure in the destination compartment, and $Q$ is the flow.

### 7.2.6.2 Baroreflex control parameters

Each control equation has 4 parameters, $\tau_X, X_M, X_m$, and $P_{2X}$. The time-constant, $\tau_X$, represents the ratio of the speed of the neurological responses and the physiological control. The fast heart rate control is achieved by stimulating the parasympathetic system modulating heart rate within a few beats, followed by input from the sympathetic system modulating heart rate on the time-scale of $\approx 12.5$ sec. Cardiac contractility and peripheral vascular resistance are primarily modulated by the sympathetic system acting on a time-scale of $\approx 12.5$ sec [Bor12]. Our model lumps sympathetic and parasympathetic stimulation. Therefore, we assume that

$$\tau_H = 6.25 < \tau_E \approx \tau_R = 12.5.$$
The maximum and minimum values for the Hill functions are set using literature ensuring that both are above/below actual observations as seen in patients with postural tachycardia syndrome. For heart rate values of 160-170 bpm may be encountered [Li14] and in POTS patients with reflex syncope [Nwa13] heart rates below 40 bpm are not uncommon [Moy09].

We allow peripheral vasculature to dilate to 1.5 times the resting radius and constrict to 0.75 times the resting radius. To relate these measurements to resistance, we recall Poseuille’s law, which state that resistance changes in proportion to the fourth power of the radius. Thus we assume that $R_m = 0.2 R_I$ and $R_M = 3 R_I$. To estimate $E_{DM}$, we refer to the increased potassium levels, which increase cardiac contractility [Lin95]. From this work, we estimate the extent to which contractility can increase under stress and assume that maximum end-diastolic elastance control ($E_{DM}$) can increase to 125% of the initial value. In principle, the heart can relax completely by a lack of stimulus. We, therefore, set the minimum end-diastolic elastance control ($E_{Dm}$) to 1% of the initial value.

Half-saturation values are calculated from initial conditions assuming that the subject is at rest, i.e., $P_c = P_c(0)$, $\frac{dX}{dt} = 0$. Using this assumption together with estimates for the maximum and minimum response the half saturation values $P_{2X}$ can be estimated from

$$P_{2X} = \frac{X_M - X(0)}{X(0) - X_m} X = E_D,$$

$$P_{2X} = \frac{X(0) - X_m}{X_M - X(0)} X = R_{up}, R_{lp}, H.$$  

### 7.2.6.3 Initial conditions

The differential equations for the cardiovascular model in equations (7.1) - (7.5) tracking blood volume are initiated at end diastole, i.e., the ventricular volume is maximal. We assume that both control and POTS patients have a healthy heart with left ventricle volumes that are representative of this normal state (see table A.1 for values). We also assume a physiologically healthy resting initial HR of 1 bps. The remaining initial conditions are set to the calculated nominal values.

### 7.2.7 Signal processing

We employ stationary signal processing to characterize oscillations seen in the model output. This process is illustrated in Figure 7.4. We first solve the differential equations using MATLAB’s [MAT19] ode15s over a time interval long enough to ensure that all transient effects have died out. We interpolate over the solution to obtain a time-series sampled uniformly at 100 Hz. We select the last 200 seconds of the $H$ and $P_{au}$ time-series and compute the one-sided power spectrum using MATLAB’s FFT algorithm. The design of our model suggests two explainable oscillations: one representing the baroreflex, which operates at approximately 0.1 Hz, and the HR, which operates at approximately 1 Hz. As shown in Figure 7.4 these two oscillations and their harmonics are the only significant spikes in the frequency domain. To quantify the magnitude of oscillations caused by our control equations, we record the power and phase of the maximum amplitude peak in the $\sim 0.1$ Hz frequency range. This process is applied at rest and during HUT.
7.2.8 Emergence of low-frequency oscillations

To capture the emergence of low-frequency \(~0.1\) Hz oscillations, we first conduct a parameter sweep changing all relevant parameters over their physiological range. Specific emphasis is on parameters in equations (7.11-7.13) facilitating the baroreflex control. This analysis is done in two steps, first detecting what parameters impact the dynamic behavior and second conducting a detailed analysis varying the critical parameters that impact the dynamic response. In addition to detecting what parameters cause the model to change behavior, we also investigate how to set parameters to capture oscillations at the \(~0.1\) Hz frequency range.

Pseudo-code for this analysis is included in Table 7.3. After solving the model for 250 seconds, the solution is examined to verify that steady state has been achieved for 200 seconds. To verify this, the interval is split in half, and the maximum and minimum heart rate \((H)\) and upper arterial BP \((P_{au})\) are calculated for each half. The relative difference between values for each half is computed and compared to a threshold \((\alpha)\). The halves are then interpolated at 100 Hz, and Fourier power spectra are computed for heart rate and BP for each half. The maximum \(~0.1\) Hz power value is recorded for each half, and the relative difference between the power of the halves is computed and compared to a threshold \((\beta)\). If all of these relative differences are less than their respective thresholds, the model is said to be in steady state, and the power spectra of the last 200 seconds are computed and recorded. If at least one of the relative differences is above the threshold, the model is solved for 20 additional seconds and checked for steady state behavior again.

Using this automated parameter exploration approach, we map Hopf bifurcations for the low-frequency oscillations and the magnitude of heart rate and blood pressure oscillations.
Table 7.3 Pseudo code for two-dimensional parameter analysis. $H([T_i, T_k])$ represents the value of heart rate ($H$) between time of $T_i$ and $T_k$, similarly for blood pressure $P_{au}$. $A_{H1}$ denotes the amplitude of the $\sim 0.1$ Hz component of the $H$ signal during $[T_0, T_1]$ as is explained in methods section 7.2.7. Similarly, $A_{P1}$ for $P_{au}$. $A_{H2}$ and $A_{P2}$ are denote the amplitude of the $\sim 0.1$ Hz component during $[T_1, T_2]$. Analysis is conducted for both rest and head-up tilt sections.

<table>
<thead>
<tr>
<th>Two-dimensional parameter analysis pseudo-code</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Input</strong>: Parameter values</td>
</tr>
<tr>
<td><strong>Output</strong>: Amplitude and frequency of $\sim 0.1$ Hz response, $H$ &amp; $P_{au}$</td>
</tr>
<tr>
<td>$\alpha \leftarrow 0.01$</td>
</tr>
<tr>
<td>$\beta \leftarrow 0.1$</td>
</tr>
<tr>
<td>$T_2 \leftarrow 250$</td>
</tr>
<tr>
<td><strong>While</strong>: $t \leq T_2$</td>
</tr>
<tr>
<td>Run model for one heartbeat, $t_H \leftarrow t +$ duration of heartbeat</td>
</tr>
<tr>
<td>IF: $t_H \geq T_2$</td>
</tr>
<tr>
<td>$T_0 \leftarrow T_2 - 200$</td>
</tr>
<tr>
<td>$T_1 \leftarrow \frac{T_0 + T_2}{2}$</td>
</tr>
<tr>
<td>$C_1 \leftarrow \frac{\max(H([T_0, T_1]) - \max(H([T_1, T_2]))}{\max(H([T_1, T_2]))} \leq \alpha$</td>
</tr>
<tr>
<td>$C_2 \leftarrow \frac{\min(H([T_0, T_1]) - \min(H([T_1, T_2]))}{\min(H([T_1, T_2]))} \leq \alpha$</td>
</tr>
<tr>
<td>$C_3 \leftarrow \frac{\max(P_{au}([T_0, T_1]) - \max(P_{au}([T_1, T_2])){\max(P_{au}([T_1, T_2]))} \leq \alpha$</td>
</tr>
<tr>
<td>$C_4 \leftarrow \frac{\min(P_{au}([T_0, T_1]) - \min(P_{au}([T_1, T_2]))}{\min(P_{au}([T_1, T_2]))} \leq \alpha$</td>
</tr>
<tr>
<td>Interpolate $H, P_{au}$ at 100 Hz to obtain $\hat{H}, \hat{P}_{au}$</td>
</tr>
<tr>
<td>Compute $A_{H1}, A_{H2}, A_{P1}, A_{P2}$</td>
</tr>
<tr>
<td>IF: $A_{H2} &gt; 0$</td>
</tr>
<tr>
<td>$C_5 \leftarrow \frac{A_{H1} - A_{H2}}{A_{H2}} \leq \beta$</td>
</tr>
<tr>
<td>ELSEIF: $A_{H1} == A_{H2}$, $C_5 \leftarrow 1$</td>
</tr>
<tr>
<td>ELSE: $C_5 \leftarrow 0$</td>
</tr>
<tr>
<td>END</td>
</tr>
<tr>
<td>IF: $A_{P2} &gt; 0$</td>
</tr>
<tr>
<td>$C_6 \leftarrow \frac{A_{P1} - A_{P2}}{A_{P2}} \leq \beta$</td>
</tr>
<tr>
<td>ELSEIF: $A_{P1} == A_{P2}$, $C_6 \leftarrow 1$</td>
</tr>
<tr>
<td>ELSE: $C_6 \leftarrow 0$</td>
</tr>
<tr>
<td>END</td>
</tr>
<tr>
<td>IF: $\min(C_1, C_2, C_3, C_4, C_5, C_6) == 0$</td>
</tr>
<tr>
<td>$T_2 \leftarrow T_2 + 20$</td>
</tr>
<tr>
<td>END</td>
</tr>
<tr>
<td>$t \leftarrow t_H$</td>
</tr>
<tr>
<td>END</td>
</tr>
<tr>
<td>Calculate and record metrics</td>
</tr>
<tr>
<td>END CODE</td>
</tr>
</tbody>
</table>
**POTS phenotypes**

We model the hyperadrenergic, neuropathic, and hypovolemic phenotypes of POTS suggested by [Mar20] by adjusting parameters (listed in Table 7.4) reflecting hypothesized pathophysiology.

**Hyperadrenergic POTS**

is characterized by high levels of circulating norepinephrine during postural change, allowing the sympathetic nervous system to respond more to BP changes. To simulate this, at the HUT onset, we further increase parameters associated with sympathetic response, including \( P_{2H} \) and \( k_H, k_E, k_R \).

**Neuropathic POTS**

is caused by partial neuropathy of the lower body vasculature, which causes abnormal blood pooling in the lower extremities. To simulate this, we decrease the control for the lower body resistance by reducing \( R_{lbM} \) and \( R_{lbm} \) after HUT.

**Hypovolemic POTS**

is obtained by decreasing the total blood volume. In our model, blood volume is calculated as a function of BMI (equation (7.15)). Simulations are conducted by changing BMI from 28 (large blood volume ~4,500 mL for an overweight young female) to 19 (representing an underweight young female, blood volume ~3,500 mL). The latter corresponds to the hypovolemic patient group discussed by Mar and Raj [Mar20]. A low blood volume alone does not compromise the baroreflex and therefore only represents a POTS phenotype if the patient is experiencing POTS symptoms. Many POTS patients with severe symptoms are young skinny females. Therefore, in addition to investigating the isolated effect of low blood volume, we study how changes in blood volume affect hyperadrenergic and neuropathic POTS patients.

To allow for a smooth parameter transition during HUT, we include a 10-second delayed onset, i.e., we let

\[
    x = \begin{cases} 
    x_0 & t < t_{HUT} + 10, \\
    (x_1 - x_0)\frac{(t-t_{HUT}-10)^d}{(t-t_{HUT}+10)^d+5^d} + x_0 & t \geq t_{HUT} + 10, 
    \end{cases}
\]

where \( x \) is the parameter being changed after HUT, \( x_0 \) is the value during rest, \( x_1 \) is the value of the parameter that is being transitioned to and \( t_{HUT} \) is the time of the HUT onset.

**7.3 Results**

Results demonstrate the emergence of low-frequency oscillations at rest and during HUT and how the phenotypes proposed by Mar and Raj [Mar20] can be simulated.
Table 7.4 Values of selected parameters before and after head-up tilt for phenotype simulations. Parameters are as follows: \(C_{au}\) - upper arterial compliance, \(P_{2H}\) - half saturation value for heart rate control, \(k_H\) - Hill coefficient for heart rate control, \(k_R\) - Hill coefficient for resistance control, \(k_E\) - Hill coefficient for left heart end diastolic elastance control, \(R_{lpM}\) - maximum value of resistance control, \(R_{lpm}\) - minimum value of resistance control.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Parameter</th>
<th>Value before tilt</th>
<th>Value after tilt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>(C_{au})</td>
<td>1.7 mL/mmHg</td>
<td>0.86 mL/mmHg</td>
</tr>
<tr>
<td></td>
<td>(P_{2H})</td>
<td>88 mmHg</td>
<td>87 mmHg</td>
</tr>
<tr>
<td></td>
<td>(k_H)</td>
<td>24 N.D.</td>
<td>34 N.D.</td>
</tr>
<tr>
<td>Hyperadrenergic</td>
<td>(k_R)</td>
<td>23 N.D.</td>
<td>32 N.D.</td>
</tr>
<tr>
<td></td>
<td>(k_E)</td>
<td>7 N.D.</td>
<td>10 N.D.</td>
</tr>
<tr>
<td></td>
<td>(P_{2H})</td>
<td>88.5 mmHg</td>
<td>89.8 mmHg</td>
</tr>
<tr>
<td></td>
<td>(C_{au})</td>
<td>1.7 mL/mmHg</td>
<td>0.86 mL/mmHg</td>
</tr>
<tr>
<td></td>
<td>(R_{lpM})</td>
<td>4.5 mmHg·s/mL</td>
<td>2.9 mmHg·s/mL</td>
</tr>
<tr>
<td>Neuropathic</td>
<td>(R_{lpm})</td>
<td>0.30 mmHg·s/mL</td>
<td>0.19 mmHg·s/mL</td>
</tr>
<tr>
<td></td>
<td>(C_{au})</td>
<td>1.72 mL/mmHg</td>
<td>0.86 mL/mmHg</td>
</tr>
</tbody>
</table>

7.3.1 Low-frequency oscillations

Our model, shown in Figure 7.1, can generate \(\sim 0.1\) Hz heart rate \((\dot{H})\) and blood pressure \((P_{au})\) oscillations observed in patient data [Ged20a]. The amplitude and frequency of the oscillations can be modulated by varying the model parameters in the baroreflex control equations \((7.11-7.13)\), including the maximum \(X_M\) and minimum \(X_m\) response, the time-constants \(\tau_X\), the half-saturation values \(P_{2X}\), and the Hill-coefficients \(k_X, X = H, R, E\).

**Oscillation frequency**

is primarily determined by time-constants \((\tau_X)\) differentiating the parasympathetic and sympathetic control. Efferent responses mediated by the parasympathetic system are significantly faster than those transmitted via the sympathetic system [Bor12], i.e., \(\tau_H \ll \tau_R = \tau_E\). The \(\sim 0.1\) Hz frequency was achieved using time-constants reported in Table A.2. The Hill coefficients \((k_X)\) also affect frequency but to a lesser extent than \(\tau_X\).

**Oscillation amplitude**

can be modulated by changing \(k_X, P_{2X}\) and \(X_M - X_m, X = H, R, E\). We studied the effect of varying all parameters over their physiological range. Results (summarized in Table 7.5) show that \(k_X, X = H, R, E\) impact the oscillation amplitude, with \(k_H\) being the most influential parameter. Increasing the Hill-coefficients \(k_X\) increases the sensitivity of the baroreflex control. A larger value of \(k_X\) gives a steeper Hill function (shown in Figure 7.3), i.e., the change in pressure needed to generate a given response decreases. Shifting the Hill function by changing the half-saturation value \((P_{2X})\) causes the operating regime to change to a steeper portion of the Hill function. This shift has the same effect as increasing \(k_X\) but has a much smaller effect on the oscillation amplitude.
Figure 7.5(a) (top panels) shows HR and BP dynamics in response to increasing $k_H$. We depict results of changing $k_H$, the most influential parameter, but similar results (not shown) are obtained when increasing $k_R$ and $k_E$, controlled by the sympathetic system. Results in Figure 7.5(a) show small oscillations (left), medium oscillations that are approximately the size found in POTS patients (middle), and large oscillations, not likely to be observed in actual patients (right). For $k_H < 6$, the system does not oscillate, at $k_H \approx 6$, oscillations emerge, and their amplitude increases with increasing values of $k_H$. Figure 7.5(b) depicts the change in amplitude and frequency as a function of $k_H$. Changing $k_X$, $X = H, R, E$ impacts the oscillation amplitude more than frequency. The frequency almost doubles (from 0.06 to 0.11 Hz) while the HR oscillation amplitude increases from $\approx 0$ to 0.3. The frequency diagrams in Figure 7.5(b) (right column) have two characteristic features, a broad distribution (vertical spread) and horizontal stripes with white spacing. The former results from noise, added to HR, to account for heart rate variability and the latter from the frequency resolution. The model is solved with a time-step of 0.01 s, with the Fourier transform calculated over a 200 s interval, giving a frequency resolution of 0.005 Hz.

As noted above, $k_H$ has the most significant impact on the system dynamics. Both the sympathetic and parasympathetic systems control HR, but as noted in the introduction, POTS may result from the expression of specific agonistic antibodies binding to $\beta_1$ and $\beta_2$ receptors [Mar20]. Since these are found on pacemaker cells modulating HR and smooth muscle cells in the vasculature, we study the response to changing $k_H$ and $k_R$. Results shown in Figures 7.6(a) and 7.6(b) reveal that increasing either $k_H$ or $k_R$ increases the amplitude of oscillations. This result agrees with the hypothesis that POTS patients have a more sensitive control system.

Other model parameters also change the dynamic behavior - but not as significant as changes in $k_X$ (specifically $k_H$). In general, the half-saturation value offsets the control at different pressure levels but does not change the sensitivity, as the slope of the sigmoidal curve remains the same. Changing the range $\Delta X = X_M - X_m$ changes the width and steepness of the curve; the latter does have some effect on sensitivity, but it is not as significant as the effect observed when increasing $k_X$. Table 7.5 lists the impact of changing each parameter on HR and BP.

Lastly, Figures 7.7(a) and 7.7(b) show the effects of blood volume and $k_H$ on low-frequency oscillations. We see that, as before, larger values of $k_H$ result in larger oscillations. We also note that lower values of total blood volume contribute to larger low-frequency oscillations during rest and HUT.

### 7.3.2 Head-up tilt (HUT)

During HUT (shown in Figure 7.2), gravity pools blood from the upper to the lower body, stimulating the autonomic nervous system. The result is a shift in blood volume and pressure, increasing in compartments below the center of gravity and decreasing in compartments above. In our model, the upper body compartments are centered around the carotid baroreceptors, while the lower body compartments are centered in the lower part of the torso. Representative model BP predictions in all compartments are shown in Figure 7.8. We note that after HUT, the pressure in the lower compartments increases while pressure in the upper compartments decreases. These simulations were generated with $k_H = 27$, which
Table 7.5 Effects on heart rate ($H$) and upper arterial blood pressure ($P_{au}$) when increasing stated parameter.

<table>
<thead>
<tr>
<th>Increased Parameter</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_H$</td>
<td>Increases $H$ &amp; $P_{au}$ oscillation amplitude</td>
</tr>
<tr>
<td>$k_R$</td>
<td>Increases $H$ &amp; $P_{au}$ oscillation amplitude</td>
</tr>
<tr>
<td>$k_E$</td>
<td>Increases $H$ &amp; $P_{au}$ oscillation amplitude</td>
</tr>
<tr>
<td>$P_{2H}$</td>
<td>Increases $H$, increases diastolic $P_{au}$</td>
</tr>
<tr>
<td>$P_{2R}$</td>
<td>Decreases $H$, increases $P_{au}$</td>
</tr>
<tr>
<td>$P_{2E}$</td>
<td>Decreases $H$, increases $H$ &amp; $P_{au}$ oscillation amplitude</td>
</tr>
<tr>
<td>$H_M - H_m$</td>
<td>Increases $H$ &amp; $P_{au}$ oscillation amplitude</td>
</tr>
<tr>
<td>$R_M - R_m$</td>
<td>Increases $H$ &amp; $P_{au}$ oscillation amplitude</td>
</tr>
<tr>
<td>$E_{DM} - E_{Dm}$</td>
<td>Increases $H$ &amp; $P_{au}$ oscillation amplitude</td>
</tr>
</tbody>
</table>

causes the system to oscillate at rest and after HUT. Without changing parameters, oscillations dampen after HUT due to volume redistribution.

Like rest, control parameters impact predicted dynamics, and $k_H$ remains the most influential parameter. Figures 7.6(a) (bottom row) shows oscillation amplitude as a function of $k_R$ and $k_H$ without noise. For these simulations, the "non-oscillatory" region appears striped, indicating bands of oscillations alternating with no oscillations. Figure 7.6(c) shows selected time-series predictions for parameter values marked on Figure 7.6(a). We note that in the non-oscillatory region, it is possible to increase $k_H$ and eliminate oscillations. These stripes are a result of the on-off behavior of emerging low-frequency oscillations. Mathematically, this behavior is common; as we change $k_R$ or $k_H$ the system undergoes repeated Hopf bifurcations. However, physiologically, small changes in a parameter have not been reported to affect the frequency response significantly. By adding noise mimicking heart rate variability (HRV) to the model, this behavior disappears (the striped pattern disappears, see Figure 7.6(b)), suggesting that the presence of HRV stabilizes the system response, as can be seen in Figures 7.6(b) and 7.6(d).

7.3.3 POTS phenotypes

Previous studies [Fed19; Mar20] suggest that POTS patients can be separated into neuropathic, hyperadrenergic, and hypovolemic phenotypes. This section discusses how each of these can be represented in our model. The phenotype encoding is based on the assumption that the cardiovascular system of POTS patients changes in response to a postural change. For this reason, select parameters change after HUT to recreate dynamics. Depending on the phenotype, we select which parameters to change. We decrease the upper body arterial compliance for all simulations to account for volume redistribution upon HUT. The values of the changed parameters before and after HUT can be seen in Table 7.4.
Figure 7.5 (a) From left to right: heart rate (H, top) and upper arterial pressure (Pau, bottom) predictions for $k_H = 10, 20, \text{ and } 30$. Note, the large amplitude oscillations in the right panel are higher than values observed in patient data but are included to illustrate the behavior of the model. (b) From left to right: maximum and minimum values for varying values of $k_H$, the amplitude of the $\sim0.1$ Hz region response, and frequency of oscillations. Enlarged red dotes show denote measurements corresponding to $k_H = 10, 20, 30$.

Control

subjects show a limited increase in HR and similar amplitudes of oscillations before and after HUT. When volume is redistributed during HUT, the baroreflex control operating regime is shifted due to upper arterial pressure decreasing. To avoid an increase in HR, we shift the HR response curve with the pressure by reducing $P_{2H}$. Simulation of a control subject can be seen with data in the left column of Figure 7.9.
Hyperadrenergic POTS

patients have increased levels of plasma norepinephrine during HUT [Mar20]. We model this by increasing \( k_i, i = H, E, R \) and \( P_{2H} \) during HUT. Results, depicted in Figure 7.9 (top row center), show that increasing these parameters increases the amplitude of the \( \sim 0.1 \) Hz oscillations (compared to the control subject - top left) and causes tachycardia during HUT, which is consistent with POTS patient data.
Figure 7.7 Two-dimensional parameter analysis of blood volume (BV) vs $k_H$. (a) Amplitudes of peak heart rate ($H$) oscillation (left) and peak upper arterial blood pressure ($P_{au}$) oscillation (right) at the $\sim 0.1$ Hz frequency band for values of BV and $k_H$ at rest (top) and head-up tilt (HUT, bottom). (b) The same information as (a) but with 2% noise. Average measurements from data [Ged20a] are marked for control patients at rest (CR), and POTS patients during head-up tilt (PH).

Figure 7.8 Results of simulation with HUT at $t = 75$. Row 1: heart rate, $H$ (bps), left ventricle pressure, $P_{lv}$ (mmHg) row 2: upper arterial pressure, $P_{au}$ (mmHg), lower arterial pressure, $P_{al}$ (mmHg) row 3: upper venous pressure, $P_{vu}$ (mmHg), lower venous pressure, $P_{vl}$ (mmHg).

Neuropathic POTS

patients experience excessive blood pooling below the thorax during HUT due to partial autonomic neuropathy. This condition is simulated by decreasing the range of resistance control in the lower body
arteries, i.e., we reduce $R_{a1p,M}$ and $R_{a1p,m}$ making this control less effective. Results from this simulation depicted in Figure 7.9 top right show that subjects exhibit tachycardia but that oscillations are dampened after HUT onset.

**Hypovolemia**

To understand how hypovolemia impacts our predictions, we reduce central blood volume by lowering the BMI. We found that hypovolemia alone cannot reproduce POTS dynamics - the model predicts low tachycardia values and no oscillations. This may be because our model cannot distinguish between healthy patients with low blood volume, who do not experience tachycardia, and POTS patients. Figure 7.9, bottom row, shows that HR is lower than in patients with a normal blood volume. However, for hyperadrenergic POTS patients, the HR and BP oscillations amplitude increase significantly, indicating that this patient group may experience a more severe response to POTS. To study this phenomenon further, we conducted a two-dimensional analysis examining the amplitude of HR and BP oscillations as a function of blood volume (BV) at rest and during HUT.

Figures 7.7(a) and 7.7(b) (top row) show that reducing blood volume at rest does not impact dynamics. However, as can be seen in the bottom row of Figures 7.7(a) and 7.7(b), reducing blood volume during HUT increases oscillation amplitude. This implies that more severe oscillations occur during HUT for patients with less blood volume. Similar to Figure 7.6, Hopf bifurcation lines can be seen in the parameter space in Figure 7.7(a) but are removed when noise is added to simulations representing heart rate variability as can be seen in Figure 7.7(b).

### 7.4 Discussion

This study developed a closed-loop baroreflex cardiovascular model and used simple signal processing to extract the frequency and amplitude of HR and BP oscillations. Results show that our model can generate oscillations in the low-frequency ($\sim 0.1$ Hz) range observed in control and POTS patients at rest and during head-up tilt (HUT) and that oscillations can be manipulated by modulating parameters associated with the baroreflex.

Our model can predict tachycardia (an increase in HR of at least 30 bpm, 40 bpm in adolescents) observed in POTS patients by increasing the half-saturation of the HR response ($P_{2H}$) or decreasing the maximum and minimum vascular resistance ($R_{1pM}$ and $R_{1pM}$). The former is significantly more effective than the latter. Moreover, by changing physiologically relevant baroreflex parameters after HUT, we can reproduce the hyperadrenergic and neuropathic POTS phenotypes suggested by [Fed19; Mar20]. Finally, we found that predictions are highly sensitive to changes in blood volume, suggesting that patients with low BMI, and low blood volume, may experience a more severe reaction than subjects with a healthy BMI and normal blood volume.
Figure 7.9 Characteristic data for a control and hyperadrenergic POTS patient (black) and model predictions (red and green) of heart rate ($H$), carotid artery blood pressure ($P_c$), and mean pressure. Simulations with 4,500 mL of blood are in the top row with simulations with 3500 mL of blood in the bottom row. $C_{au}$ is decreased after HUT for all simulations to represent constriction of vasculature upon HUT. In control $P_{2H}$ is decreased (left), $k_H$ and $P_{2H}$ are increased after HUT to replicate hyperadrenergic POTS (middle) and $k_H$ increased, $R_{lpM}$ and $R_{lpm}$ decreased to replicate neuropathic POTS (right). To compare model predictions $H$ data is scaled such that the baseline is 1 bps and blood pressure vary from 80 to 120 mmHg.

7.4.1 Low-frequency oscillations

The mathematical model used here extends previous studies [DeB87; Wil14; Mat15; Hel00; Urs98; Mar18; Urs00] predicting cardiovascular dynamics using a closed-loop lumped parameter model including the left heart, the upper and lower body systemic arteries, and veins. The latter is included to facilitate the redistribution of volume upon postural change. The baroreflex is modeled using a first-order control equation predicting the controlled quantity as a function of pressure using a sigmoidal function enforcing saturation at both high and low values of the controlled parameter.

By modulating parameters associated with the baroreflex sensitivity (the sigmoidal $k_X, X = R, E, H$), we explain the emergence and amplification of the low-frequency oscillations at rest and during HUT. Our findings agree with those reported in our previous study [Ged20a], noting that the low-frequency oscillations (sometimes referred to as Mayer waves) are observed in all subjects and that the oscillation amplitude is increased in POTS patients in particular following HUT. Our findings also agree with previous experimental studies that report more significant low-frequency oscillations in cerebral blood flow [Ste15; Med14].

While this phenomenon has been discussed in studies using signal processing to examine HR and BP time-series, only a few studies by Ottesen et al. [Ott97], and Ishbulatov et al. [Ish20] used closed loop modeling to replicate this phenomenon. Both these studies explained the emergence of oscillations by
introducing a delay in sympathetic response. In contrast, our model predicts the emergence of the \(~0.1\) Hz oscillatory response without introducing delay differential equations. A key observation of this study is that oscillations can emerge for specific regions of the parameter space using only Hill functions for baroreflex control and that oscillations do not rely on an explicit time delay. These findings agree with the hypothesis that POTS patients may have an abnormally sensitive baroreflex control supporting the hypothesis that POTS is a central nervous system disorder. Specifically, we observed that \(k_H\) is the most influential parameter for the oscillation amplitude. At \(k_H < k_{critical}\), the system does not oscillate, but as \(k_H\) increases, oscillations emerge via a Hopf bifurcation. In addition, we found that the baroreflex time-constants modulate the oscillation frequency.

To better understand how key physiological parameters modulate oscillation amplitude, we conducted a 2-dimensional parameter analysis. Figure 7.6 shows that increased peripheral resistance and HR response sensitivities \((k_R, k_H)\) increase oscillation amplitude during rest and HUT. We see in Figure 7.6 that increased blood volume decreases oscillation during HUT. This agrees with clinical insights from Klinik Mehlsen, Frederiksberg, Denmark that patients with smaller blood volume have more pronounced POTS symptoms.

### 7.4.2 Head-up tilt (HUT)

Head-up tilt test is useful for diagnosing POTS [Bry19]. For a patient tilted head up, gravity pools blood in the lower body. Since no active muscle contraction is invoked, this passive test clearly depicts the neural response to blood volume redistribution. Mathematically, we predict the tilt by accounting for the gravitational pooling of blood in the lower body as a function of the tilt angle.

A few modeling studies [Wil14; Hel00; Ish20] have examined the response to HUT. Williams et al. [Wil14] used an open-loop patient-specific model to predict arterial BP using HR as an input, while Heldt et al. [Hel00] used a closed-loop cardiovascular model with set-point representations of the baroreflex simulating HUT by increasing pressures in venous compartments, and Ishbulatov et al. [Ish20] simulate HUT by increasing pressure to the lower body arteries and internal organs. The study by Williams et al. [Wil14] did not examine low-frequency oscillations, and in the study by Heldt et al. [Hel00] the low-frequency oscillations were dampened in less than one minute after the onset of HUT, Ishbulatov et al. [Ish20] successfully recreated low-frequency oscillations after HUT but only considered healthy subjects. While these studies were able to predict the HUT response, our model is the only one that can generate closed-loop stable oscillations that agrees with POTS patient data.

Specifically, we observe that low-frequency oscillations exist and persist during HUT. However, to get adequate pulse pressure and oscillation amplitude, it is necessary to decrease upper arterial compliance to account for the constriction of vasculature upon HUT. We hypothesize that this impact can be explained by pressure and volume redistribution. We allow select parameters to change after HUT to duplicate patient data depending on the POTS phenotype appropriately.

Our studies assume that the table is tilted up at a constant speed mimicking standard clinical protocols. However, as reported in several recent studies examining tipping points [Ash17], and in the study by Kamiya et al. [Kam09], the tilt speed may impact the emergence and amplitude of oscillations.
This topic should be explored in detail in future modeling and experimental studies.

### 7.4.3 POTS phenotypes

POTS pathophysiology is complex and not completely understood. Several recent studies [Fed19; Mar20; Bry19] speculate that POTS comprise multiple phenotypes including hyperadrenergic, neuropathic, and hypovolemic POTS. Several hypotheses describing each phenotype have been put forward without clearly denoting how these manifest changes in HR and BP time-series. Hyperadrenergic POTS is believed to result from increased levels of circulating norepinephrine, while patients with neuropathic POTS have partial neuropathy in lower vascular beds. Finally, hypovolemic POTS is simply described as POTS in patients with low blood volume. Additionally, autoantibodies against $\beta_1, \beta_2, \alpha_1, M_1, M_2$ receptors may be responsible for some cases of POTS [Fed19; Fed17a].

In addition to analyzing oscillations, we simulate the two main phenotypes and study how BP and HR change in patients with normal and low blood volume. To predict hyperadrenergic POTS, we increase $P_{2H}$ and $k_X, X = H, E, R$ after HUT representing the increased plasma norepinephrine concentration during HUT. In the neuropathic case, we decrease the maximum and minimum response of the lower peripheral resistance ($R_{lpM}, R_{lpm}$) to represent neuropathy in lower extremities [Bry19]. We observe that increasing $P_{2H}$ in the hyperadrenergic case and reducing $R_{lpM}, R_{lpm}$ in the neuropathic case are essential to the presence of orthostatic tachycardia while increasing $k_X, X = H, E, R$ in the hyperadrenergic case is vital to the amplitude of low-frequency oscillations. Figure 7.9 shows minimal oscillations in the neuropathic phenotype. This motivates future work to examine whether all POTS phenotypes exhibit increased low-frequency oscillations in HR and BP or if large oscillations are unique to the hyperadrenergic phenotype.

We could not reproduce the dynamics observed in POTS patient data by decreasing blood volume alone, likely because the model cannot distinguish POTS patients from healthy patients with a low blood volume. Figure 7.9 shows that low blood volume does not produce POTS dynamics from a control simulation but can make POTS dynamics more pronounced in simulations where the dynamics are already present. However, Figure 7.7 shows that lower blood volume can result in larger oscillations during HUT. These findings imply that hypovolemia may not be a distinct phenotype but exacerbates other phenotypes. More work is needed to study the effect of hypovolemia, e.g., by introducing blood withdrawal or dehydration.

### 7.4.4 Heart rate variability (HRV)

Several previous studies [Gol91; Sha17; Li19] have addressed the importance of heart rate variability. While there is still discussion on the origin of short-term heart rate variability [Sha17], the net effect appears as noise. This study accounted for heart rate variability by adding noise to the predicted HR. The addition of heart rate variability stabilizes predictions eliminating frequent Hopf bifurcation lines seen in the top row of Figures 7.6 and 7.7. The benefits of added noise in dynamic systems with stable fixed points have been shown in [Bre90].
7.4.5 Importance of the study

This is the first study that uses a closed-loop model of the baroreflex response to explain the emergence of low-frequency HR and BP oscillations observed in both control and POTS patients, along with the increase in amplitude observed in POTS patients during HUT. The presented model is the first attempt at representing the phenotypes of POTS using a mechanistic framework. Our results advance previous results [Hel00; Ham05; Ish20] by describing oscillations during HUT with amplitudes consistent with POTS.

The clinical significance of this model is that this model can encode the POTS phenotypes. Therefore, our study provides support for the current hypothesized mechanisms of POTS. We were able to show that hypovolemia contributes to more severe oscillations, which could be linked to more severe symptoms when combined with the other phenotypes. However, we could not recreate POTS dynamics by decreasing blood volume alone. We also observed that the neuropathic phenotype resulted in tachycardia upon HUT but not increased oscillations. We successfully recreated observed dynamics by encoding the hyperadrenergic phenotypes into the model.

7.4.6 Limitations

Limitations of this work include the oversimplification of the vascular and baroreflex model. The vascular model only includes the systemic circulation and separates the body into an upper and lower body compartment. This is not anatomically correct, as the body is a continuous cylinder; however, this assumption allows us to approximate blood flow in a simplified manner. The baroreflex forms a complex negative feedback loop with numerous components, including the baroreceptors, afferent nerves, the nucleus tractus solitarius (NTS) located in the medulla oblongata, efferent nerves, and the actual cell response in the sinoatrial node as well as muscle cells. Lumping these components into four control equations is a large assumption but is done to show that oscillations can be produced even with a simple model.

Another component not accounted for is respiration, which modulates blood pressure directly by changing tissue pressure in the thorax [Ott00] and indirectly via the respiratory sinus arrhythmia [Ran19] modulating parasympathetic signal. The former adds a ~0.2 Hz oscillation in blood pressure and heart rate. The latter augments parasympathetic feedback adding a similar frequency component. As mentioned above, the model incorporates these features, but given the frequency separation, we do not anticipate they alter the principal results reported here addressing emergence and augmentation of ~0.1 Hz oscillations. This model aims to provide a simple mathematical formulation to explore the possible origins of POTS. However, more intricate models accurately representing the actual physiology are needed for further exploration.

This study simulated heart rate variability by adding white noise to predictions of heart rate at a magnitude informed by data. Adding white noise allowed us to stabilize predictions, but more work is needed to investigate if HRV can be represented by white noise. As suggested by [Gol02], it may be more appropriate to present HRV with pink noise.
Furthermore, we cannot predict the drop in arterial blood pressure immediately after HUT as observed in the data, which is most likely due to the contraction of abdominal muscles and partly a result of the Valsalva maneuver as a reflex activity during positional changes. We also note that the data shown is exemplary and did not attempt to estimate parameters based on this data. This oversimplification hinders the model in predicting the precise hypotheses of the origin of POTS, such as the exact type of hyperadrenergic antibodies. Finally, since we did not include a delay, we could not recreate the phase differences seen in [Ged20a], which are an essential difference between POTS and control patients.

The model studied here only includes basic mechanisms necessary to justify the emergence of $\sim 0.1$ Hz oscillations. Future studies should determine if $\sim 0.1$ Hz oscillations differ among phenotypes and test if it is possible to devise a more detailed cell-based model explaining the phenomenon. In addition, our model has the potential to be integrated with models modulating the systems at other frequencies, e.g., respiration, ultradian, circadian, or infradian rhythms, and it could be adapted to examine the response in patients exposed to different environments, e.g., high concentrations of carbon monoxide, or an injection of nitric oxide. Future work will contain a more in-depth description of the baroreflex to replicate these phenomena.

The inability of hypovolemia to cause tachycardia and oscillations may suggest that hypovolemia is not a distinct POTS phenotype. But it could also indicate that the proposed model needs more details or that we need another approach to model blood loss. E.g., effort should be put into exploring the effect of changes in stressed vs. unstressed volume or the relationship between blood volume and cardiac output. Moreover, the model is mechanistic and therefore does not have a parameter specifying some other symptoms that POTS patients experience, such as fatigue, lightheadedness, and brain fog. These symptoms can only be incorporated via changes in the control system.

### 7.5 Conclusions

We have presented a closed-loop differential equation model of the interactions between the baroreflex and cardiovascular system, emphasizing the emergence and amplitude of oscillations in the $\sim 0.1$ Hz frequency range. We have concluded that the HR and peripheral resistance response, represented by Hill coefficients $k_H$ and $k_R$ respectively, and total blood volume are critical to the amplitude of low-frequency oscillations while $P_{2H}, R_{lpM}$ and $R_{lpM}$ are essential to orthostatic tachycardia. Results shared here help explain clinical observations and motivate further modeling and study of POTS to understand better the disease's pathophysiological aspects and possible treatment options.

### Acknowledgment

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CHAPTER

8

MODELING THE ROLE OF ADRENERGIC AUTOANTIBODIES IN POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME (POTS)

8.1 Introduction

Postural Orthostatic Tachycardia Syndrome (POTS) affects at least 500,000 people in the United States alone [Gru08a], most of which are young females [Sha19]. The syndrome is characterized by an increase in heart rate (HR) of more than 30 beats per minute ($\geq$ 40 bpm in patients 19 years old and younger) [Fed19] upon an upright postural change. Recent studies have also shown abnormal low-frequency oscillation behavior in POTS patient HR and BP data [Ged20a; Med14; Ste15]. In addition, to receive a positive diagnosis of POTS, patients must have a history of chronic (for more than 6 months) orthostatic intolerance, an absence of orthostatic hypotension (defined as a decrease of more than 20 mmHg upon an upright postural change), and not be affected by any other condition that would provoke sinus tachycardia [Fed19]. The common symptoms of POTS include dizziness, exercise intolerance, brain fog, and headaches [Fed19; Sha19], which can significantly decrease the quality of life for patients with POTS.

The etiology of POTS is unclear. However, there are three commonly proposed mechanisms, known as phenotypes (discussed in-depth in Chapter 3): hyperadrenergic, neuropathic, and hypovolemic
POTS, which are discussed in [Fed19; Mar20; Gru08a; Bry19] and modeled in [Ged22]. Recent works have suggested that POTS could also be an autoimmune syndrome due to the discovery of agonistic autoantibodies against the $\beta_{1,2}$ receptors in POTS patients [Li14; Fed17a; GI19]. This hypothesis agrees with the notion that POTS often appears after an acute viral illness, vaccines, or a stressful event such as childbirth [Fed19]. In addition, symptoms of “long-COVID” syndrome align with the symptoms of POTS, suggesting a possible connection between POTS and COVID-19 [Raj21; Gol21]. It is not clear whether the presence of autoantibodies can cause POTS in isolation from other phenotypes, or if they enhance the effects of accompanying phenotypes.

To explore POTS etiology, some studies have examined the origin of the other symptoms besides tachycardia. For example, our previous study [Ged20a] uses nonstationary signal processing to quantify HR and blood pressure (BP) oscillations in the low-frequency range ($\sim$0.1 Hz) during rest and in response to postural change imposed by a head-up tilt (HUT) test. We found that POTS patients have larger HR and BP low-frequency oscillations during HUT than control subjects. These findings agree with Stewart et al. [Med14; Ste15], who measured low-frequency oscillations in cerebral blood flow during HUT. Large oscillations in cerebral blood flow have been shown to be associated with reduced cognitive performance in POTS patients, which could explain symptoms such as brain fog and fatigue due to insufficient cerebral flow [Ste15]. While these studies derive markers that can assist with diagnosis and explain some symptoms, they do not offer an explanation for the compromised mechanisms causing POTS.

To study POTS, we seek to derive a model that displays both postural tachycardia and low-frequency oscillations. Several studies have predicted low-frequency HR and BP oscillations. The model by Heldt et al. [Hel00] produced low-frequency oscillations in astronauts that underwent a sit-to-stand test, but the oscillations did not continue after the transition. Hammer and Saul [Ham05] used a feedback control model to study the stability of fixed points for the baroreflex but did not investigate how the system responds in the time domain. Ishbulatov et al. [Ish20] used a closed-loop baroreflex model with an explicit sympathetic delay to predict low-frequency oscillations in response to a HUT maneuver; however, they did not specifically study POTS. The models put forth in [Ish20; Ham05] did not consider abnormal physiology. The study of astronauts in [Hel00] examines altered autonomic control; however, only one of the proposed causes of the orthostatic intolerance studied mirrors a potential cause of POTS. Geddes et al. [Ged22] used a closed-loop baroreflex with separate time-scales for baroreflex control and a cardiovascular model to predict oscillations that occur in POTS patients during a HUT test. While they successfully represented the three common phenotypes of POTS, they do not explicitly model the recent finding that some POTS patients express specific agonistic autoantibodies.

We hypothesize that the presence of adrenergic agonistic autoantibodies in POTS patients is sufficient to predict postural tachycardia and increased amplitude of low-frequency oscillations, thereby causing POTS dynamics. To shed more light on what causes these symptoms, we develop a multiscale mechanistic model that describes the effects of agonistic autoantibodies on the cardiovascular system and its control. To our knowledge, no previous study has attempted to accomplish this. The results of this study give insight into the etiology of POTS, provide target systems to improve treatments for
patients with agonistic adrenergic autoantibodies, and motivate further research into the autoimmune contribution to POTS.

8.2 Methods

8.2.1 Model Development

To model the cardiovascular system and its control, we include three components: a closed-loop cardiovascular systems-level model, a baroreflex control model, and a sinoatrial node cell model. As shown in Figure 8.1, the cardiovascular system is modeled using a 0D compartmental model predicting flow, pressure, and volume in the left heart, systemic arteries, and veins. The baroreflex model predicts afferent firing as a function of carotid blood pressure. This signal is integrated into the nucleus solitary tract (NTS), from which efferent sympathetic and parasympathetic signals are transmitted to effector organs, including the heart, vasculature, and the sinoatrial node cell. The sinoatrial node responds to these signals by modulating the frequency of action potential generation, which controls the pacing of the heart. Below we describe each submodel, followed by a discussion of model integration. A table of parameters (Appendix B.1) and all equations (Appendix B.2) for the presented model are given in Appendix B.

8.2.2 Circulation

To predict flow, pressure, and blood volume in the cardiovascular system, we use a 5-compartment model [Ged22] representing the upper body arteries (au), lower body arteries (al), upper body veins (vu), and the lower body veins (vl), and the left heart (lh). This model does not include the pulmonary circulation and the right heart. This simplification is adequate for the study presented here since POTS is not thought to affect pulmonary circulation. This model can be presented as a system of differential equations conserving volume (V(t), mL) of the form

\[ \frac{dV}{dt} = Q_{in} - Q_{out}, \]

where flow (Q(t), mL/s) is related to pressure (P(t), mmHg) using Ohm’s law,

\[ Q_i = \frac{P_{i-1} - P_i}{R_i}, \quad (8.1) \]

where \( P_{i-1} \) and \( P_i \) (mmHg) denote pressure in compartments on either side of the resistor, \( R_i \) (mmHg s/mL). The pressure and volume in the upper body arteries and veins and lower body arteries are related linearly, giving

\[ P_i - P_{ui} = \frac{V_i - V_{ui}}{C_i}, \quad (8.2) \]

with \( P_{ui} \) (mmHg) denoting unstressed pressure, \( V_{ui} \) (mL) the associated unstressed volume, and \( C_i \) (mL/mmHg) is the compliance of the compartment. To account for changes in compliance as volume
Figure 8.1 Hemodynamics is controlled by the baroreflex system, which senses changes in the carotid sinus baroreceptors. Afferent signals from baroreceptor neurons are integrated into the brain and transmitted via sympathetic and parasympathetic neurons, which influence the concentrations of norepinephrine (NE) and acetylcholine (ACh). Concentrations of NE affect heart contractility and vasculature, and in addition to ACh, affect the concentration of cAMP inside the sinoatrial node (SAN). The membrane potential of the SAN is responsible for the time at which time-varying elastance function contracts, simulating a heartbeat. The systemic circulation is represented by compartments lumping upper (a_u) and lower (a_l) body arteries, upper (v_u) and lower (v_l) body veins, and the left heart (l_h). Flow (Q) through the aortic valve (a_v) is transported from the left heart to the upper body arteries, and from here, it is transported in the arteries (a) to the lower body arteries and through the upper body peripheral vasculature (u_p) to the upper body veins. A parallel connection transports flow through the lower body peripheral vasculature (l_p). From the lower body, venous flow (v) is transported to the upper body veins and finally via the mitral valve (m_v) back to the left heart. Each compartment representing the heart or a collection of arteries or veins has pressure (P), volume (V), and compliance (C).

Increases in the lower body veins (as discussed in Chapter 2), in particular after HUT, the lower venous pressure-volume relationship is of the form

$$P_{vl} - P_{uvl} = \frac{1}{m_{vl}} \log \left( \frac{V_{Mvl} - V_{uvl}}{V_{Mvl} - V_{vl}} \right),$$

(8.3)
where \( V_{vl} \) (mL) is the maximal volume, \( V_{u} \) (mL) is the unstressed volume, and \( m_{vl} \) (1/mmHg) relates nominal pressure and volume with maximal volume.

We use a time-varying elastance function to model heart contraction as

\[
E_{lh}(\gamma) = \begin{cases} 
\frac{E_S - E_D}{2} \left( 1 - \cos \left( \frac{\pi \gamma \gamma}{T_{S}} \right) \right) + E_D & 0 \leq \gamma \leq T_S \\
\frac{E_S - E_D}{2} \left( \cos \left( \pi (\gamma - T_S) \right) + 1 \right) + E_D & T_S \leq \gamma \leq T_S + T_D \\
E_D & T_S + T_D \leq \gamma \leq T,
\end{cases}
\]

(8.4)

where \( \gamma \) (s) is the time since the start of heart contraction, \( E_S \) (mmHg/mL) and \( E_D \) (mmHg/mL) are the end-systolic and end-diastolic elastance, \( T_S \) (s) is the time for end-systole and \( T_D \) (s) is the time for end-diastole. The prevent reserve flow due to heart contraction, we model the one-way valves in the left ventricle (mitral and aortic valves) as diodes. Opening and closing of the valves are driven by pressure, i.e.

\[
Q_i = \begin{cases} 
\frac{p_i - p_i}{h_i} & p_i > p_i, \text{ valve open}, \\
0 & p_i - p_i \leq p_i, \text{ valve closed}.
\end{cases}
\]

During head-up tilt, gravity applies force on the flows from the upper to lower body arteries and veins \( (Q_a) \) and veins \( (Q_v) \) [Wil14]. These flows are given by

\[
Q_a = \frac{P_{aa} - P_{al} + P_{htilt}}{R_a}, \quad Q_v = \frac{P_{vv} - P_{vl} - P_{htilt}}{R_v},
\]

(8.5)

with

\[
P_{htilt} = \rho g h \sin \left( \frac{\theta \pi}{180} \right), \quad \theta \in [0^\circ, \ldots, 60^\circ],
\]

(8.6)

where \( g = 982 \) (cm/s²) is the gravitational constant, \( \rho = 1.06 \) (g/cm³) is the density of blood, \( h \) (cm) is the estimated height between the centers of the upper and lower body compartments, and \( \theta \) is the angle of tilt. Finally, we assume valves exist between the upper and lower body veins to prevent reserve blood flow.

### 8.2.3 Cardiovascular Control

The baroreflex system controls heart rate, peripheral vascular resistance, and cardiac contractility via a negative feedback loop changing these parameters as a function of carotid blood pressure

\[
P_c = P_{aa} - \rho g \tilde{h} \sin(\theta),
\]

where \( \tilde{h} \) (cm) is the estimated height between the carotid and aortic baroreceptors. The negative feedback system, shown in Figure 8.1, consists of three components: (a) afferent nerves transmitting action potentials along the vagal nerve in response to changes in the stretch of the aortic and carotid baroreceptors, (b) integration of the signal in the nucleus solitary tract (NTS), (c) efferent sympathetic and parasympathetic signaling modulating effectors.
Afferent Nerves

The baroreceptor nerves rely on stretch sensors that sense changes in pressure in the carotid sinus and aortic arch. The nerves, part of the vagal nerve bundle for the aortic arch and sinus nerve for the carotid sinus, transmit these changes to the nucleus solitary tract (NTS). It has been suggested that the signal from the carotid sinus baroreceptors dominates during tilt [Wil14; Bor12]; therefore, we only model the sensors in the carotid sinus via Equation (8.2.3). Furthermore, the baroreceptor firing rate responds to the pressure and to the rate of change of pressure in the arteries [Guy11]. Following ideas suggested by Ursino [Urs96], we predict the pressure sensed by the baroreceptor neurons as

\[ \tau_P \frac{d \tilde{P}}{dt} = -\tilde{P} + P_c + \tau_Z \frac{d P_c}{dt}, \]  

(8.7)

where \( \tilde{P} \) tracks change in pressure, \( \tau_P \) and \( \tau_Z \) are time scales with \( \tau_Z > \tau_P \) [Urs96]. The pressure \( \tilde{P} \) then influences afferent firing rate (\( f \), Hz) as

\[ f = s_1 \tilde{P} + s_2, \]

where \( s_1 \) (Hz/mmHg) and \( s_2 \) are the gain and shift for firing frequency.

Efferent Nerves

The signal transmitted from the afferent neurons is integrated into the NTS, which sends efferent signals via sympathetic and parasympathetic neurons. As described in Chapter 2, the two neuron types respond oppositely to blood pressure change, with a drop in BP causing an increase in sympathetic signaling and a decrease in parasympathetic signaling. The timing of the signaling also differs, with sympathetic signaling being significantly slower than parasympathetic signaling. Similar to our previous study [Ged22], we model signaling in efferent (or tone) \( T_i \) as a non-dimensional quantity governed by

\[ \frac{dT_i}{dt} = -\frac{T_i}{\tau_i} + \frac{\tilde{T}(f)}{\tau_i}, \]

where \( f \) is the afferent neuron firing rate and \( \tilde{T} \) an algebraic equation that the response follows at a time scale \( \tau_i \) for sympathetic (\( T_S \)) and parasympathetic (\( T_P \)) tone. To account for saturated upper and lower firing rates, we represent \( \tilde{T} \) as an increasing (parasympathetic)

\[ \tilde{T}_P(f) = \frac{f^{k_{TP}}}{f^{k_{TP}} + f^{2k_{TP}}}, \]  

(8.8)

or a decreasing (sympathetic)

\[ \tilde{T}_S(f) = \frac{f^{k_{TS}}}{f^{k_{TS}} + f^{2k_{TS}}}, \]  

(8.9)

Hill equation where \( f_{2i} \) (Hz) is the half-saturation and \( k_i \) is the Hill coefficient for sympathetic (\( i = TS \))
and parasympathetic \((i = TP)\) tone. Nervous system transmission speed is differentiated by allowing

\[ \tau_P \ll \tau_S \]

where \(\tau_P\) (s) is the parasympathetic time scale and \(\tau_S\) (s) is the sympathetic time scale [Ged22]. In addition, we incorporate an explicit delay in the sympathetic branch, \(\tau_D\), i.e., \(\hat{T}(f(t - \tau_D))\), which is thought to be responsible for low-frequency heart rate and blood pressure oscillations [Jul06]. The tone \((T_i)\) modulates effector responses as

\[ \frac{dE_i}{dt} = -E_i + w_i(T_i) \frac{\tau_{El}}{\tau_{El}} \]

where \(w_i\) scales neural tone as

\[ w_i = w_{i,1}T_i + w_{i,2} \]

where \(w_{i,1}\) is the gain and \(w_{i,2}\) is the shift of the tones for the upper \((R_{up})\) and lower \((R_{lp})\) peripheral resistance and end-diastolic elastance \(E_D\). In a response to a drop in blood pressure, the sympathetic system increases tone, which causes vasculature to constrict, thereby increasing resistance, and cardiac contractility to increase, modeled here by decreasing end-diastolic elastance.

In addition to organ effects, these tones influence concentrations of norepinephrine \((c_{NE}, \text{mM})\) and acetylcholine \((c_{ACH}, \text{mM})\) at the sinoatrial node. These effects are predicted via first-order kinetic equations with time scales \(\tau_{NE}\) (s) and \(\tau_{ACH}\) (s),

\[ \frac{dc_{NE}}{dt} = -c_{NE} + w_{TS}(T_S) \frac{\tau_{NE}}{\tau_{NE}} \]  \(8.10\)

\[ \frac{dc_{ACH}}{dt} = -c_{ACH} + w_{TP}(T_P) \frac{\tau_{ACH}}{\tau_{ACH}} \]  \(8.11\)

### 8.2.4 Sinoatrial Node Cell

We are constructing this model to test the effects of adrenergic autoantibodies against \(\beta_1\) and \(\beta_2\) receptors, denoted collectively as \(\beta\) receptors, which are plentiful in the sinoatrial node cell. To represent these autoantibody effects, heart rate is predicted by a derived sinoatrial node (SAN) cell model that fires autonomous action potentials while being modulated by concentrations of acetylcholine and norepinephrine binding to \(M_2\) and \(\beta\) receptors, decreasing and increasing cyclic adenosine monophosphate (cAMP) concentration. The model developed here includes both \(M_2\) and \(\beta\) receptors, but only \(\beta\) receptors are affected by the presence of adrenergic agonistic autoantibodies. When acetylcholine and norepinephrine bind to \(M_2\) and \(\beta\) receptors, a chain of reactions occurs to decrease or increase cyclic adenosine monophosphate, also known as cAMP. Fluctuations in cAMP then act on cell components to modulate the action potential firing rate.

Our model is inspired by the human ion channel, exchanger, and pump dynamics put forth by Fabbri et al. [Fab17] and by the cAMP equations devised by Demir et al. [Dem99]. Our model contains calcium \((I_{CaL}, I_{Cat})\), sodium \((I_{Na}, I_{Na})\), and potassium \((I_{K}, I_{Kr}, I_{Ka}, I_{To}, I_{Kur}, I_{K,ACH})\) voltage-gated ion channel currents, a sodium-calcium exchanger \((I_{NaCa})\), and a sodium-potassium pump \((I_{NaK})\) (\(\mu A\)), that dictate ion
flow to vary membrane potential \((v, \text{mV})\) as a function of time \((t, \text{s})\),

\[
-C \frac{dv}{dt} = I_{CaT} + I_{Cal} + I_{NaCa} + I_l + I_{Kr} + I_{Ks} + I_{to} + I_{Na} + I_{NaK} + I_{Kur} + I_{K, ACh},
\]

(8.12)

where \(C \,(\text{pF})\) is the capacitance of the cell. All currents are dependent on membrane potential, i.e., \(I_i(v)\). In addition, \(I_{K,ACh}(v, c_{ACh})\) is a function of acetylcholine concentration and \(I_i(v, cAM P), i = \text{Na, NaK, CaL, Ks}\) are functions of cAMP concentration. The rate of change of cAMP is motivated by reaction kinetic representations of norepinephrine, acetylcholine, and autoantibody effects.

**Coupling scales**

On the micro-scale, ion currents dictate the firing rate of the SAN cell, and on the macro-scale, we assume that the heart begins contracting when the SAN fires an action potential. The following section connects the two models by introducing a variable, \(\gamma(v)\) \((\text{s})\), that corresponds to the time since the last action potential. Thus, the left heart time-varying elastance (defined in equation (8.4)) is a function of \(\gamma\).

To couple scales, \(\gamma\) must (1) be reset discontinuously to zero when an action potential is fired and (2) increase linearly with a slope equal to 1 after the action potential is fired. This variable is governed by a Hodgkin-Huxley-like differential equation that converges to 1 quickly when an action potential is fired and decays to 0 otherwise,

\[
\frac{dm}{dt} = g \alpha_m (1 - m) - d (1 - \alpha_m) m,
\]

(8.13)

where \(g, d \in \mathbb{R}^+\), \(g \gg d\), and \(\alpha_m(v)\) is a Hill function of the form

\[
\alpha_m = \frac{\hat{v}^{k_v}}{\hat{v}^{k_v} + v^{k_v}},
\]

(8.14)

with \(\hat{v} = v + \text{shift}\) where \(\text{shift} = 80\) to ensure positive inputs to the Hill equation. Let \(k_v = 50\) to ensure a steep transition from 0 to 1, and therefore \(v_2\) represents the threshold for which \(\alpha_m\) smoothly changes from 0 to 1. \(v_2 = 15 + \text{shift}\) can be interpreted as the threshold membrane potential that, when reached, registers the firing of an action potential. Hence, if the \(v > 15\), \(\alpha_m \approx 1\), and the stable fixed point of \(\frac{dm}{dt}\) is \(m=1\), as the second term is approximately 0. Conversely, when \(v\) is below the threshold, \(\alpha_m \approx 0\), the first term is approximately 0 and the stable fixed point is \(m=0\). When \(v\) is below the threshold, \(m\) decays to 0 exponentially. Solving this decay analytically,

\[
\beta_m = -\frac{\delta_f}{d} \ln m
\]

(8.15)

where \(\delta_f\) is the parameter that is used to time-scale the SAN cell equations. In effect, \(\beta_m\) is the time since the last heartbeat, however; when \(m\) converges back to 1 to “reset”, \(\beta_m\) changes continuously and causes the time-varying elastance function to pump in reverse, which is not desirable. For this reason, \(\gamma\)
is introduced so that the variable is 0 when $m$ is converging to 1,

$$\gamma = \frac{dm}{dt} - \frac{|dm|}{2 \frac{dm}{dt}} \beta_m. \quad (8.16)$$

The variable $\gamma$ now serves as a “local time”, or the time since the last firing of the SAN model. The approximate cardiac cycle length for our computation of $T_S$ and $T_R$ is calculated via a first-order control equation

$$\frac{dR}{dt} = \gamma - R \tau_R \quad (8.17)$$

with $\tau_R \approx 10$. This ODE essentially tracks the mean of $\gamma$, which is one-half the time of the cardiac cycle. Hence, the length of the cardiac cycle can be estimated as $RR = 2R$. Hence, using the above methods, we are able to couple scales and allow the heart to contract as a result of an action potential firing with the left heart time-varying elastance as a function of $\gamma$, i.e., $E_{Elh}(\gamma)$ calculated via Equation (8.4).

**cAMP formulation**

The sympathetic and parasympathetic efferent nerves act on the SAN cell by releasing norepinephrine (NE) and acetylcholine (ACh), which in turn influence cAMP inside the cell. When acetylcholine is released from the parasympathetic nervous system, it binds to the $M_2$ receptor, and the coupled $G_i$ protein acts to decrease cAMP and decrease action potential frequency. When norepinephrine binds to a $\beta$ receptors, the coupled $G_s$ proteins activate adenylyl cyclase, facilitating the production of cAMP. Demir et al. [Dem99] assume that both of these reaction cascades can be approximated via Michaelis-Menten kinetics (discussed in Chapter 5). In our model, we assume that adrenergic agonistic autoantibodies are present, which bind to $\beta$ receptors and increase the binding affinity of norepinephrine. In other words, in the absence of autoantibodies, norepinephrine increases the cAMP concentration via a cascade beginning with $G$ proteins, but the effect of norepinephrine is increased in the presence of these autoantibodies. A non-essential activator reaction scheme, shown in Figure 8.2 [Bot53; Seg75], represents these postulated dynamics with $R$ denoting receptors, $N$ norepinephrine, $A$ autoantibodies, and “hats” denoting the binding of components - for example, $\hat{R}N$ represents norepinephrine ($N$) binding to a receptor ($R$).

To derive a velocity dependence equation for the production of $G$ proteins, we make the following assumptions,

1. The forward and reverse reactions $k_i$, for $i = 1, 2, 3, 4$ (noted in Figure 8.2), occur much faster than the reactions denoted by $k_p$ and $\lambda k_p$. The result is an approximate equilibrium of $A$ and $N$. Mathematically, this implies that $\frac{dN}{dt} = \frac{dA}{dt} = 0$.

2. The total number of receptors, $R_t$, remains constant and is equal to the sum of the states that contain receptors: $R_t = R + \hat{RA} + \hat{RN} + \hat{RAN}$. 
Figure 8.2 Nonessential activator reaction scheme. Abbreviations are as follows: \( R \) - receptor, \( N \) - norepinephrine, \( A \) - antibody, \( G \) - G protein, \( k_i \) - rate constants. “Hats” denote the binding of reactants - for example, the binding of \( N \) and \( R \) is denoted as \( \hat{RN} \).

Using the law of mass action, the rate of change of each state is given by,

\[
\frac{dR}{dt} = -k_{1+}RN - k_{2+}RA + k_{1-}\hat{RN} + k_{2-}\hat{RA} + kp\hat{RN} \tag{8.18}
\]

\[
\frac{dN}{dt} = -k_{1+}RN + k_{1-}\hat{RN} - k_{3+}\hat{RAN} + k_{3-}\hat{RAN} \tag{8.19}
\]

\[
\frac{dA}{dt} = -k_{2+}RA + k_{2-}\hat{RA} - k_{4+}\hat{RANA} + k_{4-}\hat{RANA} \tag{8.20}
\]

\[
\frac{d\hat{RA}}{dt} = -k_{2-}\hat{RA} + k_{2+}RA - k_{3-}\hat{RAN} + k_{3+}\hat{RAN} + \lambda kp\hat{RAN} \tag{8.21}
\]

\[
\frac{d\hat{RN}}{dt} = k_{1+}RN - k_{1-}\hat{RN} - k_{4+}\hat{RANA} - k_{4-}\hat{RANA} - kp\hat{RN} \tag{8.22}
\]

\[
\frac{d\hat{RAN}}{dt} = k_{3+}\hat{RAN} - k_{3-}\hat{RANA} + k_{4+}\hat{RANA} - k_{4-}\hat{RANA} - \lambda kp\hat{RAN} \tag{8.23}
\]

\[
\frac{dG}{dt} = kp\hat{RN} + \lambda kp\hat{RAN} \tag{8.24}
\]

The first assumption implies that the reactions to form and dissociate products \( \hat{RN}, \hat{RA}, \) and \( \hat{RAN} \), with rate constants \( k_{i+} \) and \( k_{i-} \), \( i = 1, 2, 3, 4 \), occur significantly faster than the reactions to produce \( G \), denoted by rate constants \( kp \) and \( \lambda kp \). Mathematically, this implies that \( N \) and \( A \) are approximately at equilibrium, i.e., \( \frac{dN}{dt} = 0 \) and \( \frac{dA}{dt} = 0 \). Furthermore, this assumption implies that the ratio of forward and
reverse reaction rates provide the overall reaction rate. This gives

\[ K_S = \frac{k_{1-}}{k_{1+}} \]  \hspace{1cm} (8.25)
\[ K_A = \frac{k_{2-}}{k_{2+}} \]  \hspace{1cm} (8.26)
\[ K_3 = \frac{k_{3-}}{k_{3+}} \]  \hspace{1cm} (8.27)
\[ K_4 = \frac{k_{4-}}{k_{4+}} \]  \hspace{1cm} (8.28)

Using the above equivalences, we can now write the equations \( \frac{dN}{dt} \) and \( \frac{dA}{dt} \) without \( k_i \), \( i = 1, 2, 3, 4 \),

\[ \frac{dN}{dt} = -k_{1+}RN + k_{1+}K_SRN - k_{3+}RAN + k_{3+}K_3RAN \]  \hspace{1cm} (8.29)
\[ \frac{dA}{dt} = -k_{2+}RA + k_{2+}K_ARA - k_{4+}RNA + k_{4+}K_4RAN. \]  \hspace{1cm} (8.30)

As stated by Segel [Seg75], one possible solution that ensures the equilibrium assumption is to
assume that the parallel reaction rates (1 & 3, 2 & 4) are proportional, i.e., \( K_3 = \eta K_S \) and \( K_4 = \eta K_A \). With
this substitution, we can now write

\[ \frac{dN}{dt} = -k_{1+}RN + k_{1+}K_SRN - k_{3+}RAN + k_{3+}\eta K_S RAN \]  \hspace{1cm} (8.31)
\[ \frac{dA}{dt} = -k_{2+}RA + k_{2+}K_ARA - k_{4+}RNA + k_{4+}\eta K_A RAN. \]  \hspace{1cm} (8.32)

Additionally, a solution is obtained by viewing the constants in Equations (8.25) - (8.28) as dissociation
constants, meaning that they can relate their respective complexes to the reactants as

\[ \overline{RN} = \frac{RN}{K_S} \]  \hspace{1cm} (8.33)
\[ \overline{RA} = \frac{RA}{K_A} \]  \hspace{1cm} (8.34)
\[ \overline{RAN} = \frac{RAN}{\eta K_A K_S}. \]  \hspace{1cm} (8.35)

Using these equivalences, we see that the following equations are equal to zero, as needed,

\[ \frac{dN}{dt} = -k_{1+}\overline{RN} + k_{1+}K_SRN - k_{3+}\overline{RAN} + k_{3+}\eta K_S \overline{RAN} \]  \hspace{1cm} (8.36)
\[ \frac{dA}{dt} = -k_{2+}\overline{RA} + k_{2+}K_ARA - k_{4+}\overline{RNA} + k_{4+}\eta K_A \overline{RAN}. \]  \hspace{1cm} (8.37)

We have therefore verified that Equations (8.25) - (8.35) result in \( \frac{dN}{dt} = \frac{dA}{dt} = 0 \) as needed to satisfy the
equilibrium assumption. However, note that we wish to express Equations (8.36) and (8.37) in terms of
the reactants, and therefore we have two equations with three unknowns \((\bar{RA}, \bar{RN}, \bar{RAN})\). Hence, the relations put forth in Equations (8.33) - (8.35) is likely not unique.

The equilibrium assumption implies that the rate-limiting steps are the reactions with rates \(k_p\) and \(\lambda k_p\), as we assumed previously the reactions \(k_{i-}\) and \(k_{i+}\), \(i = 1, 2, 3, 4\), occur much faster. Hence, the reaction rate of the system, \(v_{NEA}\), is equal to the rate of product production, \(\frac{dG}{dt}\),

\[
v_{NEA} = \frac{dG}{dt} = k_p \bar{RN} + \lambda k_p \bar{RAN}
\] (8.38)

with the reaction rate velocity denoted by \(v_{NEA}\), rate production constant \(k_p\) \((1/(s \text{ mM}))\), a non-dimensional constant which scales \(k_p\) given the application of autoantibodies, \(\lambda\), and concentrations of bound norepinephrine \((N, \text{ mM})\) denoted \(\bar{RN}\) (mM) and receptors bound to both autoantibodies \((A, \text{ mM})\) and \(N\) denoted \(\bar{RAN}\) (mM). Our assumed reaction scheme assumes that receptors are conserved, implying that the total number of receptors, \(R_t\), remains constant and is equal to the sum of the states that involve receptors, \(R_t = R + \bar{RA} + \bar{RN} + \bar{RAN}\). Multiplying and dividing the right-hand side of the velocity equation by the total number of receptors gives

\[
v_{NEA} = \frac{k_p \bar{RN} + \lambda k_p \bar{RAN}}{R + \bar{RA} + \bar{RN} + \bar{RAN}}.
\] (8.39)

Next, each complex can be written as the product of the components in the complex divided by the product of the dissociation constants via the equivalences noted in Equations (8.33) - (8.35),

\[
v_{NEA} = R_t \frac{k_p \bar{RAN} + \lambda k_p \bar{RAN}}{R + \frac{RA}{k_A} + \frac{RN}{k_S} + \frac{RAN}{\eta k_A k_S}}.
\] (8.40)

This equation can be simplified and rewritten as

\[
v_{NEA} = R_t k_p \frac{N}{k_S} + \lambda k_p \frac{RAN}{\eta k_A k_S}.
\] (8.41)

Allowing \(v_{max} = R_t k_p\) \((1/s)\) and replacing \(N\) with \(c_{NE}\), we obtain our final equation,

\[
v_{NEA} = v_{max} \frac{c_{NE}}{K_s} + \lambda \frac{c_{NE}}{\eta k_A k_S}.
\] (8.42)

with \(c_{NE}\) (concentration of norepinephrine, mM), the concentration of autoantibodies \((A, \text{ mM})\), and reaction rate constants \(K_s\) (mM), \(K_A\) (mM), \(\lambda\) and \(\eta\) (non-dimensional).

In our model, we assume that the velocity dependence equation represents the reaction rate when norepinephrine and autoantibodies are introduced to the system, and therefore, we employ an equilibrium assumption \(\frac{dN}{dt} = \frac{dA}{dt} = 0\). This assumption states that, with respect to the reaction speed, both norepinephrine and autoantibody concentrations are approximately constant. However, we are able to modulate the concentration of norepinephrine externally to the cell since we expect the external dynamics to be much slower than reaction dynamics. Therefore, although we modulate norepinephrine...
outside the cell, we are still able to assume an equilibrium state in the reaction scheme because the reactions are happening on a much faster time scale.

Lastly, we assume that the external concentration of autoantibodies remains constant, but the same assumptions are used for autoantibody concentration as norepinephrine. Hence, in future work, modulation of autoantibody concentration could be modeled, but we use a constant value here, thus assuming that the binding and release of autoantibodies from the receptors to the extracellular space has resulted in a steady state in itself and that the concentration is constant.

To produce low-frequency oscillations with physiological amplitude during HUT, it is necessary and sufficient that the number of receptors available to bind to NE is a function of NE and autoantibody concentrations. This implies cooperative norepinephrine binding, i.e., when norepinephrine binds, it allows additional norepinephrine to bind more easily to surrounding sites. As such, $v_{\text{max}} = k_p[R]_t$ is assumed to have a minimum and maximum number of available receptors and is modeled as a Hill equation of the form

$$v_{\text{max}} = \left(v_{\text{max},M} - v_{\text{max},m}\right) \frac{c_{\text{NE}}^{k_{\text{max}}}}{c_{\text{NE}}^{k_{\text{max}}} + K_{\text{vmax}}^{k_{\text{max}}}} + v_{\text{max},m}$$

where $k_{\text{vmax}} = 20$ (non-dimensional), $K_{\text{vmax}}$ (mM) is the half-saturation point, and $v_{\text{max},m}$ (1/s) is the minimal value of $v_{\text{max}}$. To incorporate the cooperative increase due to autoantibody presence, we predict the maximal value of $v_{\text{max}}$ as

$$v_{\text{max},M} = v_{\text{max},M,\text{Control}} + k_{\text{vmax,AA}}$$

with $v_{\text{max},M,\text{Control}}$ (1/s) denoting the value of $v_{\text{max},M}$ (1/s) for control subjects and $k_{\text{vmax,AA}}$ (1/(s mM)) is a non-dimensional proportionality constant that dictates the increase in cooperativity due to autoantibodies.

In the Demir model, L-type calcium current ($I_{\text{CaL}}$), slow delayed rectifier $K^+$ current ($I_{\text{Ks}}$), funny current ($I_f$), and sodium/potassium pump current ($I_{\text{NaK}}$) are modulated by cAMP and while the ACh modulated $K^+$ current ($I_{\text{K,ACh}}$) is affected by ACh concentration. Formulation of these channels and changes made to combine model components from [Dem99] and [Fab17] can be found in Sections B.3 and B.2.

The cAMP differential equation must also incorporate the effects of acetylcholine and cAMP degradation. To do so, we combine the nonessential activator scheme (NEA NE) with the Michaelis-Menten acetylcholine (M-M ACh) and cAMP degradation (cAMP - D) terms put forth by [Dem99] to give the rate of change of cAMP as

$$\frac{dc\text{AMP}}{dt} = K_{\text{ADC}}\left(1 + v_{\text{max}} \frac{c_{\text{NE}}}{k_s} + \frac{\lambda c_{\text{NE}}}{\eta k_s k_s} \right) - \frac{c_{\text{ACH}}}{c_{\text{ACH}} + K_{\text{m,ACH}}} - \frac{V_{PDE} c\text{GMP} c\text{AMP}}{c\text{AMP} + K_{PDE} c\text{GMP}}, \quad (8.43)$$

where $c_{\text{NE}}$ is the concentration of norepinephrine, $c_{\text{ACH}}$ the concentration of acetylcholine, and $K_{\text{ADC}}$
is the rate of production, $K_{m,ACh}$ is the Michaelis-Menten constant for acetylcholine, $V_{PDE}$ marks the amount of cAMP-specific phosphodiesterase (PDE) present, $cGMP$ is the amount of Cyclic guanosine monophosphate (cGMP) present, and $K_{PDE}$ is the half-degradation concentration of cAMP by PDE. Values of cAMP parameters are reported in Table 8.1, and a full table of model parameters with units, sources, and values can be found in Section B.1.

To simplify equation (8.43), let

\[
C_1 = \frac{v_{max} \left( \frac{1}{k_s} + \frac{\lambda A}{\eta k_s} \right)}{\frac{1}{k_s} + \frac{\lambda A}{\eta k_s}},
\]

\[
C_2 = \frac{1 + \frac{A}{k_A}}{\frac{1}{k_s} + \frac{A}{\eta k_s}},
\]

\[
C_3 = V_{PDE} \cdot cGMP,
\]

\[
C_4 = k_{PDE} \cdot cGMP.
\]

With these substitutions, our cAMP equation can be written as

\[
\frac{d \text{cAMP}}{dt} = K_{AD} \left( 1 + \frac{c_{NE}}{C_2 + c_{NE}} - \frac{c_{ACH}}{c_{ACH} + K_{m,ACh}} \right) - C_3 \frac{c \text{AMP}}{c \text{AMP} + C_4}.
\]

Note, the simplified cAMP equation takes the form of a combination of Michaelis-Menten terms which govern cAMP concentration inside the cell, which then affect the L-type calcium current ($I_{CaL}$), slow delayed rectifier K$^+$ current ($I_{Ks}$), funny current ($I_f$), sodium/potassium pump current ($I_{NaK}$) and the ACh modulated K$^+$ current ($I_{KACH}$). Details of deviations from the Fabbri et al. [Fab17] to accommodate the cAMP effect equations put forth by Demir et al. [Dem99] are detailed in the appendix (Section B.3).

### 8.2.5 Model Solution

The model developed here forms a system of delay differential equations, which are stiff due to the rapidly changing dynamics in the SAN cell and scale coupling, and possess a delay to model sympathetic neurons. This system can be represented as

\[
\frac{d y}{d t} = f(t, y(t), y(t - \tau_D); \theta),
\]

with $\tau_D \in \mathbb{R}, \theta \in \mathbb{R}^{128}$, and $y = \{y_{SAN}, y_{neuro}, y_{CV}\}$, with

\[
y_{SAN} = \{v, Ca_i, Na_i, y_f, m_{Na}, h_{Na}, dL_{Cal}, fL_{Cal}, fCa_{Cal}, dT_{CaT}, fT_{CaT}, r_{Kr}, q_{to}, r_{to}, p_{aSKr}, p_{aFKr}, p_{iyKr}, n_{KS}, a_{KACH}\}
\]

\[
y_{neuro} = \{\tilde{P}, c_{NE}, c_{ACH}, cAMP, R_l, R_u, E_D, m, R\}
\]

\[
y_{CV} = \{V_{th}, V_{au}, V_{al}, V_{vl}, V_{vu}\}.
\]

The model states and parameters are given in Sections B.2 and B.1. We solve this system using an
Table 8.1 Values of cAMP equation parameters, their values, and units.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Value or equation</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_{ADC}$</td>
<td>0.008</td>
<td>mM/s</td>
</tr>
<tr>
<td>$V_{PDE}$</td>
<td>20</td>
<td>s⁻¹</td>
</tr>
<tr>
<td>cGMP</td>
<td>0.002</td>
<td>mM</td>
</tr>
<tr>
<td>$K_{PDE}$</td>
<td>82.5</td>
<td>N.D.</td>
</tr>
<tr>
<td>$K_{ACH}$</td>
<td>0.007</td>
<td>mM</td>
</tr>
<tr>
<td>$v_{max,m}$</td>
<td>1.23</td>
<td>N.D.</td>
</tr>
<tr>
<td>$v_{max,M}$</td>
<td>3.08</td>
<td>N.D.</td>
</tr>
<tr>
<td>$K_{v_{max}}$</td>
<td>$1.6 \times 10^{-5}$</td>
<td>mM</td>
</tr>
<tr>
<td>$k_v$</td>
<td>20</td>
<td>N.D.</td>
</tr>
<tr>
<td>$K_S$</td>
<td>$1.85 \times 10^{-4}$</td>
<td>mM</td>
</tr>
<tr>
<td>$K_A$</td>
<td>$7 \times 10^{-4}$</td>
<td>mM</td>
</tr>
<tr>
<td>$\eta$</td>
<td>0.9</td>
<td>N.D.</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>2.55</td>
<td>N.D.</td>
</tr>
<tr>
<td>$A$</td>
<td>$2.3 \times 10^{-4}$</td>
<td>mM</td>
</tr>
</tbody>
</table>

\[ C_1 \text{ - POTS, } A > 0 \quad v_{max} \left( \frac{1 + \frac{A}{K_S}}{\frac{1}{K_S} + \frac{\lambda A}{\eta K_A K_S}} \right) \quad \text{N.D.} \]
\[ C_1 \text{ - Control, } A = 0 \quad v_{max} \quad \text{N.D.} \]
\[ C_2 \text{ - POTS, } A > 0 \quad \frac{1 + \frac{A}{K_S}}{\frac{1}{K_S} + \frac{\lambda A}{\eta K_A K_S}} \quad \text{mM} \]
\[ C_2 \text{ - Control, } A = 0 \quad K_S \quad \text{mM} \]
\[ C_3 \quad V_{PDE} \text{ cGMP} \quad \text{mM/s} \]
\[ C_4 \quad K_{PDE} \text{ cGMP} \quad \text{mM} \]
algorithm by Guglielmi and Hairer that expands off the Radau IIA implicit Runge-Kutta methods put forth by J.C. Butcher [But64a; But64b], called RADAR5 [Gug01]. Guglielmi and Hairer extend Radau IIA to incorporate delays and present the algorithm, which is written in Fortran 77, and the stability and efficiency of the new RADAR5 method in [Gug01]. The workflow for model analysis, outlined in Figure 8.3, is detailed below with the $i$th step number corresponding to the $i$th figure component from left to right.

**Figure 8.3** Workflow for model simulations. Initial conditions ($g(t), t \leq t_0$), parameters ($\theta$), and final simulation time $t_F$ are set in MATLAB and written to .txt files. .out files are created for the model simulation to be recorded in. The executable is then called from MATLAB while passing the file names in as arguments. The model is then solved and the results are loaded into MATLAB via .out files where they are analyzed.

0. The model is first written in Fortran 77 in accordance with the structure presented in code by Guglielmi and Hairer [Gug01]. This file, along with the RADAR5 files, are compiled into an executable that accepts five file names as arguments.

   (a) The name of the .txt file containing parameter values.

   (b) The name of the .txt file containing initial conditions ($y(0)$).

   (c) The name of the .txt file containing past initial conditions ($g(t), t < 0$).

   (d) The name of the .out file that the solution with varying step sizes will be written to.

   (e) The name of the .out file that uniform step size solutions will be written to.

By passing unique file names into the executable, we are able to run parallel model simulations.

1. In MATLAB [MAT19], model parameter values and initial conditions for $y(t) \leq 0$ are calculated and simulation time is set. The MATLAB code then creates files with names that begin with generic descriptors (pars, Init, Delay_Init, sol, cont) and are followed by the date-time denoted in MATLAB to the millisecond and then followed by a 10-digit random number. Additionally, the code checks to ensure that a proposed name is not already in use before using it for a simulation. This ensures the uniqueness of file names so that model simulations can be executed in parallel. The values of parameters and initial conditions are then written to their respective .txt files.

2. The file names created in step one are then passed onto the executable when it is called from MATLAB using the `system` command.
3. The previously compiled executable solves the model and writes the resulting solution the sol file and a solution with uniform step size in the cont file.

4. The cont file is loaded into MATLAB.

5. The model is analyzed in MATLAB using the methods described below. The solution for different parameter values or initial conditions can be obtained by repeating steps 1-5.

8.2.6 Model Analysis

To quantify the model solution, we place emphasis on HR and BP oscillation amplitude during rest and HUT, as well as change in mean HR. Heart rate is calculated by finding the R peaks of membrane potential (v). The RR interval (RR, s) is assumed to be constant between R peaks, thus providing a step function as $HR = 60/RR$ (bpm). We focus on the analysis of steady-state by examining the 150 seconds before tilt and between 50 and 200 seconds after tilt. Since transients are not specifically studied, we can treat the selected signals as stationary and apply the Fourier Transform (fft function in MATLAB) to obtain frequency information. The only oscillation in HR is the low-frequency contribution, and the low-frequency and HR contribution in BP, we are able to identify the peak between 0.05-0.15 Hz [Gol99; Jul06] easily to quantify low-frequency oscillation amplitude and frequency. This method is similar to that employed in our previous study [Ged22]. Mean heart rates are calculated by taking the average of HR 150 seconds prior to tilt and between 50 and 200 seconds after tilt.

We quantify parameter effects on our model in two ways. First, we linearly vary parameters that are physiologically relevant to POTS phenotypes and record the above metrics to classify parameter regions and calibrate the model. Second, we increase and decrease all parameters, except for known constants, by a set amount, $p$, and observe the effects on the computed metrics to find influential parameters. Lastly, we assess the effects of popular POTS interventions outlined in [Mar20] on our POTS simulation. To do so, we begin with the parameterization of the model that produces desired POTS dynamics and then adjust parameters to replicate the effects of the intervention in question. These interventions can be found in Table 8.2. Note that multiple interventions have the same effect on the model. Therefore, we impose five different intervention effects on the model, with $I_i$ the percentage increase or decrease for intervention $i = 1, 2, 3, 4, 5$:

1. Increased resistance and decreased compliance in the lower body vasculature. The maximal and minimal response of the lower body resistance control ($R_{lpm}$ and $R_{lpM}$) is increased by a factor $(1 + I_1)^4$, thus assuming resistance will change proportional to the fourth power of vascular radius as predicted by Poiseuille’s law. The lower body arterial compliance and lower body venous maximal volume ($C_{al}$ and $V_{M, n}$) is decreased by a factor of $(1 - I_1)^2$, as compliance and volume change will be proportional to the squared vascular radius change.

2. Increased resistance in the entire body ($R_i, i = a, v, av, mv, upm, upM, lpM, lpm, lpm$) by a factor $(1 + I_2)^4$ and decreased compliance in the upper body and lower body arterial compartments, and decreased maximal volume in the lower body veins by a factor $(1 - I_2)^2$. 

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3. Increased lower body pressure by adding additional pressure \((1 + I_3)P_L\) to the lower body arteries and veins.

4. Increased blood volume by adding additional blood volume \((1 + I_4)BV\) to the total blood volume.

5. Decreased number of binding sites for NE by decreasing the number of available receptors on the SAN cell \([R]_t\) by \(I_5\), corresponding to \(C_1(1 - I_5)\).

---

**Table 8.2** Select interventions from [Mar20], the phenotype they are suggested for, and their effect on the presented model. Abbreviations as follows: \([R]_t\) - number of receptors for NE binding to SAN cell, \(R_L\) - lower body peripheral resistance, \(C_L\) - lower body arterial and venous compliance, \(P_L\) - lower body arterial and venous pressure, \(BV\) - total blood volume.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Intervention</th>
<th>Model encoding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperadrenergic</td>
<td>Propranolol</td>
<td>(\downarrow[R]_t)</td>
</tr>
<tr>
<td>Neuropathic</td>
<td>Compression stockings</td>
<td>(\uparrow R_L, \downarrow C_L)</td>
</tr>
<tr>
<td></td>
<td>Midodrine</td>
<td>(\uparrow R_L, \downarrow C_L)</td>
</tr>
<tr>
<td></td>
<td>Abdominal compression</td>
<td>(\uparrow P_L)</td>
</tr>
<tr>
<td>Hypovolemic</td>
<td>Fluid Hydration</td>
<td>(\uparrow BV)</td>
</tr>
<tr>
<td></td>
<td>High-sodium diet</td>
<td>(\uparrow BV)</td>
</tr>
<tr>
<td></td>
<td>Fludrocortisone</td>
<td>(\uparrow BV)</td>
</tr>
</tbody>
</table>

---

**8.3 Results**

We first investigate how changes in parameters that are important to representing POTS pathophysiology affect model predictions of low-frequency HR and BP oscillations and changes in HR due to a postural change. We compare predictions to patient data and then examine pressure and volume in cardiovascular compartments. Next, we quantify the ability of all model parameters to affect frequency metrics. We then specifically examine cAMP equation parameters to assess the hypothesis that autoantibodies can affect frequency metrics before concluding with the effects of popular POTS interventions.

**8.3.1 Patient simulations**

Control simulations (without autoantibodies, \(A = 0\), shown in Figure 8.4, illustrate the model’s ability to generate realistic predictions of HR and BP. Figure 8.4 also shows that POTS simulations, with \(A > 0\) and increased value of \(V_{M,v,t}\) to simulate the effects of autoantibodies binding to the vasculature (values in Table 8.3), oscillate more than controls, exhibit postural tachycardia, and resemble patient data.

Figure 8.5 shows pressure predictions for all five compartments before and after HUT for a POTS patient simulation. Pressures remain in the physiological range; however, pulse pressure after tilt is smaller than expected in healthy adults (22 mmHg vs 30 mmHg). Figure 8.6 shows volume predictions...
Table 8.3 Parameter values used for simulations in Figure 8.4. $A$ represents the concentration of autoantibodies in the sinoatrial node. $V_{\text{MVL}}$ denotes the maximum stressed volume in the lower body venous compartment, which represents the effects of autoantibodies binding to $\beta$ receptors in vascular smooth muscle cells, although an explicit model of vascular smooth muscle cells is not included here.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Control</th>
<th>POTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A$</td>
<td>mM</td>
<td>0</td>
<td>$2.3 \times 10^{-4}$</td>
</tr>
<tr>
<td>$V_{\text{MVL}}$</td>
<td>mL</td>
<td>95</td>
<td>214</td>
</tr>
</tbody>
</table>

Figure 8.4 Control (left) and POTS (right) model simulations (blue) of heart rate (HR, top row) and blood pressure (BP, bottom row) before and after tilt (denoted by the dashed black line) plotted with patient data (gray). Patient data is shifted vertically to align with model predictions.

for all compartments. We observe that stroke volume before tilt approximately matches literature values [Bev60; KB20; Tan96], and that stroke volume after tilt is lower than in healthy adults. Additionally, the shift in blood volume is approximately double in healthy adults upon a postural change [Mat91].

8.3.2 Parameter Space Exploration

This section quantifies the effects of parameters on the system. First, as illustrated in Figure 8.7, we increase and decrease all parameters (that are not known constants, for example, the Faraday constant) by 2% and 5% with respect to our POTS patient parameterization and record the HR and BP low-frequency oscillation amplitude ($A_{HR}$ and $A_{BP}$) at rest after 10,000 seconds of simulation to ensure
the achievement of steady-state. We observe that the majority of parameters cause small changes in oscillations, with some causing the elimination of oscillations. However, most parameters in the model are not believed to change as a result of autoantibodies.

To specifically examine parameters thought to be modulated by the presence of agonistic adrenergic autoantibodies, Figure 8.8 shows the systematic variation of $C_1$, the scale for the NE to cAMP Michaelis-Menten equation, $C_2$, the Michaelis-Menten constant for the same equation, $A$, the concentration of autoantibodies, and $V_{M, vl}$, the maximum volume in the lower body veins. We observe that increasing $C_1$ causes larger oscillations at rest but decreases oscillations at HUT and the change in HR. Increasing $C_2$ serves to decrease oscillations at rest and HUT, as well as change in HR, except for values greater than $8 \times 10^{-4}$ where oscillations appear again during rest. Increasing $A$ increases oscillation amplitude at rest but more so during HUT. Finally, increasing the value of $V_{M, vl}$ decreases oscillations and increases postural change in HR.
8.3.3  Effects of interventions

To quantify the effects of interventions on a simulated POTS patient, we begin with a POTS patient simulation with adrenergic agonistic autoantibodies and vary parameters to represent interventions. There are multiple treatments for POTS; however, many interventions have the same effect on the model. In Figure 8.9, columns depict the effects of (1) a POTS patient without treatment, (2) increased resistance and decreased compliance in the lower body vasculature, (3) increased resistance and decreased compliance in the entire system, (4) increased lower body pressure, (5) increased blood volume, and (6) decreased number of binding sites for NE. It should be noted that an intervention that can decrease the number of autoantibodies would be effective, as shown in Figure 8.8. Of the interventions, we see that increasing resistance and decreasing compliance (3) is the most effective at decreasing postural tachycardia; however, oscillations are still abnormally large. Additionally, some interventions allow tachycardia to persist and increase oscillation amplitude (columns 2, 4, & 6 in Figure 8.9).
**Figure 8.7** Amplitudes of low-frequency heart rate (HR, top) and blood pressure (BP, bottom) oscillations during rest are depicted by color when parameter \( i \) (horizontal axis) is increased or decreased by 5% or 2% (vertical axis) from the POTS parameterization that gives the time series prediction shown in Figure 8.4. Note that the base POTS simulation low-frequency amplitude for HR (\( \sim 4 \text{ bpm} \)) and BP (\( \sim 20 \text{ mmHg} \)) are shown in the middle row of each panel, denoted by 0% change, and the colors in the surrounding panels denote oscillation amplitude and not the relative change. The model is solved at rest for 10,000 seconds, with oscillations quantified for the last 150 seconds. Parameters are ranked from largest to smallest relative change from POTS simulation low-frequency HR and BP oscillation amplitude, with parameter numbers corresponding to:

1-10: \( k_{DL}, V_{DL}, Na_o, K_{mNa}, I_{NaK,\text{max}}, Ca_o, f_5, f_P, P_{CaL}, \tau_D \)
11-20: \( \tau_Z, \tau_p, \delta, C_3, C_{aq}, K_{ADC}, R_{upM}, \tau_S, E_m \)
21-30: \( K_{mK}, K_o, C_p, C_{pu}, K_{mT_Ca}, K_{ci}, C_al, g_{tor}, K_{NaCa}, K_{ACH} \)
31-40: \( R_{pm}, g_{K}, K_{co}, K_{2no}, K_{3no}, K_{1no}, V_{Mvl}, P_{Cat}, K_i, E_m \)
41-50: \( \tau_{ACH}, K_{1ni}, K_{Ca}, g_{K}, g_{Na}, K_{2ni}, K_{3ni}, Q_n, m_v, R_{upm} \)
51-60: \( v_2, R_{pm}, Q_{ci}, g_{K}, B_{p}, \alpha_{CA}, shift, R_{al}, K_{cni} \)
61-70: \( R_{mv}, g, E_{mm}, d, R_{av}, g_f, K_{mf}, \alpha, y_{shift}, Q_{co} \)
71-74: \( g_{NaL}, b_m, g_{K_s}, \alpha_a \)

### 8.4 Discussion

This study developed a multiscale model of the cardiovascular system and its control that incorporates the effects of adrenergic agonistic autoantibodies. This model supports our hypothesis that these antibodies are sufficient to cause POTS dynamics - namely, increased amplitude of low-frequency oscillations and postural tachycardia, which is supported by the POTS autoimmune hypothesis [Ver18; Li14; GI21; Dah16]. This work extends previous studies examining POTS phenotypes via mathematical modeling [Ged22] and supports signal processing results put forth in [Ged20a; Med14; Ste15]. Addi-
tionally, this work holds mathematical significance as it furthers the quest to represent low-frequency oscillations in mathematical models [Ish20; Hel00; Ham05] and the effects of postural change [Olu05; Ott10; Wil14; Mat15].

Low-frequency oscillations are present in healthy controls as there is a delay in healthy sympathetic function [Jul06]. In this model, we represent the sympathetic transmission speed with an explicit delay, as has been done in other studies [Ish20; Ham05], while other studies produced low-frequency oscillations by only varying neuron time-scales [Ged22]. We show here that the presence of autoantibodies can increase the amplitude of these oscillations and cause postural tachycardia. In our model, the autoantibody effects are represented as a nonessential activator reaction scheme, implying that the autoantibodies increase the rate at which the NE to cAMP cascade occurs. This increased rate could decrease the total time from baroreceptor firing to cAMP production in the SAN cell, thus making the total sympathetic response to heart rate faster. This would cause an excessive response from the sympathetic branch, which then changes heart rate more than appropriate per a given change in blood pressure.

Our results, shown in Figure 8.4, suggest that the presence of autoantibodies in our multiscale model can generate predictions that resemble POTS data. Furthermore, Figures 8.7 and 8.8 show the importance of autoantibodies in the amplitude of oscillations at rest and HUT as well as postural tachycardia. In addition, we observe that low-frequency oscillation amplitude is primarily affected by SAN cell cAMP parameters, while postural tachycardia is mainly a result of autoantibody effects on the vasculature. Figure 8.7 shows that other system parameters are able to affect oscillations; however, we do expect these parameters to differ as a result of autoantibodies. These parameters may therefore be important to the amplitude of oscillations in control subjects but are unable to explain the increased amplitude in POTS patients. However, as noted in [Ged22], these other parameters may support hypotheses for other POTS
phenotypes. Lastly, of the interventions simulated in Figure 8.9, we observe that the intervention effects on model parameters assist but are minimal when compared to the impact of reducing the concentration of antibodies, seen in Figure 8.8. Additionally, some interventions (for example, compression stockings), decrease postural tachycardia but increase oscillation amplitude, which could make symptoms such as brain fog worse.

Clinical implications of this work are two-fold: we have provided an explanation for the autoimmune hypothesis of POTS and, by doing so, have suggested a new way to address the syndrome. Current clinical protocols suggest various non-pharmaceutical interventions (i.e. compression stockings) for initial treatment and stress the importance of identifying the phenotype of POTS for patient-specific treatment [Mar20; Fed19]. Our work suggests the importance of testing for autoantibodies and mitigating their effects in an effort to treat the core problem rather than symptoms. We have shown here that adrenergic agonistic autoantibodies that have been found in POTS patients can play a role in the observed dynamics of POTS. However, our work cannot definitively state whether the presence of these antibodies is mutually exclusive with the other phenotypes. It is likely that hyperadrenergic, neuropathic, and hypovolemic patients are correctly diagnosed but that the presence of these antibodies in a subset of patients either exacerbates symptoms or explains the presence of previously unexplained aspects of the syndrome.

The ability of autoantibodies to modulate oscillation amplitude and vascular constriction suggests that it is possible to treat and minimize postural tachycardia but continue to have abnormally large low-frequency HR and BP oscillations - which may cause various symptoms of POTS such as brain
fog and fatigue. In essence, it is possible current medical interventions are only treating part of the syndrome and leaving another component to persist and continue to cause symptoms.

A limitation of our model is the lumping of the NE to cAMP and ACh to G protein cascades. The non-essential activator and Michaelis-Menten reaction schemes provide powerful but simple representations of signaling cascades. However, the necessity for $v_{\text{max}}$ to be a function of NE to obtain sufficient oscillations after tilt implies that this term is non-constant and, therefore, that a more complex reaction scheme should be employed to capture true dynamics. The non-essential reaction scheme allows us to study the effects of increased autoantibodies, but only with respect to the dissociation constant $K_A$. $A$ is only present in the resulting reaction velocity equation as the ratio $A/K_A$; therefore, without an estimation of $K_A$, which is not currently available from data, this model is not able to estimate the concentration of autoantibodies, $A$. While the model replicates the amplitude of low-frequency oscillations in POTS patients, it is unable to predict the phase metric put forth in [Ged20a]. Lastly, we observe that pulse pressure decreases more than expected in data, and therefore control equations for arterial compartments should be incorporated in future work.

Future work should attempt to convert this model to a patient-specific model. Doing so, and incorporating optimization and parameter estimation techniques, could allow for the estimation of autoantibody effects in a POTS patient based on only HR and BP data, thus assisting in phenotype diagnosis with minimal cost/effort to the patient. In conclusion, this study has developed a model consisting of the cardiovascular system, its neural control, and the sinoatrial node cell model, to illustrate the sufficiency of adrenergic agonistic autoantibodies to cause POTS HR and BP dynamics. Implications of this work include the support of the autoimmune POTS autoimmune hypothesis, the need to test for autoantibodies in POTS patients, and the quantification of the efficacy of common medical interventions.
An excessive increase in heart rate upon postural change is the defining characteristic of Postural Orthostatic Tachycardia Syndrome (POTS). Using state-of-the-art non-stationary signal processing, we showed that POTS patients have increased low-frequency (∼0.1 Hz) oscillation amplitude and decreased instantaneous phase difference between pressure and heart rate responses. These findings motivated the derivation of two novel mathematical models of the cardiovascular system and its control. The first reproduces POTS heart rate and blood pressure dynamics, encoding the hyperadrenergic, neuropathic, and hypovolemic phenotypes of POTS. The second model encodes the effects of adrenergic agonistic autoantibodies on the sinoatrial node and vasculature. This model showed that the presence of these autoantibodies can cause the oscillatory dynamics observed in POTS patients as well as tachycardia.

Quantification of oscillatory dynamics

The application of non-stationary signal processing is critical for POTS patient data due to the increase in heart rate after an orthostatic change. Results presented in this dissertation agree with previous studies [Med14; Ste15] that examined oscillations in blood pressure, heart rate, and cerebral blood flow. Stewart et al. [Ste15] postulated that these oscillations in cerebral blood flow could lead to POTS symptoms such as brain fog. Our study (Chapter 4) used a non-stationary signal processing technique called Uniform Phase Empirical Mode Decomposition (UPEMD) to ensure the accurate representation of the recordings. UPEMD produces stationary representations of the low-frequency portion of the heart rate and blood pressure signals in the time domain. Results showed that POTS patients have increased low-frequency (∼0.1 Hz) oscillations in heart rate and blood pressure. Using the resulting stationary low-frequency representations, we extracted the instantaneous phase of each and quantified the phase
interaction of the two signals as a scalar quantity, $M_h$. We showed that $M_h$ is orthostatic-invariant, meaning that the metric is approximately the same during rest and head-up tilt. However, we found that $M_h$ differs between the POTS and control groups. This novel metric shows promise for identifying POTS dynamics without invoking orthostatic tests.

**Representation of three phenotypes**

To better understand the etiology of POTS, we derived a novel mathematical model that represents the cardiovascular system and its control. Using this model, we studied three POTS phenotypes: the hyperadrenergic, neuropathic, and hypovolemic phenotypes. Our model derivation was guided by our desire to test the hypothesis that an increased baroreflex sensitivity causes larger low-frequency heart rate and blood pressure oscillations in POTS patients. Using this model, we were able to predict low-frequency oscillations with amplitudes of a healthy control subject and POTS patient. These results further add to other studies that have predicted low-frequency oscillations but have not studied POTS [Ish20; Hel00; Ham05].

Results show that POTS dynamics can be generated by modulating parameters representing the hyperadrenergic phenotype. Model representations of the neuropathic phenotype produce orthostatic tachycardia but not increased oscillations after the positional change. Reducing blood volume, indicative of the hypovolemic phenotype, increases the severity of both the hyperadrenergic and neuropathic model predictions but could not produce POTS dynamics on its own. Additionally, we observed that the responsiveness of the control, represented by Hill coefficients, was the primary source of changes in low-frequency oscillation amplitude. This suggests the central role of control response in the prediction of low-frequency dynamics and, therefore, the understanding of POTS. A limitation of this model is the lumped formulation of the control that prevents us from studying dynamics at the cellular level, which is needed to examine the effects of autoantibodies.

**Multiscale mode of autoantibody effects**

In recent years, autoantibodies have been observed in some POTS patients [Li14; GI19; Fed17a]; however, their role in the syndrome is controversial as it is not clear if the expression of antibodies is a cause or a symptom. While this debate has been well-posed physiologically, the study presented here is the first to model the effects of autoantibodies on the cardiovascular system and its control in POTS patients. We specifically consider the presence of autoantibodies against $\beta_{1,2}$ receptors [Fed17a; Li14; GI19], although the presence of autoantibodies against the $\alpha_1$ can exacerbate the effects predicted here, and other autoantibodies against the angiotensin II type 1, $M_2$, and $M_4$, receptors have also been observed [Li22; GI19; Yu18].

To examine these effects, we derive a novel model combining the cardiovascular system control model with a sinoatrial node cell. The sinoatrial node cell model predicts the effects of autoantibodies binding to the $\beta_{1,2}$ receptors in the SA node. Results show that autoantibody binding to the sinoatrial node increases low-frequency oscillation amplitude, while autoantibodies binding to $\beta_{1,2}$ receptors in
the vasculature are responsible for orthostatic tachycardia. In addition, we hypothesize that autoantibodies binding to the $\alpha_1$ receptors in vasculature would further increase tachycardia. These results support the hypothesis that the presence of adrenergic autoantibodies can cause POTS heart rate and blood pressure dynamics. As is true for the other mechanisms of POTS, the presence of adrenergic autoantibodies is likely not mutually exclusive with other phenotypes. It is likely that the presence of autoantibodies acts in conjunction with the previously discussed phenotypes to manifest POTS symptoms. Representations of common POTS interventions illustrate the importance of clinicians determining a patient's phenotype to treat the correct cause of the syndrome.

### 9.1 Future work

The future of POTS research hinges on understanding the pathophysiology, which is broadly divided into the analysis of patient data and representing how altered physiological states can cause the observed data. Of particular interest would be to generate a large sample size study with POTS patient groups separated by carefully diagnosed phenotypes and a control group. Each participant should undergo a series of autonomic tests, including head-up tilt, active standing, and other maneuvers stimulating the autonomic control system, recording electrocardiogram, continuous non-invasive arterial pressure, sympathetic tone, cerebral blood flow, and experienced symptoms. In addition, the patient's age, weight, sex, blood volume, past medical history, autoantibody test results, and POTS symptoms should be documented. This data would enable signal processing, clustering, machine learning, and mathematical modeling to be applied to assist in understanding pathophysiology and diagnosis. This study would present significant benefits to the medical community.

A study applying the signal processing methods shown in Chapter 6 on a large data set is currently underway. The work here presents a lumped parameter model and a more detailed model representing a sinoatrial node cell. Future models should include a vascular smooth muscle cell to predict vasculature response to autoantibodies against the $\beta_{1,2}$ and $\alpha_1$ receptors. Improved models should also seek to represent the heart rate and blood pressure low-frequency phase interaction, $M_h$. By optimizing a model to represent the dynamics observed in a patient, it could be possible to estimate physiological parameters, thus assisting in determining the phenotype of a patient. This patient-specific modeling approach could be instrumental to the future characterization of POTS patient physiology.

While providing the correct qualitative behavior, the results presented here need further scrutiny. In particular, our studies generate blood pressure oscillations that have a larger amplitude than expected. This may be due to the RC-circuit formulation of the cardiovascular model and may be remedied by adding additional circuit compartments as it provides more buffering of the dynamics. The model presented in Chapter 8 predicts an accurate decrease in pulse pressure for control simulations; however, the pulse pressure drops more than expected in POTS simulations. The pulse pressure will be increased either by decreasing upper arterial compliance, as done in Chapter 7, or by modeling the sympathetic control of vascular compliance.

In combination, these future studies could allow patient electrocardiograms and continuous non-
invasive arterial pressure data to be analyzed via non-stationary signal processing methods, which could then directly assist in diagnosis but could also inform a patient-specific model that estimates parameter values pertinent to POTS phenotype pathophysiology, thus aiding in clinical diagnosis and treatment as well.


Dahan, S et al. Postural orthostatic tachycardia syndrome (POTS)—a novel member of the autoimmune family. 2016.


Segel, I. H. “Enzyme kinetics: behavior and analysis of rapid equilibrium and steady state enzyme systems” (1975).


APPENDICES
Model parameters for the model presented in Chapter 7
Table A.1 Nominal patient values used to calculate parameter value and initial conditions.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value or Equation</th>
<th>Units</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>$h$</td>
<td>Height</td>
<td>167 cm</td>
<td>cm</td>
<td>[Col16]</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
<td>19*, 28 kg/m$^2$</td>
<td></td>
<td>[WHO20]</td>
</tr>
<tr>
<td>BV</td>
<td>Total blood vol</td>
<td>0.495BM$^{0.425}$h$^{1.575}$−1954 mL</td>
<td>mL</td>
<td>[Nad62; DB16]</td>
</tr>
<tr>
<td>CO</td>
<td>Cadiac output</td>
<td>BV/60 mL</td>
<td>s</td>
<td>[Wil14]</td>
</tr>
<tr>
<td>H</td>
<td>Heart rate</td>
<td>0.96 bps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T</td>
<td>Cardiac cycle</td>
<td>1/H</td>
<td>s</td>
<td></td>
</tr>
</tbody>
</table>

**Volume distribution**

| $V_a$  | Arteries                     | 0.15 BV mL                             | mL      | [Bor12]     |
| $V_v$  | Veins                        | 0.85 BV mL                             | mL      | [Bor12]     |
| $V_{ub}$ | UB supine               | 0.8 $V_i^{**}$ mL                    | mL      | [Wil89]     |
| $V_{ib}$ | LB supine                | 0.2 $V_i^{**}$ mL                    | mL      | [Wil89]     |
| $V_{M,lh}$ | Max left heart   | 110 mL                                 | mL      | [Bor12]     |
| $V_{m,lh}$ | Min left heart | 50 mL                                  | mL      | [Bor12]     |

**Unstressed volumes**

| $V_{a,u}$ | Arteries                     | 0.7 $V_a$ mL                           | mL      | [Ben67]     |
| $V_{v,u}$ | Veins                        | 0.925 $V_v$ mL                        | mL      | [Ben67]     |
| $V_{lh,u}$ | Left heart                  | 10 mL                                  | mL      | [Cai09]     |

**Nominal pressures**

| $P_{au}$ | UB arteries                  | $\frac{1}{2}80 + \frac{1}{2}120$ mmHg |         | [DeM20]     |
| $P_{ai}$ | LB arteries                  | 0.99 $P_{au}$ mmHg                     | mmHg    | [Wil14]     |
| $P_{vu}$ | UB veins                     | 2.75 mmHg                              | mmHg    | [Bor12]     |
| $P_{vi}$ | LB veins                     | 1.1 $P_{vu}$ mmHg                      | mmHg    | [Wil14]     |
| $P_{lh}$ | Left heart                   | 2.5 mmHg                               | mmHg    | [Bor12]     |

Abbreviations: vol - volume, UB - upper body, LB lower body

* hypovolomic patient.

** $i = a$ arteries and $i = v$ veins.
Table A.2 Nominal parameter values, their descriptions, value or equation, unit, and references. Unit abbreviations are: millimeters of mercury (mmHg), seconds (s), milliliters (mL), beats per second (bps), non dimensional (nd). The cardiovascular parameters were the same for all phenotypes simulated, while the baroreflex control parameters differ.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value or Equation</th>
<th>Units</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resistances</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$R_{iv}$</td>
<td>Valves</td>
<td>$1.0 \times 10^{-4}$</td>
<td>mmHg s</td>
<td></td>
</tr>
<tr>
<td>$R_{up}$</td>
<td>UB periph</td>
<td>$\frac{p_{ib}-p_{up}}{0.2 , CO}$</td>
<td>mmHg s</td>
<td></td>
</tr>
<tr>
<td>$R_a$</td>
<td>UB→LB art</td>
<td>$0.2 , CO$</td>
<td>mmHg s</td>
<td></td>
</tr>
<tr>
<td>$R_{lp}$</td>
<td>LB periph</td>
<td>$0.2 , CO$</td>
<td>mmHg s</td>
<td></td>
</tr>
<tr>
<td>$R_v$</td>
<td>LB→UB veins</td>
<td>$0.2 , CO$</td>
<td>mmHg s</td>
<td></td>
</tr>
<tr>
<td><strong>Compliances</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{au}$</td>
<td>Art UB</td>
<td>$\frac{V_{a,u,s}-V_{a,u}}{p_{au,s}}$</td>
<td>mL mmHg</td>
<td></td>
</tr>
<tr>
<td>$C_{al}$</td>
<td>Art LB</td>
<td>$\frac{V_{a,l}-V_{a,l}}{p_{al}}$</td>
<td>mL mmHg</td>
<td></td>
</tr>
<tr>
<td>$C_{vu}$</td>
<td>Veins UB</td>
<td>$\frac{V_{v,u}}{p_{vu}}$</td>
<td>mL mmHg</td>
<td></td>
</tr>
<tr>
<td><strong>Elastances</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_{ES}$</td>
<td>LH end systole</td>
<td>$\frac{V_{i,s}-V_{i,s}}{p_{ES}}$</td>
<td>mL mmHg</td>
<td></td>
</tr>
<tr>
<td>$E_{ED}$</td>
<td>LH end diastole</td>
<td>$\frac{V_{i,s}}{p_{i,s}}$</td>
<td>mL mmHg</td>
<td></td>
</tr>
<tr>
<td><strong>Heart rate time-constants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T_S$</td>
<td>End systole</td>
<td>$0.45(0.52 - \frac{0.11}{T})$</td>
<td>s</td>
<td>[Akh81; KJ85; Jan10]</td>
</tr>
<tr>
<td>$T_D$</td>
<td>End diastole</td>
<td>$0.55(0.52 - \frac{0.11}{T})$</td>
<td>s</td>
<td>[Akh81; KJ85; Jan10]</td>
</tr>
<tr>
<td><strong>Baroreflex sensitivities (Hill coefficients)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k_R$</td>
<td>Resistance</td>
<td>23</td>
<td>N.D.</td>
<td></td>
</tr>
<tr>
<td>$k_E$</td>
<td>LH End diastole</td>
<td>7</td>
<td>N.D.</td>
<td></td>
</tr>
<tr>
<td>$k_H$</td>
<td>Heart rate</td>
<td>27</td>
<td>N.D.</td>
<td></td>
</tr>
<tr>
<td><strong>Baroreflex time-scales</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>$\tau_R$</td>
<td>Resistance</td>
<td>12.5</td>
<td>s</td>
<td></td>
</tr>
<tr>
<td>$\tau_E$</td>
<td>LH End diastole</td>
<td>12.5</td>
<td>s</td>
<td></td>
</tr>
<tr>
<td>$\tau_H$</td>
<td>Heart rate</td>
<td>6.25</td>
<td>s</td>
<td></td>
</tr>
<tr>
<td>$\tau_P$</td>
<td>Mean UB art BP</td>
<td>2.5</td>
<td>s</td>
<td></td>
</tr>
<tr>
<td><strong>Baroreflex maximum (M) and minimum (m) saturations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$H_M$</td>
<td>Heart rate max</td>
<td>3.3</td>
<td>bps</td>
<td>[Nes13]</td>
</tr>
<tr>
<td>$H_m$</td>
<td>Heart rate min</td>
<td>0.3</td>
<td>bps</td>
<td></td>
</tr>
<tr>
<td>$R_{ip,M}$</td>
<td>LB periph resist max</td>
<td>$3 , R_{ip}$</td>
<td>mmHg s</td>
<td></td>
</tr>
<tr>
<td>$R_{ip,m}$</td>
<td>LB periph resist min</td>
<td>$0.2 , R_{ip}$</td>
<td>mmHg s</td>
<td></td>
</tr>
<tr>
<td>$R_{up,M}$</td>
<td>UB periph resist max</td>
<td>$3 , R_{up}$</td>
<td>mmHg s</td>
<td></td>
</tr>
<tr>
<td>$R_{up,m}$</td>
<td>UB periph resist min</td>
<td>$0.2 , R_{up}$</td>
<td>mmHg s</td>
<td></td>
</tr>
<tr>
<td>$E_{D,M}$</td>
<td>LH ED elastance max</td>
<td>$1.25 , E_D$</td>
<td>mL mmHg</td>
<td>[Lin95]</td>
</tr>
<tr>
<td>$E_{D,m}$</td>
<td>LH ED elastance min</td>
<td>$0.01 , E_D$</td>
<td>mL mmHg</td>
<td></td>
</tr>
<tr>
<td><strong>Baroreflex half-saturation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P_{IH}$</td>
<td>Heart rate</td>
<td>$\frac{p_{au}(H-H_{HI})}{H_{HI}}$</td>
<td>mmHg</td>
<td></td>
</tr>
<tr>
<td>$P_{IR}$</td>
<td>Periph resist</td>
<td>$\frac{p_{au}(R_{up}-R_{IR})}{R_{up}}$</td>
<td>mmHg</td>
<td></td>
</tr>
<tr>
<td>$P_{IE}$</td>
<td>LH elastance</td>
<td>$\frac{p_{au}(E_{D}-E_{IE})}{E_{D}}$</td>
<td>mmHg</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: UB - upper body, LB - lower body, LH - left heart, art - arteries, periph - peripheral, LH, BP - blood pressure, ED - end diastole.
* $i v = a v$ aortic valve, $i v = m v$ mitral valve.
** $i p = u p$ upper body peripheral, $i p = l p$ lower body peripheral.
B.1 Parameters, equations, and sources

Below are tables displaying the parameters and equations used in our model. References are in order - if there is more than one citation, then the source prior to another cited the latter for the desired information, with the original paper listed furthest to the right. If multiple papers are used for data, they are combined into one bracket.

† Denotes automatic optimization by the authors of the paper.
◦ Denotes paper containing data.
$a \rightarrow b$ Denotes the value was changed from $a$ in the cited study to value $b$ in this manuscript.
▷ Denotes that a parameter could change as a result of POTS

Fabbri et al. [Fab17] optimized their model to fit the action potential and cytosolic calcium transient traces from [Ver07a; Ver13]. Optimization was performed using the Nelder-Mead simplex method. Steps were also taken to ensure optimized parameters fell within the physiological range. Ottesen et al. [Ott14] ensured a subset of practically identifiable parameters. Optimized against rat and human data using a least squares cost function that compared computed and measured heart rate. Employed a Levenberg-Marquart gradient-based method.
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Value or Equation</th>
<th>Units</th>
<th>Description</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>57</td>
<td>pF</td>
<td>cell capacitance</td>
<td>[Fab17], [Ver07a]^p</td>
</tr>
<tr>
<td>L_{cell}</td>
<td>67</td>
<td>µm</td>
<td>cell length</td>
<td>[Fab17], [Ver07a]^p</td>
</tr>
<tr>
<td>R_{cell}</td>
<td>3.9</td>
<td>µm</td>
<td>cell radius</td>
<td>[Fab17], [Ver07a]^p</td>
</tr>
<tr>
<td>V_{part}</td>
<td>0.46 → 0.4728</td>
<td>N.D.</td>
<td>part of cell volume occupied with myoplasm</td>
<td>[Fab17]</td>
</tr>
<tr>
<td>V_{cell}</td>
<td>\pi R^2_{cell} L_{cell}</td>
<td>µm^3</td>
<td>cell volume</td>
<td>[Fab17]</td>
</tr>
<tr>
<td>V_i</td>
<td>V_{hart} V_{cell}</td>
<td>µm^3</td>
<td>myoplasmic volume</td>
<td>[Fab17]</td>
</tr>
<tr>
<td>Ca_o</td>
<td>1.8</td>
<td>mM</td>
<td>extracellular Ca^{2+} concentration</td>
<td>[Fab17]</td>
</tr>
<tr>
<td>Ca_i</td>
<td>9.2 \times 10^{-6}</td>
<td>mM</td>
<td>intracellular Ca^{2+} concentration</td>
<td>[Fab17]</td>
</tr>
<tr>
<td>K_o</td>
<td>5.4</td>
<td>mM</td>
<td>extracellular K^+ concentration</td>
<td>[Fab17]</td>
</tr>
<tr>
<td>K_i</td>
<td>140</td>
<td>mM</td>
<td>intracellular K^+ concentration</td>
<td>[Fab17]</td>
</tr>
<tr>
<td>N_a_o</td>
<td>140</td>
<td>mM</td>
<td>extracellular Na^+ concentration</td>
<td>[Fab17], [Ver07a]^p</td>
</tr>
<tr>
<td>Symbol</td>
<td>Value or Units</td>
<td>Description</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>----------------</td>
<td>-------------</td>
<td>-----</td>
<td></td>
</tr>
<tr>
<td>( v_{\text{shift}} )</td>
<td>80 mV</td>
<td>Shift for Hill equation domain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( k_v )</td>
<td>50 N.D.</td>
<td>( a_{m_v} ) Hill coefficient</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( v_2 )</td>
<td>( 15 + v_{\text{shift}} ) mV</td>
<td>Half saturation for ( a_{m_v} ) Hill equation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( g_{m_v} )</td>
<td>300 s(^{-1})</td>
<td>Exponential growth coefficient in ( \frac{d m_v}{d t} )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( d_{m_v} )</td>
<td>0.1 s(^{-1})</td>
<td>Exponential decay coefficient in ( \frac{d m_v}{d t} )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \delta_t )</td>
<td>0.27 N.D.</td>
<td>Cell equation time scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symbol</td>
<td>Value or Units</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>----------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$F$</td>
<td>96485 C/mol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$R$</td>
<td>8314.472 J/(kmol K)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$T$</td>
<td>310 K</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$g$</td>
<td>-982 cm s$^2$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\rho$</td>
<td>1.06 g/cm$^3$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$h_c$</td>
<td>25 cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_{Na}$</td>
<td>$(RT/F)\log\left(\frac{N_{ao}}{N_{ai}}\right)$ mV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_{mh}$</td>
<td>$(RT/F)\log\left(\frac{N_{ao}+0.12K_o}{N_{ai}+0.12N_{ai}}\right)$ mV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_K$</td>
<td>$(RT/F)\log\left(\frac{K_o}{K_i+0.12N_{ao}}\right)$ mV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_{Ks}$</td>
<td>$(RT/F)\log\left(\frac{K_o+0.12N_{ao}}{K_i}\right)$ mV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_{Ca}$</td>
<td>$0.5(RT/F)\log\left(\frac{Ca_o}{Ca_{sub}}\right)$ mV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_I$</td>
<td>-22 mV</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Ionic values**

- $F$: Faraday constant
- $R$: Universal gas constant
- $T$: Absolute temperature for 37°C
- $g$: Gravitational constant
- $\rho$: Density of blood
- $h_c$: Distance between baroreceptors
- $E_{Na}$: Reversal potential for Na$^+$
- $E_{mh}$: Reversal potential for fast Na$^+$
- $E_K$: Reversal potential for K$^+$
- $E_{Ks}$: Reversal potential for slow K$^+$
- $E_{Ca}$: Reversal potential for Ca$^{2+}$
- $E_I$: Reversal potential for $I_t$
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Value or Units</th>
<th>Description</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>$g_{fNa}$</td>
<td>0.00268 $\mu S$</td>
<td>funny current - Na</td>
<td>[Fab17], [Ver07a]°</td>
</tr>
<tr>
<td>$g_K$</td>
<td>0.00159 $\mu S$</td>
<td>funny current - K</td>
<td>[Fab17], [Ver07a]°</td>
</tr>
<tr>
<td>$P_{CaL}$</td>
<td>0.4578 nA/mM</td>
<td>L-type current</td>
<td>[Fab17]†</td>
</tr>
<tr>
<td>$P_{CaT}$</td>
<td>0.04132 nA/mM</td>
<td>T-type current</td>
<td>[Fab17]†</td>
</tr>
<tr>
<td>$g_{Kr}$</td>
<td>0.00424 $\mu S$</td>
<td>delayed rectifier - rapid</td>
<td>[Fab17], [Ver07a; Dro97]°</td>
</tr>
<tr>
<td>$g_{Ku}$</td>
<td>$1.539 \times 10^{-4}$ $\mu S$</td>
<td>delayed rectifier - ultrarapid</td>
<td>[Fab17]†</td>
</tr>
<tr>
<td>$g_{Ks,F}$</td>
<td>0.00065 $\mu S$</td>
<td>delayed rectifier - slow</td>
<td>[Fab17]†</td>
</tr>
<tr>
<td>$g_{K,ACh}$</td>
<td>0.00345 $\mu S$</td>
<td>delayed rectifier - ACh</td>
<td>[Fab17], [DiF89]°</td>
</tr>
<tr>
<td>$g_{io}$</td>
<td>$3.5 \times 10^{-3}$ $\mu S$</td>
<td>transient outward</td>
<td>[Fab17], [Mal09]°</td>
</tr>
<tr>
<td>$g_{Na}$</td>
<td>0.0223 $\mu S$</td>
<td>Na$^+$</td>
<td>[Fab17], [Nob89]°</td>
</tr>
<tr>
<td>$K_{Na,Ca,F}$</td>
<td>0.08105 → 0.1621 nA</td>
<td>Na$^+$ - K$^+$ pump</td>
<td>[Fab17]†</td>
</tr>
<tr>
<td>$K_{Na,Ca}$</td>
<td>3.343 → 4 nA</td>
<td>Na$^+$ - Ca$^{2+}$ exchanger</td>
<td>[Fab17]†</td>
</tr>
</tbody>
</table>

**Conductances**

**Ion effects on ion currents**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Value or Units</th>
<th>Description</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_{fCa}$</td>
<td>0.0075 s$^{-1}$</td>
<td>Used to calculate $\tau_{fCa}$ (time scale)</td>
<td>[Fab17], [Fer91]°</td>
</tr>
<tr>
<td>$K_{m,fCa}$</td>
<td>0.000338 mM</td>
<td>Half-saturation for $f Ca_\infty$</td>
<td>[Fab17], [Fer91]°</td>
</tr>
<tr>
<td>$K_{m,Kp}$</td>
<td>1.4 mM</td>
<td>half-maximum $K_o$ for $l_{NaK}$</td>
<td>[Fab17], [Kur02], [Sak96]°</td>
</tr>
<tr>
<td>$K_{m,Nap}$</td>
<td>14 mM</td>
<td>half-maximum $Na_i$ for $l_{NaK}$</td>
<td>[Fab17], [Kur02], [Sak96]°</td>
</tr>
<tr>
<td>Symbol</td>
<td>Value or Units</td>
<td>Description</td>
<td>Ref</td>
</tr>
<tr>
<td>--------</td>
<td>----------------</td>
<td>-------------</td>
<td>-----</td>
</tr>
<tr>
<td>$K_{1ni}$</td>
<td>395.3 mM</td>
<td>intracellular $\text{Na}^+$ binding to first site on NaCa</td>
<td>[Fab17], [Kur02], [Dok96], [Mat92], [Hag88]°</td>
</tr>
<tr>
<td>$K_{1no}$</td>
<td>1628 mM</td>
<td>extracellular $\text{Na}^+$ binding to first site on NaCa</td>
<td>[Fab17], [Kur02], [Dok96], [Mat92], [Hag88]°</td>
</tr>
<tr>
<td>$K_{2ni}$</td>
<td>2.289 mM</td>
<td>intracellular $\text{Na}^+$ binding to second site on NaCa</td>
<td>[Fab17], [Kur02], [Dok96], [Mat92], [Hag88]°</td>
</tr>
<tr>
<td>$K_{2no}$</td>
<td>561.4 mM</td>
<td>extracellular $\text{Na}^+$ binding to second site on NaCa</td>
<td>[Fab17], [Kur02], [Dok96], [Mat92], [Hag88]°</td>
</tr>
<tr>
<td>$K_{3ni}$</td>
<td>26.44 mM</td>
<td>intracellular $\text{Na}^+$ binding to third site on NaCa</td>
<td>[Fab17], [Kur02], [Dok96], [Mat92], [Hag88]°</td>
</tr>
<tr>
<td>$K_{3no}$</td>
<td>4.663 mM</td>
<td>extracellular $\text{Na}^+$ binding to third site on NaCa</td>
<td>[Fab17], [Kur02], [Dok96], [Mat92], [Hag88]°</td>
</tr>
<tr>
<td>$K_{ci}$</td>
<td>0.0207 mM</td>
<td>intracellular $\text{Ca}^{2+}$ binding to NaCa transporter</td>
<td>[Fab17], [Kur02], [Dok96], [Mat92], [Hag88]°</td>
</tr>
<tr>
<td>$K_{cni}$</td>
<td>26.44 mM</td>
<td>intracellular $\text{Na}^+$ and $\text{Ca}^{2+}$ simultaneous binding to NaCa</td>
<td>[Fab17], [Kur02], [Dok96], [Mat92], [Hag88]°</td>
</tr>
<tr>
<td>$K_{co}$</td>
<td>3.663 mM</td>
<td>extracellular $\text{Ca}^{2+}$ binding to NaCa transporter</td>
<td>[Fab17], [Kur02], [Dok96], [Mat92], [Hag88]°</td>
</tr>
<tr>
<td>$Q_{ci}$</td>
<td>0.1369 N.D.</td>
<td>intracellular $\text{Ca}^{2+}$ occlusion reaction of NaCa</td>
<td>[Fab17], [Kur02], [Dok96], [Mat92], [Hag88]°</td>
</tr>
<tr>
<td>$Q_{n}$</td>
<td>0.4315 N.D.</td>
<td>$\text{Na}^+$ occlusion reaction of NaCa</td>
<td>[Fab17], [Kur02], [Dok96], [Mat92], [Hag88]°</td>
</tr>
<tr>
<td>Symbol</td>
<td>Value or Units</td>
<td>Description</td>
<td>Ref</td>
</tr>
<tr>
<td>----------</td>
<td>----------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>CAMP equation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$K_{ADC}$</td>
<td>0.008 mM/s</td>
<td>cAMP production rate</td>
<td>[Dem99]</td>
</tr>
<tr>
<td>$V_{PDE}$</td>
<td>20 s⁻¹</td>
<td>cAMP degradation rate</td>
<td>[Dem99], [Hag89]</td>
</tr>
<tr>
<td>cGMP</td>
<td>0.002 mM</td>
<td>Guanosine cyclic monophosphate</td>
<td>[Dem99]</td>
</tr>
<tr>
<td>$K_{PDE}$</td>
<td>82.5 N.D.</td>
<td>cAMP degradation</td>
<td></td>
</tr>
<tr>
<td>$K_{AC h}$</td>
<td>0.007 mM</td>
<td>Half-saturation for ACh</td>
<td>[Dem99]</td>
</tr>
<tr>
<td>$v_{max, m}$</td>
<td>1.75 N.D.</td>
<td>Maximum reaction rate for velocity equation</td>
<td></td>
</tr>
<tr>
<td>$v_{max, M, Control}$</td>
<td>3.1 N.D.</td>
<td>Maximum reaction rate for velocity equation</td>
<td></td>
</tr>
<tr>
<td>$k_{v_{max, A}}$</td>
<td>2600 N.D.</td>
<td>Autoantibody cooperativity proportionality constant</td>
<td></td>
</tr>
<tr>
<td>$K_{v_{max}}$</td>
<td>$1.6 \times 10^{-5}$ mM</td>
<td>Half saturation for $v_{max}$</td>
<td></td>
</tr>
<tr>
<td>$k_v$</td>
<td>20</td>
<td>Hill coefficient for $v_{max}$</td>
<td></td>
</tr>
<tr>
<td>$K_S$</td>
<td>$1.85 \times 10^{-4}$ mM</td>
<td>Dissociation constant for NE to receptor binding</td>
<td></td>
</tr>
<tr>
<td>$K_A$</td>
<td>$7 \times 10^{-4}$ mM</td>
<td>Dissociation constant for autoantibody to receptor binding</td>
<td></td>
</tr>
<tr>
<td>$\eta$</td>
<td>0.9</td>
<td>Increase in binding affinity for Receptor-antibody to NE</td>
<td>N.D.</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>1</td>
<td>Increase in reaction speed for Receptor-antibody-NE to cAMP</td>
<td>N.D.</td>
</tr>
<tr>
<td>$A \triangleleft$</td>
<td>$2.3 \times 10^{-4}$ mM</td>
<td>Amount of extracellular antibodies</td>
<td></td>
</tr>
<tr>
<td>$C_1 \triangleleft$</td>
<td>$\frac{v_{max} \left( \frac{K_S}{K_S + \frac{\lambda A}{\kappa_S}} \right)}{\frac{1}{\kappa_S + \frac{\lambda A}{\kappa_A K_S}}}$</td>
<td>N.D. Scale of NE cAMP Hill term</td>
<td></td>
</tr>
<tr>
<td>$C_2 \triangleleft$</td>
<td>$\frac{1 + \frac{\lambda A}{K_A}}{\frac{K_S}{K_S + \frac{\lambda A}{\kappa_A K_S}}}$</td>
<td>mM Half-saturation of NE cAMP Hill term</td>
<td></td>
</tr>
<tr>
<td>$C_3$</td>
<td>$V_{PDE cGMP}$</td>
<td>mM Scale of cAMP degradation Hill term</td>
<td></td>
</tr>
<tr>
<td>$C_4$</td>
<td>$K_{PDE cGMP}$</td>
<td>mM Half-saturation of NE cAMP Hill term</td>
<td></td>
</tr>
<tr>
<td>Symbol</td>
<td>Value or Units</td>
<td>Description</td>
<td>Ref</td>
</tr>
<tr>
<td>--------</td>
<td>----------------</td>
<td>-------------</td>
<td>-----</td>
</tr>
<tr>
<td>$T_S(0)$</td>
<td>0.2</td>
<td>N.D.</td>
<td>Percentage of maximum sympathetic activity at rest</td>
</tr>
<tr>
<td>$T_P(0)$</td>
<td>0.8</td>
<td>N.D.</td>
<td>Percentage of maximum parasympathetic activity at rest</td>
</tr>
<tr>
<td>$w_{S,1}$</td>
<td>4.19</td>
<td></td>
<td>Norepinephrine gain from neural tone</td>
</tr>
<tr>
<td>$w_{S,2}$</td>
<td>0</td>
<td></td>
<td>Norepinephrine shift from neural tone</td>
</tr>
<tr>
<td>$k_{TS}$</td>
<td>10</td>
<td>N.D.</td>
<td>Sympathetic Hill coefficient</td>
</tr>
<tr>
<td>$P_{2S}$</td>
<td>$P_{S}(0)\left(\frac{T_S(0)}{1-T_S(0)}\right)^{\frac{3}{2}}$</td>
<td>mmHg</td>
<td>Half-saturation point for sympathetic Hill function</td>
</tr>
<tr>
<td>$w_{P,1}$</td>
<td>2.31</td>
<td></td>
<td>Acetylcholine gain from neural tone</td>
</tr>
<tr>
<td>$T_{P,2}$</td>
<td>0</td>
<td></td>
<td>Acetylcholine shift from neural tone</td>
</tr>
<tr>
<td>$k_{TP}$</td>
<td>10</td>
<td>N.D.</td>
<td>Parasympathetic Hill coefficient</td>
</tr>
<tr>
<td>$P_{2P}$</td>
<td>$P_{P}(0)\left(\frac{1-T_P(0)}{T_P(0)}\right)^{\frac{3}{2}}$</td>
<td>mmHg</td>
<td>Half-saturation point for parasympathetic Hill function</td>
</tr>
<tr>
<td>$\tau_S$</td>
<td>12.5</td>
<td>s</td>
<td>Sympathetic tone time scale</td>
</tr>
<tr>
<td>$\tau_P$</td>
<td>6.25</td>
<td>s</td>
<td>Parasympathetic tone time scale</td>
</tr>
<tr>
<td>$\tau_{NE}$</td>
<td>9.1</td>
<td>s</td>
<td>Sympathetic to NE time scale</td>
</tr>
<tr>
<td>$\tau_{ACH}$</td>
<td>0.2</td>
<td>s</td>
<td>Parasympathetic to ACh time scale</td>
</tr>
<tr>
<td>$\tau$</td>
<td>2.5</td>
<td>s</td>
<td>Sympathetic delay</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Afferent nerves</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau_P$</td>
<td>1</td>
</tr>
<tr>
<td>$\tau_Z$</td>
<td>1.25</td>
</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
</tr>
<tr>
<td>( h t )</td>
<td>Height</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>BV( \rightarrow )</td>
<td>Total blood vol</td>
</tr>
<tr>
<td>CO</td>
<td>Cadiac output</td>
</tr>
</tbody>
</table>

Volume distribution

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value or Equation</th>
<th>Units</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_a )</td>
<td>Arteries</td>
<td>0.15 BV</td>
<td>mL</td>
<td>[Bor12]</td>
</tr>
<tr>
<td>( V_v )</td>
<td>Veins</td>
<td>0.85 BV</td>
<td>mL</td>
<td>[Bor12]</td>
</tr>
<tr>
<td>( V_{ub} )</td>
<td>UB supine</td>
<td>0.8 ( V_i^{**} )</td>
<td>mL</td>
<td>[Wil89]</td>
</tr>
<tr>
<td>( V_{lb} )</td>
<td>LB supine</td>
<td>0.2 ( V_i^{**} )</td>
<td>mL</td>
<td>[Wil89]</td>
</tr>
<tr>
<td>( V_{M, lh} )</td>
<td>Max left heart</td>
<td>110</td>
<td>mL</td>
<td>[Bor12]</td>
</tr>
<tr>
<td>( V_{m, lh} )</td>
<td>Min left heart</td>
<td>50</td>
<td>mL</td>
<td>[Bor12]</td>
</tr>
</tbody>
</table>

Unstressed volumes

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value or Equation</th>
<th>Units</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_{a,u} )</td>
<td>Arteries</td>
<td>0.7 ( V_a )</td>
<td>mL</td>
<td>[Ben67]</td>
</tr>
<tr>
<td>( V_{v,u} )</td>
<td>Veins</td>
<td>0.925 ( V_v )</td>
<td>mL</td>
<td>[Ben67]</td>
</tr>
<tr>
<td>( V_{lh,u} )</td>
<td>Left heart</td>
<td>10</td>
<td>mL</td>
<td>[Cai09]</td>
</tr>
</tbody>
</table>

Nominal pressures

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value or Equation</th>
<th>Units</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P_{au} )</td>
<td>UB arteries</td>
<td>( \frac{2}{5} 80 + \frac{2}{5} 120 ) mmHg</td>
<td>[DeM20]</td>
<td></td>
</tr>
<tr>
<td>( P_{al} )</td>
<td>LB arteries</td>
<td>0.99 ( P_{au} ) mmHg</td>
<td>[Wil14]</td>
<td></td>
</tr>
<tr>
<td>( P_{vu} )</td>
<td>UB veins</td>
<td>2.75 mmHg</td>
<td>[Bor12]</td>
<td></td>
</tr>
<tr>
<td>( P_{vl} )</td>
<td>LB veins</td>
<td>1.1 ( P_{vu} ) mmHg</td>
<td>[Wil14]</td>
<td></td>
</tr>
<tr>
<td>( P_{lh} )</td>
<td>Left heart</td>
<td>2.5 mmHg</td>
<td>[Bor12]</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: vol - volume, UB - upper body, LB - lower body

* hypovolumic patient.

** \( i = a \) arteries and \( i = v \) veins.
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Value or Equation</th>
<th>Units</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_{iv}$</td>
<td>Valves</td>
<td>$1.0 \cdot 10^{-4}$</td>
<td>mmHg s/ml</td>
<td>[Ged22]</td>
</tr>
<tr>
<td>$R_a$</td>
<td>UB→LB art</td>
<td>$\frac{p_{ah}-p_{al}}{0.2 \cdot CO}$</td>
<td>mmHg s/ml</td>
<td>[Ged22]</td>
</tr>
<tr>
<td>$R_v$</td>
<td>LB→UB veins</td>
<td>$\frac{p_{ah}-p_{au}}{0.2 \cdot CO}$</td>
<td>mmHg s/ml</td>
<td>[Ged22]</td>
</tr>
<tr>
<td>$C_{au}$</td>
<td>Art UB</td>
<td>$\frac{V_{a,u}-V_{a,u,u}}{p_{au}}$</td>
<td>mL mmHg</td>
<td>[Ged22]</td>
</tr>
<tr>
<td>$C_{al}$</td>
<td>Art LB</td>
<td>$\frac{V_{a,l}-V_{a,l,u}}{p_{al}}$</td>
<td>mL mmHg</td>
<td>[Ged22]</td>
</tr>
<tr>
<td>$C_{vu}$</td>
<td>Veins UB</td>
<td>$\frac{V_{v,u}-V_{v,u,u}}{p_{vu}}$</td>
<td>mL mmHg</td>
<td>[Ged22]</td>
</tr>
<tr>
<td>$E_{ES}$</td>
<td>LH end systole</td>
<td>$\frac{p_{h,D}}{V_{LH}}$</td>
<td>mmHg s/ml</td>
<td>[Ged22]</td>
</tr>
<tr>
<td>$R_{lp,M}$</td>
<td>LB periph resist max</td>
<td>$3R_{lp}$</td>
<td>mmHg s/ml</td>
<td>[Ged22]</td>
</tr>
<tr>
<td>$R_{lp,m}$</td>
<td>LB periph resist min</td>
<td>$0.2R_{lp}$</td>
<td>mmHg s/ml</td>
<td>[Ged22]</td>
</tr>
<tr>
<td>$R_{up,M}$</td>
<td>UB periph resist max</td>
<td>$3R_{up}$</td>
<td>mmHg s/ml</td>
<td>[Ged22]</td>
</tr>
<tr>
<td>$R_{up,m}$</td>
<td>UB periph resist min</td>
<td>$0.2R_{up}$</td>
<td>mmHg s/ml</td>
<td>[Ged22]</td>
</tr>
<tr>
<td>$E_{DM}$</td>
<td>LH ED elastance max</td>
<td>$1.25E_D$</td>
<td>mmHg s/ml</td>
<td>[Lin95]</td>
</tr>
<tr>
<td>$E_{D,m}$</td>
<td>LH ED elastance min</td>
<td>$0.01E_D$</td>
<td>mmHg s/ml</td>
<td>[Ged22]</td>
</tr>
</tbody>
</table>

Abbreviations: UB - upper body, LB - lower body, LH - left heart, art - arteries, periph - peripheral, LH, BP - blood pressure, ED - end diastole.

* $iv = av$ aortic valve, $iv = mv$ mitral valve.

** $ip = up$ upper body peripheral, $ip = lp$ lower body peripheral.
<table>
<thead>
<tr>
<th>Description</th>
<th>Equation number(s)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>$c AM P$</td>
<td>B.2</td>
<td>[Dem99; Seg75]</td>
</tr>
<tr>
<td>$c AM P$ effects</td>
<td>B.4 - B.8</td>
<td>[Dem99]</td>
</tr>
<tr>
<td>$I_f$</td>
<td>B.9 - B.13</td>
<td>[Fab17],[Ver07b; Ver10; Ver07a],[Dok96]</td>
</tr>
<tr>
<td>$I_{CaL}$</td>
<td>B.14 - B.28</td>
<td>[Fab17; Dem99],[Sev12],[Kur02; Mal09]</td>
</tr>
<tr>
<td>$I_{CaT}$</td>
<td>B.29 - B.35</td>
<td>[Fab17],[Sev12],[Sar03]</td>
</tr>
<tr>
<td>$I_{Kr}$</td>
<td>B.36 - B.46</td>
<td>[Fab17],[Sev12],[Ono95; Mal09; Shi87]</td>
</tr>
<tr>
<td>$I_{Ks}$</td>
<td>B.47 - B.52</td>
<td>[Fab17; Dem99],[Sev12],[Mal09; Kur02],[Zha00]</td>
</tr>
<tr>
<td>$I_{K,ACh}$</td>
<td>B.53 - B.57</td>
<td>[Fab17],[Him08],[Sar03]</td>
</tr>
<tr>
<td>$I_{K,ACh} - \alpha_a$</td>
<td>B.58</td>
<td>[Dem99]</td>
</tr>
<tr>
<td>$I_{to}$</td>
<td>B.60 - B.66</td>
<td>[Fab17],[Sev12],[Mal09],[Kur02]</td>
</tr>
<tr>
<td>$I_{Na}$</td>
<td>B.68 - B.79</td>
<td>[Fab17],[Sev12],[Nob89]</td>
</tr>
<tr>
<td>$I_{NaK}$</td>
<td>B.81</td>
<td>[Fab17; Dem99],[Sev12],[Kur02]</td>
</tr>
<tr>
<td>$I_{NaCa}$</td>
<td>B.82 - B.97</td>
<td>[Fab17],[Kur02],[Dok96],[Mat92]</td>
</tr>
<tr>
<td>$I_{Kur}$</td>
<td>B.98 - B.104</td>
<td>[Fab17]</td>
</tr>
<tr>
<td>$Na i$</td>
<td>B.105</td>
<td>[Fab17]</td>
</tr>
<tr>
<td>Left heart timing fraction</td>
<td>B.106 - B.107</td>
<td>[Ged22],[Akh81; KJ85; Jan10]</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>B.108 - B.124</td>
<td>[Ged22],[Wil14; Ott13; Har82; Pst17]</td>
</tr>
<tr>
<td>Afferent</td>
<td>B.125 - B.127</td>
<td>[Wil14; Urs96]</td>
</tr>
<tr>
<td>Peripheral Resistance and</td>
<td>B.128 - B.137</td>
<td>[Ged22]</td>
</tr>
<tr>
<td>End-diastolic elastance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tone and NE/ACh concentrations</td>
<td>B.138 - B.141</td>
<td>[Ott14],[Olu06a; Ott11]</td>
</tr>
<tr>
<td>Scale coupling</td>
<td>B.142 - B.148</td>
<td></td>
</tr>
</tbody>
</table>
\section*{B.2 Equations}

\textbf{Voltage equation}

\[-C \frac{dv}{dt} = I_{\text{CaT}} + I_{\text{CaL}} + I_{\text{NaCa}} + I_t + I_{\text{Kr}} + I_{\text{Ks}} + I_{\text{to}} + I_{\text{Na}} + I_{\text{NaK}} + I_{\text{Kur}} + I_{\text{K,ACh}} \] (B.1)

\textbf{cAMP}

\[ \frac{dc\text{AMP}}{dt} = K_{\text{ADC}} \left( 1 + C_1 \frac{c_{NE}}{c_{ACH} + K_{ACH}} \right) - C_3 \frac{c\text{AMP}}{c\text{AMP} + C_4} \] (B.2)

\[ v_{\text{max}} = (v_{\text{max},1} - v_{\text{max},2}) \frac{c_{NE}^{20}}{c_{NE}^{20} + K_{V_{m}}^{20}} + v_{\text{max},2} \] (B.3)

\[ F_{c\text{AMP},\text{CaL}} = 0.4 \left( 1 + \frac{4.5 \cdot c\text{AMP}}{c\text{AMP} + 0.0065} \right) + 0.03157 \] (B.4)

\[ F_{c\text{AMP},\text{Ks}} = g_{ks} \left( 0.62 \left( 1 + 2.6129 \frac{c\text{AMP}}{c\text{AMP} + 0.0065} \right) \right) \] (B.5)

\[ V_{\text{half}} = \frac{20.5}{1 + e^{\frac{-c\text{AMP} - 0.0034}{0.0005}}} - 78.56 \] (B.6)

\[ y_{\infty} = \frac{1}{1 + e^{v - v_{\text{hall}}/9}} \cdot 0.165 \] (B.7)

\[ F_{c\text{AMP},\text{NaK}} = I_{\text{NaK, max}} \left( \frac{1.6}{1 + e^{\frac{-c\text{AMP} - 0.00375}{0.00075}}} + 0.99 \right) \] (B.8)

\[ I_f \]

\[ I_t = I_{\text{Na}} + I_k \] (B.9)

\[ I_{\text{Na}} = y \cdot g_{f_{\text{Na}}} \cdot (V - E_{\text{Na}}) \] (B.10)

\[ I_k = y \cdot g_{f_{\text{k}}} \cdot (V - E_{\text{k}}) \] (B.11)

\[ \frac{dy}{dt} = \frac{y_{\infty} - y}{\tau_y} \] (B.12)

\[ \tau_y = \left( \frac{0.36 \cdot (v + 148.8)}{e^{0.066(v+148.8)} - 1} + \frac{0.1(v + 87.3)}{1 - e^{-0.2(v+87.3)}} \right)^{-1} - 0.054 \] (B.13)
\[ I_{\text{Cal}} = F_{\text{cAMP,Cal}}(I_{\text{siCa}} + I_{\text{siK}} + I_{\text{siNa}}) \]  

\[ I_{\text{siCa}} = \frac{2 P_{\text{Cal}} v}{R T \left( 1 - e^{-\frac{2\nu}{R T}} \right)} \left( Cai - Ca o e^{-\frac{\nu}{R T}} \right) dL \frac{df Ca}{dt} \tag{B.14} \]

\[ I_{\text{siK}} = \frac{0.000365 P_{\text{Cal}} v}{R T \left( 1 - e^{-\frac{\nu}{R T}} \right)} \left( Ki - Ko e^{-\frac{\nu}{R T}} \right) dL \frac{df Ca}{dt} \tag{B.15} \]

\[ I_{\text{siNa}} = \frac{0.0000185 P_{\text{Cal}} v}{R T \left( 1 - e^{-\frac{\nu}{R T}} \right)} \left( Na i - Na o e^{-\frac{\nu}{R T}} \right) dL \frac{df Ca}{dt} \tag{B.16} \]

\[ \frac{dL}{dt} = \frac{L_{\infty} - L}{\tau_{dL}} \tag{B.17} \]

\[ \frac{df L}{dt} = \frac{f L_{\infty} - f L}{\tau_{f L}} \tag{B.18} \]

\[ \frac{df Ca}{dt} = \frac{f Ca_{\infty} - f Ca}{\tau_{f Ca}} \tag{B.19} \]

\[ dL_{\infty} = \frac{1}{1 + e^{-\frac{(-16.45 + 1.8)}{4.337}}} \tag{B.20} \]

\[ a_{dL} = \frac{-0.2839(v + 41.8)}{e^{-\frac{(v+16.45)}{4.337}} - 1} - \frac{0.0849(v + 6.8)}{e^{-\frac{(v+6.8)}{4.8}} - 1} \tag{B.21} \]

\[ \beta_{dL} = \frac{0.01143(v + 1.8)}{e^{-\frac{1.8}{2.5}} - 1} \tag{B.22} \]

\[ \tau_{dL} = \frac{0.001}{a_{dL} + \beta_{dL}} \tag{B.23} \]

\[ f L_{\infty} = \frac{1}{1 + e^{-\frac{43.74}{3.3}}} \tag{B.24} \]

\[ \tau_{f L} = 0.001 \left( 44.3 + 230 e^{-\frac{(6.16)^2}{18}} \right) \tag{B.25} \]

\[ f Ca_{\infty} = \frac{K m_{f Ca}}{K m_{f Ca} + Cai} \tag{B.26} \]

\[ \tau_{f Ca} = \frac{0.001 f Ca_{\infty}}{a_{f Ca}} \tag{B.27} \]
\[ I_{\text{CaT}} = \frac{2 P_{\text{CaT}} v}{R T \left( 1 - e^{-\frac{2v}{R T}} \right)} \left( Cai - Cao e^{\frac{2v}{RT}} \right) dT \ fT \] (B.29)

\[
\frac{ddT}{dt} = \frac{dT_\infty - dT}{\tau_dT} \\
\frac{dfT}{dt} = \frac{fT_\infty - fT}{\tau_fT} \\
dT_\infty = \frac{1}{1 + e^{-v + 38.3}} \\
\tau_dT = \frac{0.001}{1.068 \left( e^{-\frac{v + 38.3}{30}} + e^{-\frac{v + 38.3}{30}} \right)} \\
fT_\infty = \frac{1}{1 + e^{v + 58.7 \frac{7}{38.3}}} \\
\tau_fT = \frac{1}{16.67 \left( e^{-\frac{v + 75}{83.3}} + e^{\frac{v + 75}{15.38}} \right)} \\
I_{\text{Kr}}
\]

\[ I_{\text{Kr}} = g_{\text{Kr}} (v - E_K) (0.9 \ p aF + 0.1 \ p aS) \ piy \] (B.36)

\[
\frac{dpaF}{dt} = \frac{pa_{\infty} - paF}{\tau_{paF}} \\
\frac{dpaS}{dt} = \frac{pa_{\infty} - paS}{\tau_{paS}} \\
\frac{dpiy}{dt} = \frac{piy_\infty - piy}{\tau_{piy}} \\
pa_{F\infty} = \frac{1}{1 + e^{-\frac{v + 19.044}{7.6607}}} \\
pa_{S\infty} = \frac{1}{1 + e^{-\frac{v + 19.044}{7.6607}}} \\
piy_{\infty} = \frac{1}{1 + e^{\frac{v + 28.6}{22.6}}} \\
\tau_{paF} = \frac{1}{30 e \frac{v}{\pi} + e^{2v}} \\
\tau_{paS} = \frac{0.84655354}{4.2 e \frac{v}{\pi} + 0.15 e^{2v}} \\
\tau_{piy} = \frac{1}{100 e^{\frac{v}{100\pi}} + 656 e^{\frac{v}{100\pi}}} \\
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\[ I_{Ks} = F_{cAMPKs} (v - E_{Ks}) n^2 \] (B.47)

\[ \frac{dn}{dt} = \frac{n_{\infty} - n}{\tau_n} \] (B.48)

\[ n_{\infty} = \sqrt{\frac{1}{1 + e^{-n + 0.6383}} \cdot \frac{28}{1 + e^{-n + 0.6383}}} \] (B.49)

\[ \alpha_n = \frac{28}{1 + e^{-n + 0.6383}} \] (B.50)

\[ \beta_n = e^{-n + 0.6383} \] (B.51)

\[ \tau_n = \frac{1}{\alpha_n + \beta_n} \] (B.52)

\[ I_{KACH} \]

\[ I_{KACH} = g_{KACH} (v - E_K) \left(1 + e^{\frac{v + 20}{30}}\right) a \] (B.53)

\[ \frac{da}{dt} = \frac{a_{\infty} - a}{\tau_a} \] (B.54)

\[ \beta_a = 10 e^{0.0133 (v + 40)} \] (B.55)

\[ a_{\infty} = \frac{a_a}{\alpha_a + \beta_a} \] (B.56)

\[ \tau_a = \frac{1}{\alpha_a + \beta_a} \] (B.57)

\[ a_a = \frac{1}{1000} \left(3.5988 - 0.025641 + \frac{0.0000012155}{e_{ACH}}\right) \] (B.58)

\[ I_{10} \]
\[ I_{\text{Na}} = g_{\text{Na}} \left( v - E_{\text{m}} \right) q r \]  
(B.60)

\[ \frac{dq}{dt} = \frac{q_{\infty} - q}{\tau_q} \]  
(B.61)

\[ \frac{dr}{dt} = \frac{r_{\infty} - r}{\tau_r} \]  
(B.62)

\[ q_{\infty} = \frac{1}{1 + e^{\frac{v + 4.67}{15}}} \]  
(B.63)

\[ \tau_q = 0.0006 \left( 65.17 e^{-0.08 \left( v + 44 \right)} + 0.065 e^{0.1 \left( v + 45.93 \right)} + 10.1 \right) \]  
(B.64)

\[ r_{\infty} = \frac{1}{1 + e^{\frac{v + 20.3}{15}}} \]  
(B.65)

\[ \tau_r = 0.000924 \left( 15.59 e^{0.09 \left( v + 30.61 \right)} + 0.369 e^{-0.12 \left( v + 23.84 \right)} + 2.98 \right) \]  
(B.66)

\[ I_{\text{Na}} \]

\[ I_{\text{Na}} = g_{\text{Na}} m^3 h \left( v - E_{\text{m}} \right) \]  
(B.68)

\[ \frac{dm}{dt} = \frac{m_{\infty} - m}{\tau_m} \]  
(B.69)

\[ \frac{dh}{dt} = \frac{h_{\infty} - h}{\tau_h} \]  
(B.70)

\[ m_{\infty} = \frac{1}{1 + e^{\frac{v + 42.004}{8.4106}}} \]  
(B.71)

\[ E_{0m} = v + 41 \]  
(B.72)

\[ a_m = \frac{200 E_{0m}}{1 - e^{-0.1 E_{0m}}} \]  
(B.73)

\[ \beta_m = 8000 e^{-0.056 \left( v + 66 \right)} \]  
(B.74)

\[ \tau_m = \frac{1}{a_m + \beta_m} \]  
(B.75)

\[ h_{\infty} = \frac{1}{1 + e^{\frac{v + 48.04}{4.066}}} \]  
(B.76)

\[ \alpha_h = 20 e^{-0.125 \left( v + 75 \right)} \]  
(B.77)

\[ \beta_h = \frac{2000}{320 e^{-0.1 \left( v + 75 \right)} + 1} \]  
(B.78)

\[ \tau_h = \frac{1}{a_m + \beta_m} \]  
(B.79)

\[ I_{\text{NaK}} \]
\[ I_{NaK} = F_{cAMP,NaK} \left( 1 + \left( \frac{K_{m_{Kp}}}{Ko} \right)^{1.2} \right)^{-1} \left( 1 + \left( \frac{K_{m_{Nap}}}{Nai} \right)^{1.3} \right)^{-1} \left( 1 + e^{\frac{-(v-E_{Na}+110)}{20}} \right)^{-1} \] (B.80)

\[ I_{NaCa} = \frac{K_{NaCa} (x2 k21 - x1 k12)}{x1 + x2 + x3 + x4} \] (B.82)

\[ x1 = k41 k34 (k23 + k21) + k21 k32 (k43 + k41) \] (B.83)

\[ x2 = k32 k43 (k14 + k12) + k41 k12 (k34 + k32) \] (B.84)

\[ x3 = k14 k43 (k23 + k21) + k12 k23 (k43 + k41) \] (B.85)

\[ x4 = k23 k34 (k14 + k12) + k14 k21 (k34 + k32) \] (B.86)

\[ k43 = \frac{Nai}{K3ni + Nap} \] (B.87)

\[ k12 = \frac{Na}{Kcni} e^{\frac{-Q_{ci} v}{R T}} \] (B.88)

\[ k14 = \frac{Nai}{K2ni} (1 + \frac{Nai}{K3ni}) \] (B.89)

\[ k41 = e^{\frac{-Q_{ci} v}{2 R T}} \] (B.90)

\[ di = 1 + \frac{Cai}{Kci} \left( 1 + e^{\frac{-Q_{ci} v}{k2}} + \frac{Nai}{Kcni} \right) + \frac{Nai}{K1ni} \left( 1 + \frac{Nai}{K2ni} \left( 1 + \frac{Nai}{K3ni} \right) \right) \] (B.91)

\[ k34 = \frac{Nao}{K3no + Nap} \] (B.92)

\[ k21 = \frac{Na}{K2no} e^{\frac{-Q_{no} v}{R T}} \] (B.93)

\[ k23 = \frac{Nao}{K2no} \left( 1 + \frac{Nao}{K3no} \right) e^{\frac{-Q_{no} v}{2 R T}} \] (B.94)

\[ k32 = e^{\frac{-Q_{no} v}{2 R T}} \] (B.95)

\[ do = 1 + \frac{Cao}{Kco} \left( 1 + e^{\frac{-Q_{co} v}{2 R T}} \right) + \frac{Nao}{K1no} \left( 1 + \frac{Nao}{K2no} \left( 1 + \frac{Nao}{K3no} \right) \right) \] (B.96)

\[ I_{Kur} \]
\[ I_{Kur} = g_{Kur} \cdot r_{Kur} \cdot s_{Kur} (v - E_K) \quad \text{(B.98)} \]

\[ \frac{dr_{Kur}}{dt} = \frac{r_{Kur\infty} - r_{Kur}}{\tau_{r_{Kur}}} \quad \text{(B.99)} \]

\[ \frac{ds_{Kur}}{dt} = \frac{s_{Kur\infty} - s_{Kur}}{\tau_{s_{Kur}}} \quad \text{(B.100)} \]

\[ r_{Kur\infty} = \frac{1}{1 + e^{\frac{v + 6}{\tau_{r_{Kur}}}}} \quad \text{(B.101)} \]

\[ \tau_{r_{Kur}} = \frac{0.009}{1 + e^{\frac{v + 5.1}{12}}} + 0.0005 \quad \text{(B.102)} \]

\[ s_{Kur\infty} = \frac{1}{1 + e^{\frac{v + 7.5}{10}}} \quad \text{(B.103)} \]

\[ \tau_{s_{Kur}} = \frac{0.59}{1 + e^{\frac{v + 60}{10}}} + 3.05 \quad \text{(B.104)} \]

\[ \frac{dNai}{dt} = \frac{- (I_{Na} + I_{iNa} + I_{siNa} + 3 I_{NaK} + 3 I_{NaCa})}{V_i F} \quad \text{(B.105)} \]
Cardiovascular equations

\[ T_S = 0.45 \left( 0.52 - \frac{0.11}{RR} \right) \quad (B.106) \]
\[ T_D = 0.55 \left( 0.52 - \frac{0.11}{RR} \right) \quad (B.107) \]
\[ E_{th} = \begin{cases} \frac{E_S - E_D}{2} \left( 1 - \cos \left( \frac{\pi \gamma}{T_S} \right) \right) + E_D & 0 \leq \gamma < T_S \\ \frac{E_S - E_D}{2} \cos \left( \frac{\pi (\gamma - T_S)}{T_D} \right) + E_D & T_S \leq \gamma < T_S + T_D \\ E_D & T_S + T_D \leq \gamma \leq RR \end{cases} \quad (B.108) \]
\[ P_{th} = E_{th} V_{th} \quad (B.109) \]
\[ P_{au} = E_{au} V_{au} \quad (B.110) \]
\[ P_{al} = E_{al} V_{al} \quad (B.111) \]
\[ P_{vu} = E_{vu} V_{vu} \quad (B.112) \]
\[ P_{vl} = \frac{1}{m_{vl}} \log \left( \frac{V_{Mvl}}{V_{Mvl} - V_{vl}} \right) \quad (B.113) \]
\[ Q_{av} = \begin{cases} \frac{P_{th} - P_{au}}{R_{av}} & P_{th} > P_{au} \\ 0 & P_{th} \leq P_{au} \end{cases} \quad (B.114) \]
\[ Q_{mv} = \begin{cases} \frac{P_{vu} - P_{th}}{R_{mv}} & P_{vu} > P_{th} \\ 0 & P_{vu} \leq P_{th} \end{cases} \quad (B.115) \]
\[ Q_v = \begin{cases} \frac{P_{vl} - P_{vu} - \rho g h C_{pa} \sin(\theta)}{R_v} & P_{vl} > P_{vu} \\ 0 & P_{vl} \leq P_{vu} \end{cases} \quad (B.116) \]
\[ Q_a = \frac{P_{au} - P_{al} + \rho g h C_{pa} \sin(\theta)}{R_a} \quad (B.117) \]
\[ Q_{up} = \frac{P_{au} - P_{vu}}{R_{up}} \quad (B.118) \]
\[ Q_{lp} = \frac{P_{al} - P_{vl}}{R_{lp}} \quad (B.119) \]
\[
\frac{dV_{au}}{dt} = Q_v - Q_a - Q_{up} \tag{B.120}
\]
\[
\frac{dV_{al}}{dt} = Q_a - Q_{lp} \tag{B.121}
\]
\[
\frac{dV_{vl}}{dt} = Q_{lp} - Q_v \tag{B.122}
\]
\[
\frac{dV_{vu}}{dt} = Q_{up} - Q_v - Q_{mv} \tag{B.123}
\]
\[
\frac{dV_{lh}}{dt} = Q_{mv} - Q_{av} \tag{B.124}
\]

Afferent nerves

\[
P_C = P_{au} - \rho g \hat{h} \sin(\theta) \tag{B.125}
\]
\[
\frac{d\bar{P}}{dt} = \frac{1}{\tau_p} \left( P_C - \bar{P} + \tau_Z \frac{dP_C}{dt} \right) \tag{B.126}
\]
\[
f = \bar{P} \tag{B.127}
\]
Efferent nerves

\[ \tilde{T}_p(f) = \frac{f^{k_p}}{f^{k_p} + f^{k_p}_{2p}} \]
\[ \frac{d T_p}{d t} = \frac{-T_p + \tilde{T}_p(f)}{\tau_p} \]  
(B.129)

\[ \tilde{T}_s(f) = \frac{f^{k_s}}{f^{k_s} + f^{k_s}_{2s}} \]
\[ \frac{d T_s}{d t} = \frac{-T_s + \tilde{T}_s(f)}{\tau_s} \]  
(B.131)

\[ \tilde{R}_{up} = (R_{up,M} - R_{up,m}) T_s + R_{up,m} \]
\[ \frac{d R_{up}}{d t} = \frac{-R_{up} + \tilde{R}_{up}}{\tau_R} \]  
(B.133)

\[ \tilde{R}_{ip} = (R_{ip,M} - R_{ip,m}) T_s + R_{ip,m} \]
\[ \frac{d R_{ip}}{d t} = \frac{-R_{ip} + \tilde{R}_{ip}}{\tau_R} \]  
(B.135)

\[ \tilde{E}_D = -(E_{D,M} - E_{D,m}) T_s + E_{D,M} \]
\[ \frac{d E_D}{d t} = \frac{-E_D + \tilde{E}_D}{\tau_E} \]  
(B.137)

\[ w_s = w_{s,1} T_s + w_{s,2} \]
\[ \frac{dc_{NE}}{d t} = \frac{-c_{NE} + T_s}{\tau_{NE}} \]  
(B.139)

\[ w_s = w_{p,1} T_s + w_{p,2} \]
\[ \frac{dc_{ACH}}{d t} = \frac{-c_{ACH} + T_p}{\tau_{ACH}} \]  
(B.141)

Scale coupling equations

\[ \hat{v} = v + v_{shift} \]
\[ \alpha_{m_v} = \frac{\hat{v}^{k_v}}{\hat{v}^{k_v} + \tilde{v}^{k_v}} \]  
(B.142)

\[ \frac{d m_v}{d t} = g_{m_v} \alpha_{m_v} (1 - m_v) - d m_v (1 - \alpha_{m_v}) m_v \]  
(B.144)

\[ \beta_{m_v} = -\frac{\delta_t}{d} \log(m_v) \]  
(B.145)

\[ \gamma = \frac{\frac{d m_v}{d t}}{2 \frac{d m_v}{d t}} - \frac{\frac{d m_v}{d t}}{\beta_{m_v}} \]  
(B.146)

\[ \frac{d R}{d t} = \frac{\gamma - R}{\tau_R} \]  
(B.147)

\[ RR = 2R \]  
(B.148)
B.3 Sinoatrial node (SAN) cell model formulation

Our sinoatrial node cell (SAN) model is inspired by models by Fabbri et al. [Fab17] and Demir et al. [Dem99]. We utilize the Fabbri model as a base and build off of it to include cAMP effects. Our incorporation of cAMP effects is outlined below and is largely motivated by the work by Demir [Dem99].

L-type Calcium Current ($I_{CaL}$): The original formulation of L-type Calcium Current ($I_{CaL}$) in Fabbri is

$$I_{CaL} = I_{siCa} + I_{siK} + I_{siNa}$$  \hfill (B.149)

Mimicking the formulation by Demir, we multiply by $F_{cAMP, CaL}$, allowing $I_{CaL}$ to be

$$I_{CaL} = F_{cAMP, CaL} (I_{siCa} + I_{siK} + I_{siNa})$$  \hfill (B.150)

where

$$F_{cAMP, CaL} = 0.4 \left( 1 + \frac{4.5 \text{cAMP}}{\text{cAMP} + 0.0065} \right) + 0.03157$$  \hfill (B.151)

as is stated in Demir.

Slow delayed rectifier K+ current ($I_{Ks}$) In Fabbri $I_{Ks}$ is

$$I_{Ks} = g_{Ks} (V - E_{Ks}) n^2$$  \hfill (B.152)

where $g_{Ks}$ is the conductance, $V$ is the membrane voltage, $E_{Ks}$ is the reversal potential for the slow delayed rectifier current, and $n$ is a gating variable. In accordance with Demir, our new formulation is

$$I_{Ks} = F_{cAMP, Ks} (V - E_{Ks}) n^2$$  \hfill (B.153)

with

$$F_{cAMP, Ks} = g_{Ks} \left( 0.62 \left( 1 + 2.6129 \left( \frac{\text{cAMP}}{\text{cAMP} + 6.5 \times 10^{-3}} \right) \right) \right).$$  \hfill (B.154)

Funny current ($I_f$): We elect to replace the steady-state for gating variable $y$ ($y_\infty$), from Fabbri with $y_\infty$ from Demir. Additionally, we multiply $y_\infty$ by 0.165 to scale the flux of $I_f$ to match the original Fabbri model.

$$\frac{dy}{dt} = \frac{y_\infty - y}{\tau_y}$$  \hfill (B.155)

$$y_\infty = \frac{1}{1 + e^{-\frac{V_{\text{half}}}{y}}} \times 0.165$$  \hfill (B.156)

$$V_{\text{half}} = \frac{20.5}{1 + e^{-\frac{\text{cAMP} - 0.0034}{650}}} - 78.56.$$  \hfill (B.157)

Sodium/potassium pump current ($I_{NaK}$): Fabbri puts forth the following equation for the
sodium/potassium pump current

\[ I_{\text{NaK}} = I_{\text{NaK,max}} \left( 1 + \left( \frac{K_{mKp}}{K_o} \right)^{1.2} \right)^{-1} \left( 1 + \left( \frac{K_{mNaP}}{Nai} \right)^{1.3} \right)^{-1} \left( 1 + e^{-\frac{(V-E_{Na}+110)}{20}} \right)^{-1} \]  \quad (B.158)

where \( I_{\text{NaK,max}} \) is the maximum current, \( K_{mKp} \) is the half-maximal for \( K_o \), \( K_o \) is the extracellular \( K^+ \) concentration, \( K_{mNaP} \) is the half-maximal for \( Na i, Nai \) is the intracellular concentration of \( Na^+ \), and \( E_{Na} \) is the reversal potential for sodium. Similar to Demir, to introduce cAMP into this equation, we set

\[ F_{cAMPNaK} = I_{\text{NaK,max}} \left( \frac{1.6}{1 + e^{-0.00375 - 0.00015 + 0.99}} \right) \]  \quad (B.159)

and allow our new equation to be

\[ I_{\text{NaK}} = F_{cAMPNaK} \left( 1 + \left( \frac{K_{mKp}}{K_o} \right)^{1.2} \right)^{-1} \left( 1 + \left( \frac{K_{mNaP}}{Nai} \right)^{1.3} \right)^{-1} \left( 1 + e^{-\frac{(V-E_{Na}+110)}{20}} \right)^{-1} \]  \quad (B.160)

\( I_{K,ACh} \): In the original Fabbri model the value of \( \alpha_a \), which is the opening rate for the \( a \) gate of \( I_{K,ACh} \), is held as a constant value as a function of the value of ACh that is in the system, which is a constant value. In order to allow for dynamic changes, we allow \( \alpha_a \) to be a function of \( c_{ACh} \), which is given by a differential equation and multiplied the formulation given by Fabbri by \( \frac{1}{140} \) to scale the dynamics to be relatively close to the value present in the Fabbri model. In other words, in Fabbri, \( \alpha_a \) is calculated as

\[ \alpha_a = \frac{3.5988 - 0.025641}{1 + \frac{0.000012155}{c_{ACh}^{1.0051}}} + 0.025641 \]  \quad (B.161)

where \( ACh \) is a constant value. In our model we reformulate this to be

\[ \alpha_a = \frac{1}{140} \left( \frac{3.5988 - 0.025641}{1 + \frac{0.000012155}{c_{ACh}^{1.0051}}} + 0.025641 \right) \]  \quad (B.162)

where \( c_{ACh} \) is a variable for the concentration of acetylcholine.

Removal of Sarcoplasmic Reticulum (SR) and Calcium Buffering.

In addition to adding cAMP effects, our SAN cell model differs from the base Fabbri model by lacking a sarcoplasmic reticulum and calcium buffering equations. To determine calcium dynamics inside the cell we include one compartment that receives/releases \( Ca^{2+} \) to the extracellular space via ion channels and pumps. The Fabbri model uses three compartments for the presence of calcium inside the cell - the subsarcolemmal space, the cytosol, and the SR. These compartments are important for fitting the exact dynamics of the action potential; however, for our purposes, we do not need to fit the action potential exactly, and instead wish to only track when the action potential occurs. The volume of this single
compartment is equal to the sum of the volumes of the three intracellular compartments in the Fabbri model. To account for changes in calcium flux, we recognize that the sodium-calcium pump is working approximately twice as much as in the original Fabbri model and therefore double the maximum rate at which the sodium-potassium pump operates \( I_{\text{NaK, max}} \) to allow for a reasonable concentration of \( \text{Na}^+ \) in the cell.

**Time scaling equations**

The fully formulated SAN cell model produces a heart rate that is below the normal range (60-100 bpm). For this reason, we time-scale the SAN cell equations to produce a heart rate of approximately 60 bpm at rest. All cell differential equations are of the form

\[
\frac{d \tilde{y}_i}{dt} = \delta t \frac{d y_i}{dt}
\]

(B.163)

where \( \frac{d \tilde{y}_i}{dt} \) is the \( i^{th} \) SAN differential equation from the original Fabbri model, \( \delta \) is our time scaling parameter, and \( \frac{d y_i}{dt} \) is the time-scaled differential equation for the \( i^{th} \) SAN variable.