ABSTRACT

STURDY, JACOB. Physiological Origins of Baroreceptor Firing Patterns: Mechanical and Electrophysiological Features. (Under the direction of Mette S Olufsen.)

The short term regulation of blood pressure and flow is critical for maintaining homeostasis in mammals, as they constantly engage in posture changing activities while pursuing food, anticipating threats, and socializing. The baroreflex system is a negative feedback control mechanism, which effects short term cardiovascular regulation in response to changes in blood pressure. The signal, which evokes this response, is a change in blood pressure causing deformation of the arterial wall, stimulating stretch sensitive neurons called baroreceptors. In response the neurons modulate their firing rates to encode information about the state of blood pressure in the circulatory system. This signal is carried along the vagus nerve to the nucleus solitary tract, where the efferent parasympathetic and sympathetic signals are coordinated to appropriately change peripheral resistance to blood flow, as well as directly effecting the heart rate and force of contraction.

Dysfunction of the baroreflex is associated with a number of disorders including orthostatic intolerance, syncope, and hypertension. The baroreflex also interacts with the physiological responses to inflammation and hypovolemia. These issues motivate the study of the baroreceptors as they are the physiological detectors of circulating blood pressure. In particular, since the etiology of orthostatic intolerance and syncope are not well understood, a better understanding of the baroreflex and baroreceptors may improve diagnosis and treatment of these debilitating conditions. In particular a basic physiological question of the role of multiple baroreceptor types remains open, as it is well known that there are myelinated (A-type) and unmyelinated (C-type) baroreceptors, which exhibit unique firing patterns.

This study focuses on improving the understanding of the baroreflex using mathematical modeling to characterize the mechanisms transducing the signal of blood pressure from a mechanical stimulus to a neural signal. Mathematical modeling provides a useful method for encapsulating experimentally observed features of baroreceptor neurons as well as allowing rigorous quantitative analysis of baroreceptor firing rate data. In particular, we attempt to model the distinction of A- and C-type baroreceptor neurons, which differ both in their response to blood pressure stimuli and the efferent effects they induce. To provide a mathematical model that distinguishes between baroreceptor types, this study attempts represent the biophysical features of this system with fidelity to what is known about each part involved. With this model parameter estimation may be used to fit model output to A-type and C-type responses, and the parameters differences revealed may provide insights into the physiological differences giving rise to the distinct response of A- and C-type neurons.
Physiological Origins of Baroreceptor Firing Patterns:
Mechanical and Electrophysiological Features

by
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DEDICATION

To Elle, my wandering companion, thank you for setting off to explore the universe with me.
The author was born in a small town where Bugs Bunny perennially forgets to take a left turn. Growing up in Albuquerque, NM and for a brief stint in Shoreview, MN, he grew to love animals and nature through various pets and regularly camping, hiking, and when possible skiing. While in high school the author became aware of the use of mathematics to describe the dynamics of living things, and this idea took root and motivated him to pursue Mathematics at George Fox University.

At George Fox University the Richter Scholars program provided an opportunity to try his hands at Computational Science. Working with Dr. Robert Hamilton, he studied the behavior of Alfvén waves generated by the solar wind and propagating through the plasma filling the solar system. This experience confirmed an interest in pursuing academic research, and the author continued his studies at North Carolina State University in the Biomathematics Program.

He was attracted to the long tradition of Biomathematics at the university and further impressed by the culture of interdisciplinary collaboration present. He began working with Dr. Mette Olufsen and the Cardiovascular Dynamics Group to study the regulation of the cardiovascular system, developing and discussing models and methods of analysis motivated by physiological questions about this system.

After his Masters he plans to continue studying the cardiovascular system at the Norwegian University of Science and Technology (NTNU) in the Biomechanics program.
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INTRODUCTION

The cardiovascular system (CVS) is a physiological marvel that is manifest in all large organisms in one form or another. This system overcomes the limitations of diffusion as a means to transport food, waste, hormones, and even heat throughout an organism. These functions are performed effectively only if the cardiovascular system remains at homeostasis. To maintain homeostasis, the cardiovascular system requires a number of regulatory negative feedback systems that ensure the system adapts to externally induced changes, such as the drop in pressure caused by a postural change from sitting to standing. One such system is the baroreflex, which effects changes in vascular resistance and heart rate in order to restore blood pressure and flow to a homeostatic state. In addition to providing a means of maintaining adequate blood flow, the baroreflex is thought to play a role in a number of disorders such as orthostatic intolerance, syncope, and hyper- or hypo-tension, as well as in the cardiovascular response to inflammation and hypovolemia. Thus, improved understanding of the baroreflex system may provide useful insights for diagnosing and treating individuals suffering from cardiovascular disorders. This is especially significant as cardiovascular disease is the leading cause of both death and disability in the United States, at an estimated cost of over $300 billion each year [42].

This thesis considers the firing characteristics of afferent baroreceptor neurons, which have been anatomically classified into two groups: myelinated (A-type) and unmyelinated (C-type). These specialized neurons serve as blood pressure sensors providing information to the baroreflex system about the status of the circulatory system. However, the manner in which A-type neurons accomplish this is distinct from that of C-type neurons. Further, the selective stimulation of A- or C-type neurons results in different efferent responses.

We attempt to develop a comprehensive set of mathematical models of the baroreceptors with particular emphasis on the representation of the biophysical systems underlying blood pressure
transduction. These include the mechanical properties of the arterial wall, the viscoelastic nature of connective tissue and cellular deformation, and the voltage-gated ion channel kinetics of the neuron itself.

The development of such a model will improve the understanding of the different response characteristics of A- and C-type baroreceptor neurons, as well as laying the groundwork to investigate the known differences in A- and C-type stimulation on the efferent baroreflex [32].

1.1 Summary of Contents

The remainder of this thesis is arranged as follows:

Chapter 2 describes the physiology of the baroreflex in the context of the cardiovascular system as a whole. It also presents a detailed account of studies of the afferent baroreceptor neurons under various loading, outlining the characteristics which should be represented in an effective model of the baroreceptor firing rate.

Chapter 3 introduces a simple mechanical description of the coupling of the baroreceptor neurons to the arterial wall. This published study also analyzed the suitability of relating the afferent firing patterns directly to the mechanical deformation of the nerve ending, and demonstrates the ability to reproduce all of the baroreceptor phenomena reported from experimental studies.

Chapter 4 expands this framework, incorporating a detailed neuronal model of action potential generation. This model allows for consideration of the distinct electrophysiological characteristics of the baroreceptor neurons belonging to the A- or C-type classes. Additionally, this model touches on a number of open questions regarding the mechanical or neuronal origin of certain baroreceptor features, such as the frequency response profile.

Chapter 5 discusses the significance of results from these studies, which developed a comprehensive model of baroreceptor physiology and demonstrated its ability to reproduce various characteristics of baroreceptor firing. It also outlines areas for further investigation, discussing how these models may provide a useful tool for analysis of physiological hypotheses about the baroreflex system. Chapter 5 presents some additional simulations from the model presented in Chapter 4, which serve as a preliminary investigation for some of these questions.
2.1 Chapter Summary

The goal of this chapter is to review the physiology of the baroreceptor neurons in the broader context of the baroreflex response of the cardiovascular system. This chapter first considers the structure and function of the cardiovascular system. Then, the baroreflex response is described from the origin of the afferent signals in the baroreceptors to the postsynaptic effects of the efferent neurons innervating the heart and vascular tissue. The baroreceptors are discussed in detail following this summary of the overall physiology of the baroreflex. The physiology reviewed in this chapter serves to provide a basis to contextualize the development of baroreceptor neuron models, which is the primary focus of this dissertation.

2.2 The Cardiovascular System

The cardiovascular system is an advective transport system carrying oxygen and nutrients to tissues, flushing away waste products, and communicating endocrine signals by carrying hormonal factors [67]. This system is necessary in larger organisms where diffusion is not a feasible means of transport due to the length scales involved (the transportation of glucose a centimeter via diffusion takes nearly 15.4 hours). The CVS consists of two parallel fluid circuits, both of which are driven by the heart (the overall structure is diagrammed in Figure 2.1).

The heart consists of two pumps operating in parallel. The right ventricle drives the pulmonary circuit, which carries blood to the lungs where oxygen is absorbed and carbon dioxide is released, and subsequently returns to the left atrium to fill the left ventricle, which drives the systemic circuit. Oxygenated blood is forced through the aorta and a series of branching vessels until it reaches the
Figure 2.1: Overview of the circuit structure of the cardiovascular system. Blood flows to each major organ in parallel branching multiple times to ensure thorough coverage of all tissues. (Figure 1.5 on p. 4 of [67] reproduced with permission.)
capillary beds in tissues throughout the body. The transfer of material (primarily O$_2$ and CO$_2$) between tissues and the blood occurs in these capillary beds. After flowing through the capillary beds, blood is collected in a series of merging venous vessels which carry the blood back towards the heart terminating in the vena cava and filling the right atrium to be pumped through the pulmonary circuit again.

The branching of both arteries and veins results in a nearly four hundred fold increase in net cross-sectional area of vessels. The cross-sectional area of individual vessels in each stage of branching decreases dramatically from the very large aorta and vena cava to the microscopic capillaries, where diffusion of materials occurs (see Figure 2.2).

The homeostatic operation of the CVS is critical as the functions of every other physiological system depend on the CVS to consistently provide their nutrient needs and to remove the waste they produce. A number of systems exist to enable the CVS to respond to changes in physiological parameters including CO$_2$ concentration and blood pressure. In addition, other mechanisms modulate the system to respond to increased demands during exercise and digestion. This systems require spe-
cialized sensory physiology (e.g. chemosensitive and mechanosensitive neurons) and mechanisms to effect changes in the circulation. Since circulation is advection driven by the heart, these mechanisms must modulate the load on the pump by varying vessel resistance and by modulating the force and frequency of cardiac contractions. This modulation is enabled via specialized smooth muscle cells in the vessel wall, and cardiac myocytes of the heart. These cells have specialized receptors that respond to neurotransmitters released by the various control systems.

2.3 The Baroreflex

One such control system is the baroreflex, which regulates blood pressure through a negative feedback loop on the time scale of seconds to minutes [67]. Investigation of this system began with Cooper, who in 1836 observed that occlusion of the carotid sinus resulted in increased systemic blood pressure [98]. Ludwig and Cyon observed that stimulation of the aortic nerve or carotid sinus nerve results in a depressor response of falling heart rate and decreasing blood pressure [13]. Subsequently Heymans demonstrated the presence of pressure sensitive receptors in the arterial wall [13] which are now called baroreceptors (baro being Latin for pressure). Following these initial investigations, many others have studied cardiovascular control [57] and produced an excellent overall understanding of the various subsystems involved in producing the baroreflex response.

The baroreflex system responds to changes in blood pressure, sensed by baroreceptors in the aortic arch and carotid sinuses. The layout of this system is presented in Fig. 2.3, which shows the path from signal initiation in the arterial baroreceptors to the efferent release of neurotransmitters on the heart and vascular smooth muscle cells. The system is described in the following paragraphs, and further details are presented in subsequent sections dedicated to the afferent and efferent physiology.

Baroreceptors are specialized neurons with cell bodies located in the nodose ganglion and stretch sensitive endings embedded in the arterial wall [29]. The nerve endings have mechanosensitive ion channels that open and close in response to deformations of the nerve endings caused by variation of arterial wall distension, which is determined by blood pressure. The changes in mechanosensitive current cause a change in the frequency of action potentials in the baroreceptors, thus encoding information about blood pressure through frequency modulation.

This information is processed in the nucleus solitary tract (NTS) where the afferent signals are processed and efferent sympathetic and parasympathetic tones are modulated. High blood pressure causes an increase in baroreceptor activity which inhibits the sympathetic efferents and enhances the parasympathetic efferents. The inhibition of sympathetic efferents causes vasodilation of systemic arteries by allowing smooth muscle cells in the vasculature to relax and decreasing the contractility of the heart. The enhancement of the parasympathetic afferents causes an increase in acetylcholine (ACh) released on the sinoatrial (SA) and atrioventricular (AV) nodes, which decreases
the heart rate. In general, the parasympathetic tone dominates the response to increased blood pressure and the sympathetic the response to decreased blood pressure [57], though both are modulated in each case.

2.3.1 Afferent baroreflex physiology

The baroreflex begins with the encoding of blood pressure in a neural signal. This is accomplished by the baroreceptor nerve endings embedded in the outer most layer of the arterial wall, the adventitia [59]. Baroreceptors are present throughout the circulatory system, but have particularly significant expressions in four areas: the carotid bodies, the aortic arch between the left internal carotid and the left subclavian, the veno-atrial junctions, and the main pulmonary artery. The baroreceptors at the juncture of the veins and atria and in the main pulmonary artery are low pressure baroreceptors [13] and are thought to be responsible for sensing the fullness of the circulatory system. The
receptors within the carotid and aortic bodies are high pressure baroreceptors and are more acutely sensitive to blood pressure. These nerve endings encode information about the state of arterial wall deformation through mechanosensitive ion channels that open and close in a manner dependent on the mechanical state of the nerve ending. This variation in current modulates the frequency of action potential generation. The individual axons gather to form nerve bundles emanating from the aortic arch or carotid sinus that join the vagus (Cranial Nerve X) or glossopharyngeal (Cranial Nerve IX) respectively. These nerves terminate in the medullary brain stem. In rats, this aortic fiber consists exclusively of mechanosensitive neurons, whereas the carotid fiber is known to also contain chemosensitive neurons [32].

2.3.2 Baroreflex integration in the brain stem

The baroreceptor signal is processed in the medulla oblongata where the carotid and aortic nerve fibers and other cardiovascular afferents terminate in the NTS (see Fig. 2.3) [67]. The neurons in the NTS receive inputs from a number of these afferents, and thus their output is dependent on multiple inputs from various afferent modalities [67]. These neurons transmit the signal to various other control centers such as the hypothalamus, cerebellum, and other locations within the medulla. In particular, they synapse on the inhibitory vagal efferents in the nucleus ambiguus and the caudal vasodepressor area of the medulla. They also project to the parvocellular neurons of the paraventricular nucleus, which in turn influence sympathetic efferents (see Fig. 2.3).

2.3.3 Efferent baroreflex mechanisms

As discussed in the previous section, the nucleus ambiguus generates a tonic inhibitory output, and this results in continuous release of acetylcholine (ACh) on the SA node of the heart, keeping the heart rate lower than it would otherwise be. The effects of this innervation are summarized below with details taken from Boron and Boulpaep [13, Ch 14]. The vagus nerve, which is parasympathetic, releases ACh onto the SA and AV nodes, slowing the intrinsic pacemaker activity of the myocytes in these regions (see Fig. 2.4). ACh decreases the hyperpolarizing (funny) K+ current in the SA node, reducing the steepness of the phase 4 depolarization. Second, ACh opens G protein coupled inward-rectifying K+ channels, increasing K+ conductance and making the maximum diastolic potential of SA nodal cells more negative. Third, ACh reduces the Ca2+ current in the SA node, thereby reducing the steepness of the depolarization of the pacemaker action potential and moving the threshold to more positive values. All three effects cooperate to lengthen the depolarization phase of pacemaker cells in the SA node; the net effect is to lower the heart rate.

Sympathetic efferents begin in the rostral ventrolateral medulla and synapse with adrenergic preganglionic neurons in the T1-L3 vertabrae. These, in turn, synapse with the paravertebral ganglia where the signal is relayed to postganglionic sympathetic neurons that release norepinephrine.
Figure 2.4: Diagram of the cardiac myocyte response to parasympathetic and sympathetic stimulation. (Figure 4.9 on p. 59 reproduced with permission from [67].)
on smooth muscle cells throughout the vasculature and the cardiac myocytes [13, 67]. Sympathetic neurons innervate the heart and vasculature throughout the body. Norepinephrine acts through $\beta_1$-adrenergic receptors to produce an increase in heart rate by two mechanisms. First, it increases the K$^+$ “funny” current in the nodal cells, thereby increasing the steepness of the phase 4 depolarization. Second, norepinephrine increase Ca$^{2+}$ current in all myocardial cells. This steepens the depolarization phase of SA and AV nodal cells and decreases their threshold. Catecholamines do not appear to change the maximum diastolic potential. However, they do cause shorter action potentials as a result of their actions on these currents.

Sympathetic vasoconstriction is achieved through norepinephrine binding to $\alpha$-adrenergic receptors of the smooth muscle tissue in the arterial wall as shown in Fig. 2.5. If the receptor is $\alpha_1$-type, this will cleave PIP into IP$_3$, whereas $\alpha_2$-type receptors inhibit adenylyl-cyclase and thus inhibit production of cyclic AMP (cAMP). Both IP$_3$ and cAMP increase cytoplasmic Ca$^{2+}$ and thus stimulate contraction of the smooth muscle.

2.3.4 Significance of sympathetic and parasympathetic response

The baroreflex has historically been referred to as the general response of bradycardia to increased blood pressure and the response of tachycardia and vasoconstriction to decreased blood pressure. These effects are thought to be mediated via both the sympathetic and parasympathetic nervous systems. Recent studies have investigated the differences in operation and origin of the sympathetic and parasympathetic branches of these systems [86, 95]. They found the carotid and aortic afferent systems have different effects on the efferent response to changes in blood pressure, thus motivating an improved understanding of how the efferent signal is generated in response to the transduction of blood pressure.

2.4 Blood pressure transduction

Although the functional pathways of the baroreflex are known, there are a number of features still under investigation, for example, the difference in contribution of aortic and carotid baroreceptors to the sympathetic and parasympathetic response [86, 95]. Another is the different frequency response characteristics of direct stimulation of A- and C-type aortic baroreceptors [33]. To understand the proper function of the baroreflex, it is important to be able to characterize the particularities of each subsystem, a task which requires understanding of the underlying physiology of the subsystems.

In particular, this study seeks to improve the understanding of blood pressure transduction via the baroreceptor neurons. To this end, we consider the physiology of arterial wall deformation, the corresponding nerve ending stimulation, and the electrophysiological characteristics of baroreceptor neurons themselves. Each of these components may be further broken into underlying consitu-
Figure 2.5: Diagram of the vascular myocyte response to sympathetic stimulation. (Figure 12.7 on p. 231 reproduced with permission from [67].)
tive parts, such as the viscoelastic characteristics of the arterial wall tissue and the nerve endings, and the voltage-gated ion channels determining the generation of action potentials in baroreceptor neurons. This section will summarize various studies which have investigated these components.

2.4.1 Arterial Wall

The arterial wall consists of three layers the intima, media, and adventitia. The intima is made up of the epithelial cells lining the artery, and a thin layer of collagen, smooth muscle cells, and fibroblasts [11]. This layer does not contribute to arterial mechanics under normal conditions [46]. The boundary of the intima and media is the interior elastic lamina. The media is mostly composed of smooth muscle cells bound between the interior and exterior elastic laminae by collagen fibers, and it is the main contributor to defining the characteristics of arterial wall distension in response to blood pressure [11]. The smooth muscle cells do not seem to contribute significantly to the passive mechanical characteristics of the arterial wall [109]. The adventitia consists of collagen, myofibroblasts, the vasculature supplying the arterial wall with oxygen and nutrients, and both afferent and efferent nerves [109]. It is thought, the collagen is critical in preventing rupture of the vessels at high pressures as it provides external support to the internal tissues of the wall.

The combined action of these layers determines the overall mechanical behavior of the arterial wall, which is well-known to be viscoelastic in larger animals [107, 110]. The significance of viscoelasticity in smaller animals, such as the rat or mouse is less established, though there is evidence for significant viscoelastic effects in the mouse pulmonary arteries [112]. Brown et al. found a lack of a frequency dependent response in the rat aorta [20], and Boutouyrie et al. [14] demonstrated the viscoelasticity of the in vivo rat abdominal aorta produced only a slight hysteresis in the area-pressure relationship. Further, this relationship was much less significant than that in the in vitro preparation.

Perhaps more significant than the presence of viscoelasticity is the nonlinear response of vessel area to increasing blood pressure. Many studies have documented the nonlinear response of vessel area, with high stiffness at low pressures, a region of decreased, nearly constant stiffness at middle pressures, and increased stiffness and saturation beyond a certain higher pressure [11, 34, 78, 107]. In vivo, the arteries are connected to the tissues surrounding them and thus deformation is thought to occur primarily in circumferential and radial directions as opposed to the axial direction [39]. The deformation of arteries near branch points may be sensitive to the geometric characteristics and inhomogeneities of the tissue, though most studies have considered the arteries from an isotropic perspective [34]. An example of such an anisotropic feature is the orientation of the elastic fibers in the arterial wall, which has been studied by Holzapfel et al. [46].

The primary features relevant to baroreceptor stimulation are the shape of the nonlinear response to pressure, the role of viscoelasticity, and the relation between circumferential and longitudinal stress and strain.
2.4.2 Nerve ending

In rats, it is noted that the innervation of the aortic arch is via the aortic depressor nerve (ADN), so called because direct stimulation depresses cardiac output. This nerve fiber is composed entirely of mechanosensitive neurons [32]. The carotid sinus nerve consists of mechanosensitive baroreceptors as well as chemosensitive neurons, which monitor oxygen, carbon-dioxide, and pH levels of the blood. To our knowledge, the most detailed study of the structure of the baroreceptor nerve endings was accomplished by Krauhs et al. [59]. This study observed the aortic nerve branched near the aorta, where nerve bundles consisting of a single myelinated neuron and several unmyelinated fibers entered the adventitia and followed a helical path towards the media of the aortic arch. Near the exterior elastic laminae, the myelinated neurons lost their myelin sheath and the individual neurons’ endings separated from the bundle to continue into the laminae of the adventitia. Axonal bulging was observed past this point, and the surface of the cellular membrane was noted to be irregular. The terminal region of the axons was connected to and surrounded by the basal laminae between two elastic laminae of the adventitia, though some endings were observed to continue through fenestrations into multiple laminae.

2.4.3 Baroreceptor neurons

The electrophysiology of baroreceptor neurons has primarily been studied using enzymatic dispersion techniques to isolate individuals neurons from the nodose ganglion [91]. These neurons are identified as baroreceptor neurons using a staining technique, which applies lipophilic dyes to the aortic arch. The dye is then transported along the baroreceptor axon up to the brainstem where it allows identification of neurons with projections to the stained region [76]. Once the neurons are identified, various electrophysiological techniques are used to understand the excitability of the baroreceptor neurons as well as characterizing the ion channels present in their membranes. These methods are effective at isolating particular electrophysiological features, though they have the downside of cutting off the mechanosensitive endings that serve as an input in vivo.

The most distinguishing characteristic of electrophysiological interest is the myelination of the axon, as myelinated and unmyelinated neurons have markedly different action potentials [69, 90]. The A-type neurons exhibit a shorter duration action potential with faster depolarization and straight forward repolarization, whereas the C-type neurons have a broader action potential with a characteristic hump in the repolarization phase.

Beyond these primary differences in anatomy and physiology, the distributions of ion channels in A- and C-type neurons differ. Schild and Kunze [91, Table 1] have reviewed various studies that have identified certain specific ion channels as present through various pharmacological, immunohistochemical, and genetic techniques. These studies have identified voltage-gated and calcium activated ion channels, which carry potassium, sodium, and calcium currents. The most prominent
currents in both A- and C-type neurons are sodium and potassium channels with rapid kinetics (Nav1.7 and Kv1.4 or Kv4.3). C-type neurons uniquely express a calcium-activated potassium current (KCa1.1) and a tetrodotoxin (TTX) insensitive sodium current (Nav1.8), which are not present in A-type neurons. In addition to these currents, the C-type potassium current is distributed through a number of channel types (Kv1.1, Kv1.2, Kv1.6, Kv1.3), whereas the A-type neuron has a large portion of whole cell current dominated by a 4-Aminopyridine (4AP) sensitive potassium current. The 4AP sensitive current is thought to be separated into two channels, one with rapidly inactivating dynamics ($I_A$) and another with much slower inactivation dynamics ($I_D$) on the scale of 7 seconds. $I_A$ is suspected to correspond to Kv1.4 or Kv4.3, whereas $I_D$ is suspected to correspond to Kv2.1 or Kv2.2. It is also known that there are calcium channels and nonselective HCN channels present in the baroreceptor neurons, the importance of which is not fully understood, though some studies suggest the calcium channels do not play a significant role in the nerve ending region [5, 61].

### 2.4.4 Functional characteristics

The functional characteristics of baroreceptors have been studied in a number of experiments, using primarily in situ recordings of baroreceptor neurons in excised vessels of various animals including monkeys, rats, rabbits, and dogs [20, 26, 28, 40, 92, 102]. These have identified several features of the baroreceptors’ firing patterns that have been found across many of these species and have provided a set of distinct characteristics useful for understanding the variability in baroreceptor firing rate responses. Of particular note are the features of threshold, saturation, overshoot and adaptation, post excitatory depression (PED), hysteresis, and frequency response, which we define in the following section.

**Threshold** refers to the pressure above which the neuron's firing rate responds to changes in pressure. Fig. 2.6 shows the ramp response of A- and C-type neurons where this feature may be seen. The A-type neurons begin to fire only when the ramp stimulus reaches the threshold pressure, whereas C-type neurons are active at all pressures but begin to fire more frequently for pressures above the threshold pressure [92].

**Saturation** describes both the pressure at which the firing rate no longer increases for additional pressure, as well as the frequency achieved at this pressure. Both A- and C-type neurons show saturation, but A-type neurons saturate at higher frequencies and lower pressures than C-type neurons (see Fig. 2.6).

**Overshoot and adaptation** are exhibited in response to a step increase in pressure. Both A- and C-type neurons may be slowly adapting neurons that dramatically increase firing (overshoot) at the onset of the increase and then slowly decay (adaptation) toward a new steady firing rate corresponding to the new pressure [19] (see Fig. 3.7.)

**Post excitatory depression** is a cessation of firing following a sudden drop in pressure. The dura-
Figure 2.6: The figure shows ramp stimulus (bottom) and firing rate response data for A- and C-type neurons from a dog carotid artery, data are extracted from Seagard et al. [92]. This stimulus is typical with a slope of 2 mmHg/sec, and a number of others have used a similar stimulus to find similar results in many species [40, 64].

The cessation of the ramp stimulus is dependent on both the duration of the previous pressure level as well as the height of the pressure drop [64, 111]

**Hysteresis** refers to the asymmetric response of the firing rate to a sequential rise and fall in pressure. This is observed by noting the different firing rates for a given pressure when pressure is increasing as opposed to decreasing. This has been characterized by a number of studies including the work of Coleridge et al. as well as Katona and Barnett [26, 53].

**Frequency response** describes the relative response of a baroreceptor's firing rate response to a sinusoidal pressure stimulus of constant amplitude, but varying frequency. A-type neurons have relatively increased firing rates for stimulus between frequency of 1 and 9 Hz as compared to outside this range. C-type neurons have the higher firing rates for lower frequencies, resulting in a monotonically decreasing frequency response [20]. These characteristics are shown in Fig. 2.7.

### 2.4.5 Categorization of Baroreceptor Neuron Types

The work of Brown et al. [19, 20] thoroughly investigated the response of rat aortic baroreceptors to pressure stimuli of step and sinusoidal responses. In these papers, aortic baroreceptor nerves were isolated from both normotensive (NTR) and hypertensive (SHR) rats, various pressure profiles were imposed on the aortic arch, and the firing rate responses of individual baroreceptor neurons were recorded. The first study [19] identified three types of baroreceptor neurons: slowly adapting neurons, rapidly adapting neurons, and spontaneously active neurons. This study is based on 31 neu-
Figure 2.7: Left panel shows example firing rate response to a sinusoidal pressure stimulus for an A-type neuron. Right panel shows the gain and phase response for both A- and C-type neurons from Brown et al. [20]. The gain was normalized by setting the gain for the lowest stimulus frequency to 0.

rons, and in particular, only 7 of these were of the unmyelinated variety. Brown et al. categorized the neurons studied into the three identified groups. These types may be summarized as:

- Slowly adapting neurons respond with an initial overshoot in firing rate followed by decay to steady state.
- Rapidly adapting neurons exhibit an initial response but quickly cease firing in response to continued stimulus. A discharge event may occur concomitantly with the cessation of stimulus.
- Spontaneously active neurons discharge even with no applied pressure but show a similar response to step stimulus as slowly adapting fibers. Brown et al. attribute this spontaneous firing to the distorting effects of excision on the receptor apparatus.

In the second study [20], aortic baroreceptor nerves were isolated in the same manner but were stimulated using dynamic (sinusoidal) pressure forms. The goal of this study was to investigate the frequency response characteristics of baroreceptors. In this paper, the neurons are categorized as myelinated (A-type) or unmyelinated (C-type) baroreceptors and as being from NTR or SHR. Brown et al. conclude the spread of firing rates is greater in C-type baroreceptors; however, the response varies more in A-type neurons and is greater as evidenced by comparing [Figure2,3] [20]. Further, C-type baroreceptors have a higher static threshold and show monotonically decreasing gain with increased frequency stimulus.

Another study by Seagard et al. [92, 93] investigated carotid baroreceptors in mongrel dogs. This study categorized baroreceptors as type-1 and type-2, corresponding to large diameter A-type and
small diameter A-type or C-type neurons respectively. This was determined by considering conduction velocities. The key difference in these studies was found by considering a ramp stimulus. The type-1 neurons have a distinct threshold stimulus pressure, above which firing is initiated starting at a nonzero rate. On the other hand, type-2 neurons do not show a distinct threshold but rather show a gradual sigmoid response from zero firing to saturation. Both types show saturation though type-1 neurons in general have higher firing rates. Further, type-2 neurons generally have a wider range of functional sensitivity. There is significant variability within these groups as shown in [Figure 6] [92].

Seagard et al. [15] also considered the impact of applying the chemical 4AP to both types of neurons and found that type-1 neurons converted their firing rate response to those of type-2 neurons. This suggests the key role of the $I_A$ or $I_D$ currents in determining the threshold pressure characteristics of the neuron.

Schild et al. [90] characterized nodose neurons based solely on myelination type (A or C), and noted the primary distinction between sustained firing exhibited in the A-type neurons, whereas C-type neurons exhibited an initial response followed by quiescence.

Fan et al. [33] investigated the effects of direct stimulation of baroreceptor neurons in the rat aortic depressor nerve. Using methods to selectively stimulate A- or C-type neurons, they identified particular frequency sensitivities of the depressor reflex. A-type stimulation at low frequencies did not effect a change in mean arterial pressure, whereas combined stimulation of A- and C-type neurons did.

The studies reviewed in this section have demonstrated a number of firing pattern characteristics observed in baroreceptors, several of which are different between A- and C-type neurons. This is not surprising, as studies have also shown differences in the underlying physiology of these two neuron types. Not only are the neurons' behaviors unique, other studies have demonstrated that A- and C-type neurons elicit a unique efferent response. These results suggest that an accurate model of blood pressure transduction must be able to reproduce the distinctions between A- and C-type neurons' ramp and frequency responses, as well as exhibiting the features that are common to both: saturation, overshoot and adaptation, PED, and hysteresis. Additionally, a detailed biophysical model should represent the underlying subsystems with fidelity. Thus, the arterial wall mechanics and neuron electrophysiology should be modeled in a manner to account for the experimentally observed characteristics of these subsystems.

## 2.5 Physiological Modeling

In this study, we attempt to improve the physiological understanding of blood pressure transduction using mathematical modeling. We develop a series of models which are able to reproduce the various features summarized in this chapter. In particular, we focus on characterizing the afferent portion of the barorflex through models which are able to reproduce the qualitative features of barorecep-
tor firing patterns enumerated here, as well as fitting specific data gathered from various studies of baroreceptor functionality. Thus, the physiological details accounted for in this chapter will motivate mathematical models, and they will also provide a baseline understanding against which model results will be compared. These models may be used to investigate what parts of the underlying physiology are likely critical in producing specific features of the baroreceptor firing rate response.
For this manuscript I applied the integrate-and-fire neuron framework to model baroreceptor (Fig. 3.5 and Eq. 3.22) and implemented the model to perform simulations (Fig. 3.8 and Fig. 3.10). In addition to model development I also set up the computational environment used to estimate model parameters (Tables 3.3-3.5) using the optimization codes of C.T. Kelley for the smooth models, and \textit{fminsearch} from \textit{MATLAB} for those using the integrate-and-fire neuron model. Finally, I contributed to writing the manuscript in particular parts discussed above, as well as relating the results of this study to various features of baroreceptor physiology associated with the models studied.

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**Modeling the afferent dynamics of the baroreflex control system**

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**Abstract**

In this study we develop a modeling framework for predicting baroreceptor firing rate as a function of blood pressure. We test models within this framework both quantitatively and qualitatively using data from rats. The models describe three components: arterial wall deformation, stimulation of mechanoreceptors located in the BR nerve-endings, and modulation of the action potential frequency. The three sub-systems are modeled individually following well-established biological principles. The first submodel, predicting arterial wall deformation, uses blood pressure as an input and
outputs circumferential strain. The mechanoreceptor stimulation model, uses circumferential strain as an input, predicting receptor deformation as an output. Finally, the neural model takes receptor deformation as an input predicting the BR firing rate as an output. Our results show that nonlinear dependence of firing rate on pressure can be accounted for by taking into account the nonlinear elastic properties of the artery wall. This was observed when testing the models using multiple experiments with a single set of parameters. We find that to model the response to a square pressure stimulus, giving rise to post-excitatory depression, it is necessary to include an integrate-and-fire model, which allows the firing rate to cease when the stimulus falls below a given threshold. We show that our modeling framework in combination with sensitivity analysis and parameter estimation can be used to test and compare models. Finally, we demonstrate that our preferred model can exhibit all known dynamics and that it is advantageous to combine qualitative and quantitative analysis methods.

Author Summary

Many people have experienced lightheadedness when standing up, yet the exact cause of this phenomenon remains unknown. For some people, lightheadedness occurs because of anomalies in the blood pressure control system, which keeps blood flow and pressure at homeostasis. One way to explore this system is via mathematical modeling, which can offer valuable insights into the complex dynamic processes. This study develops a framework for modeling activity of the baroreceptor neurons. The models consist of three components reflecting three physiological mechanisms relating blood pressure to the baroreceptor firing rate: modulation of arterial blood pressure causes dilation of the arterial wall, stimulating mechanoreceptors within the baroreceptor nerve endings, emanating from the aortic arch and carotid sinus, which in turn modulates the firing rate of the baroreceptor neurons. This signal is integrated in the brain stem, stimulating baroreflex efferents to counteract the pressure increase. In this study, we review the main static and dynamic features of the baroreceptor firing activity, and show, using a combination of modeling techniques and rat aortic baroreceptor data, how to build a computationally efficient, yet biologically correct model. These models are important components for describing efferent responses, such as: heart rate, contractility or stroke volume.

3.1 Introduction

The main role of the cardiovascular (CV) system is to provide adequate oxygenation of all tissues, a function which is achieved by maintaining homeostasis of blood flow and pressure. When a mammal is subjected to an orthostatic maneuver (e.g., running, jumping, etc.), its blood volume is redistributed, moving the system state away from homeostasis [52]. To re-establish homeostasis a
The number of control mechanisms are activated regulating vascular resistance and compliance, and cardiac pumping efficiency and frequency. An important contributor to this control system is the baroreflex, which uses specialized neurons called baroreceptors (BR) for signaling [12]. The BR neurons originate in the arterial wall and terminate in the nucleus solitary tract (NTS), where sensory information is integrated. These neurons are continuously stimulated via activation/inhibition of mechanosensitive receptors responding to changes in arterial wall stretch imposed by pulsating blood pressure [43]. This stimulus modulates the formation of action potentials propagating along the BR nerves terminating in the NTS, where efferent signals are generated to regulate heart rate, cardiac contractility, as well as vascular resistance and compliance. It is known that the baroreflex system contributes to short-term blood pressure regulation, operating on a time-scale of seconds to minutes [27]. For example, upon head-up tilt, blood is pooled in the lower extremities, increasing blood pressure in the lower body, while decreasing it in the upper body, causing an imbalance, which persists until the baroreflex system is activated. Figure 3.1 shows a schematic representation of the baroreflex pathways. While the BR pathways are generally well established, analysis of the complete control system, including afferent and efferent signaling, is hindered by the difficulty of measuring the activity of each component without disrupting the feedback loop. For example, in vivo, only macroscopic quantities can be measured non-invasively including heart rate and blood pressure. From such measurements it is difficult to examine how the individual components of the system interact and consequently it is difficult to determine which sub-systems are compromised in subjects experiencing baroreflex failure [55] or decreased arterial baroreflex sensitivity [63]. These difficulties limit the development of targeted diagnosis procedures and treatment plans aiming to alleviate symptoms for patients.

Mathematical modeling is an eminent tool for gaining more insight into this complex feedback loop, offering a stringent and systematic way to identify underlying mechanisms of the system. For example, the only way to estimate model parameters and thereby suggest essential biomarkers, which may not be directly measurable, is by using models in combination with direct measurements. Modeling also offers a way to understand complex systems, as it makes the inaccessible accessible, a concept denoted the “mathematical microscope” [81].

This paper focuses solely on the afferent part of the baroreflex system, while future studies will address efferent signaling and integration of the two parts within a system level model. Since the 1950s researchers have put forward numerous mathematical models [2, 24, 50, 64, 66, 68, 82, 97, 99, 100, 103, 115], which tried to integrate known dynamics with hypothesized mechanisms in order to provide more understanding of the system as a whole. Many insights have been gained, however, most of these models were developed to describe BR response to a particular stimulus, rather than to a range of stimuli eliciting all known responses. Therefore they all lead to different hypotheses explaining the system mechanisms. Inspired by shortcomings of previous studies, we developed a modeling framework containing model components reflecting physiological pathways. This framework splits the
afferent signaling into three parts describing vessel wall deformation, mechanoreceptor stimulation, and the frequency of action potential generation. For each component we propose multiple models, which we test both qualitatively and quantitatively. This new approach allows us to understand the contribution of each component model to the overall signal. For example, if the objective is to build a BR model that can reflect the response to a sinusoidal pressure stimulus observed experimentally, the modeling framework can be used to identify which combinations of components are sufficient to describe the experimental outcome, and which component models may be excluded from possible explanations of observed features. Moreover, we show how our framework may be used to inform hypotheses, by suggesting a particular component mechanism responsible for generating a given pressure-response feature of BR firing.

3.2 Methods

3.2.1 Experimental data and its features

In this section we describe the main qualitative characteristics of BR firing rate as well as the data used for quantitative model tests.

Qualitative features of the BR firing rate

Although BR firing patterns depend on the type of BR, e.g., whether they are connected to myelinated or unmyelinated axons [20], there are a number of features nearly all BR neurons exhibit. We characterize these according to observations obtained by stimulating isolated rat aortic BR neurons with a range of pressure stimuli including: sinusoidal, step increases and decreases, and ramp increases and decreases (Figure 3.2). The most commonly noted features of the BR response to imposed pressure stimuli include: saturation and threshold, adaptation and overshoot, as well as post-excitatory depression and rectification. Below, we describe each of these firing rate patterns in more detail.

**Threshold.** Observed in response to a step or ramp increase in pressure. This phenomenon was first described by Bronk and Stella [16, 17] in the 1930s. They observed that a small step increase from a given baseline blood pressure did not trigger BR firing, but when the pressure was increased above a certain threshold, the BR nerve began to fire continuously. The threshold was later observed to increase with an increased baseline pressure [4, 25, 28, 60]. Moreover, Seagard et al. [92] observed that the type of baroreceptor (myelinated or unmyelinated) strongly affects the threshold pressure. The precise mechanisms underlying the threshold phenomena remains unknown, but it is thought to be attributed to the characteristics of ion channels associated with generation of action potentials [3].

**Saturation.** Observed in response to a ramped increase of blood pressure. As the pressure is increased linearly, the BR firing rate first increases almost linearly (with pressure). Then, at a given frequency, the firing rate approaches some limiting value (the saturation level) [25]. This phenomenon
Figure 3.1: **Schematic representation of the BR feedback system.** Stretch sensitive BR neurons originate in the carotid sinuses and the aortic arch. In these arteries, dynamic changes in blood pressure cause vessel deformation, modulating stretch of mechanoreceptors channels found in the BR nerve endings. Stimulation of these receptors modulates frequency of action potential formation, a signal integrated in the NTS. From the NTS, efferent sympathetic and parasympathetic outputs are generated determining the concentrations of neurotransmitters acetylcholine and noradrenaline, which stimulate or inhibit heart rate, cardiac contractility, vascular resistance and compliance, the latter via activation of smooth muscle cells constricting or dilating the radius of arteriolar vessels.

was also observed by Bronk and Stella [16, 17]. They noted that for normotensive rabbits, the firing rate saturates around 120-140 Hz. Later, Seagard et al. [92] studied saturation by stimulating a single carotid BR nerve fiber, extracted from a mongrel dog, with a slow linearly increasing pressure. This experiment showed firing rate saturation at 46.5 ± 2.5 Hz. These observations led to the separation of nerves as type I (large myelinated aortic (A) nerve fibers) and type II (smaller aortic (A) and unmyelinated carotid (C) nerve fibers). They observed type I BR neurons displayed a discontinuous firing pattern, characterized by a sudden onset of discharge at the average threshold pressure of 73.3 ± 5.2 mmHg, whereas type II neurons displayed a continuous, sigmoidal firing pattern saturat-
ing at 19.2 ± 2.1 mmHg.

**Overshoot and Adaptation.** Observed in response to a step change in pressure. The firing rate responds by immediately increasing the rate of discharge, followed by a slow adaptation to a new lower steady state value. Brown et al. [19, Figure 5] noted that the relationship between the size of the overshoot and the level of the pressure stimulus is almost linear. The adaptation level depends on the magnitude of the pressure change. This phenomenon was first observed by Landgren [64, p.7], who discovered that 50% of adaptation occurs within 0.1s following the the pressure stimulus, 95% is completed after 30s, whereas full adaptation requires a very long time, more than 2 min. It was later confirmed by Srinivasen and Nudelman [99] and Brown et al. [18], though from these later studies it is not clear that adaptation requires three distinct timescales. Moreover, Brown [18] noted that the frequency of the adapted firing rate is the same whether the baseline pressure level is reached from a higher or a lower pressure level. Several studies have observed that the level of the steady-discharge is proportional to the applied pressure [19, 20]. No mechanism has been established as the cause of adaptation; however, Franz et al. [36, p.823] propose viscoelastic relaxation as the source of adaptation in the firing rate.

**Post-excitatory depression (PED).** Observed following a step-decrease in pressure. In response to this stimulus the BR firing ceases for a short period, after which it recovers to a rate corresponding to the newly established pressure level. While the term PED was put forward by Brown et al. [18, 88], who studied the phenomena extensively, it was first observed by Bronk and Stella [16] when they noticed that BR firing ceased during diastole. Later, Wang et al. [111] observed that the length of the pause depends on the depth of the pressure drop. Brown [88, p.504], suggested that an electrogenic-sodium pump could be the potential mechanism for this phenomena.

**Asymmetry (or hysteresis).** Observed following a sequential rise and fall of blood pressure (see sinusoidal, square, and triangular stimulus shown in Figure 3.2). This phenomenon was described by Katona and Barnett [53], but have also been discussed by Coleridge, Angell, Pelletier et al. [7, 8, 25, 85]. These studies all observed that the BR firing rate exhibits asymmetrical responses to rising and falling blood pressure. However, asymmetry can be observed in response to any stimuli involving a symmetric increase and decrease in pressure. Thus it may also be observed in PED and in response to periodic sinusoidal forcing. In the time-domain, it may not be easy to see that a sinusoidal stimulation leads to asymmetry, but it can be observed by depicting BR firing as a function of pressure, which gives rise to hysteresis loops. This phenomenon is closely related to adaptation and overshoot, thus viscoelastic relaxation exhibited by the arterial wall, could explain its origin.

**Description of experimental data**

So far we have focused on describing the qualitative features of the BR firing rate. However, if the objective is to understand how these responses are modulated in disease or between species it may
be important to predict the BR firing rate quantitatively.

Below we describe the main features of data used for quantitative predictions. Data were obtained by digitizing results reported by Brown et al. [20] and Saum et al. [88]. From these studies we extracted data from a total of six experiments, grouped with respect to the applied pressure stimulus: sinusoidal, step increase with four different amplitudes, and a square pulse. These stimuli are depicted in Figure 3.2A-C.

Sinusoidal pressure stimulus. To test the models’ abilities to mimic in vivo dynamics, we used data reported by Brown et al. [20, Figure 2A]. They stimulated the stretch-sensitive receptors using a sinusoidal pressure stimulus mimicking the natural blood pressure rhythm and recorded the corresponding BR firing rate. Several studies [26, 37, 97, 113, 115] have reported similar experiments. This type of data allows us to evaluate whether the model can exhibit asymmetry and rectification. The study [20] reports firing rate responses recorded from 11 experiments using myelinated aortic BR axons extracted from Wistar-Lewis strain normotensive rats aged 4-6 months. For each experiment

Figure 3.2: Various types of BR input pressure. To test our models we applied a number of pressure stimuli: (A) sinusoidal, (B) step increases, (C) square (step increase followed by a step decrease), (D) ramp and triangular. The above stimuli were used for testing the models’ responses both qualitatively and quantitatively.
the neuron was stimulated using sinusoidal pressure wave with a frequency of 20 Hz, an amplitude of 5 mmHg, and a mean pressure of 127 mmHg. Steadily oscillating pressures were recorded over a period of 5 seconds. More details about experimental preparation can be found in [19, 88]. To obtain a smooth input stimulus, we fit the data to a sinusoidal function of the form

\[ p(t) = p_0 + 2.5 \sin(p_2 - p_1 t), \]  

(3.1)

where \( p_0 = 127 \text{ mmHg} \). We estimated parameters \( p_1 \) and \( p_2 \) using the initial values \( p_1 = 6.45 \) and \( p_2 = 46.75 \) both radians/s.

**Multistep pressure stimulus.** To demonstrate overshoot followed by adaptation, we digitized BR firing rate data reported in [20, Figure 5]. This study shows BR discharge in response to four pressure step increases from a baseline pressure of 115 mmHg. The four step-increase stimuli are: 13 (to 128), 19 (to 134), 22 (to 137), and 28 (to 143) mmHg (Figure 3.2B). Experiments were done over a period of 12s, allowing the BR firing rate to adapt to a new steady level of discharge. In this study we used data reported by Brown et al. [20], though several experimental studies have reported similar observations [19, 108]. It should be noted, that no graph depicts the pressure stimulus. Brown et al. [20] reported the baseline pressure as well as the level of the pressure increase, but not the exact time denoting the onset of the stimulus. We modeled the stimulus using a smooth function of the form

\[ p(t) = \frac{p_{up}(t^{\kappa_u} + \delta_u^\kappa_u)}{t^{\kappa_u} + (p_{up}/p_{dow})\delta_u^\kappa_u}, \]  

(3.2)

where \( p_{dow}, p_{up} \) (mmHg) denote the baseline pressure and the increased pressure, respectively; \( \delta_u \) (s) denotes the onset of the pressure step increase, and \( \kappa_u \) denotes the steepness of the increase. For the dataset under consideration the values \( p_{dow} = 115 \text{ mmHg} \), and \( p_{up} = \{128, 134, 137, 143\} \text{ mmHg} \) were taken from [20], while we estimated \( \delta_u \) and \( \kappa_u \). Initial values for these parameters were set to \( \delta_u = 1.1 \text{ s} \) and \( \kappa_u = 10 \text{ s} \) approximating the onset described in the experiment [20, Figure 5].

**Square pressure pulse stimulus.** To capture PED, we digitized data reported in Saum et al. [88, Figure 1], which examined PED and adaptation in slowly adapting aortic BR neurons extracted from normotensive and spontaneously hypertensive rats. Though this phenomenon has also been reported in several other studies including [36, 64, 88, 96, 111]. The study by Saum et al. [88] stated that PED could be elicited either mechanically by employing single or double pressure steps, or electrically by stimulating myelinated aortic BR axons extracted from normotensive Wistar-Lewis rats aged 4-6 month. This data shows a steady state discharge was elicited by stimulating the nerve with a baseline pressure of 140 mmHg. After 4 s the pressure was increased by 40 mmHg to 180 mmHg for a period of 4 s, after which it was reset to the baseline pressure of 140 mmHg. To allow the neuron to fully recover following the pressure drop, data were recorded over a period of 20 s. In order to avoid the problem
of non-differentiability we modeled the pressure stimulus using the smooth function

\[ p(t) = p_b + p_{up} \tanh(\kappa(t - \delta_u))/2 - p_{dow} \tanh(\kappa(t - \delta_d))/2, \]

(3.3)

where \( \tanh \) is the hyperbolic tangent. For this stimulus we used \( p_b = 140 \text{mmHg}, p_{up} = 40 \text{mmHg}, p_{dow} = 40 \text{mmHg}, \kappa = 20 \text{s}^{-1}, \) while \( \delta_u (s), \delta_d (s) \) were estimated.

### 3.2.2 Models

To model the dynamics, which produce the BR firing rate in response to given blood pressure stimuli, we include three components separating distinct physiological pathways, and for each component we develop a number of linear and nonlinear models. The three components (Figure 3.3) include: arterial wall deformation, mechanoreceptor stimulation, and action potential generation. As a driving force for the models we use arterial pressure, which determines arterial wall deformation quantified by the wall strain. The wall deformation stimulates the stretch sensitive mechanoreceptors found in the BR nerve endings within the arterial wall. Thus changes in blood pressure modulate the opening of these channels, and thereby the current flowing through them, which determine the rate at which action potentials are formed. The time between subsequent action potentials determines the firing rate, and thus our models relate the receptor strain to the frequency of action potentials, thereby allowing us to predict the BR firing rate. For each model component, described below, we review previous modeling methodologies and use these to inform the design of the new component models, collectively used to describe the firing rate of afferent BR neurons in response to an applied blood pressure stimulus.

**Arterial wall deformation**

BR nerves originate in the wall of the aortic arch and the carotid sinus and terminate in the NTS [94]. Action potentials transmitted along these nerves are generated by stimulation of mechanoreceptors found in the wall. These nerves are stimulated by pressure pulses passing through the ves-
sel, and their firing patterns are modulated in response to changes of the frequency and magnitude of the pressure stimulus. It is well known \[110\] that the arterial wall deforms viscoelastically, though little is known about how this deformation impacts stimulation of the mechanoreceptors. This section describes models predicting the vessel strain as a function of blood pressure, while the next section describes characterization of mechanoreceptor stretch, which in turn modulates BR firing rate.

A detailed description of the arterial wall strain requires complex, anisotropic, viscoelastic models, accounting for dynamics associated with each layer of the wall as well as the interaction between the layers \[110\]. While such models can provide detailed description of wall deformation, without additional data they are not suitable for integration in higher-level models determining the BR firing rate. Another class of models are those assuming that the arterial wall is isotropic. These models represent the wall as a thin shell, and since arteries are tethered in the longitudinal direction, viscoelastic deformation is dominantly in the circumferential direction (cf. \[39\]). Such models determine the cross-sectional strain of the arterial wall in response to induced changes in applied stress, corresponding to the blood pressure \[106\]. Again, depending on the fidelity needed, these “stress-strain” models can be simplified. The simplest stress-strain models ignore viscous deformation and treat the wall as purely elastic. The stress-strain relationship may be either linear or nonlinear. In this study we consider three wall models, of which one is linear and elastic \((W_e, \text{subscript } e \text{ for elastic})\), one is linear and viscoelastic \((W_{ve}, \text{subscript } ve \text{ for viscoelastic})\), and one is nonlinear and elastic \((W_{ne}, \text{subscript } n \text{ for nonlinear and } e \text{ for elastic})\).

**Linear elastic wall model** \((W_e)\). For a thin walled elastic vessel with an isotropic wall, neglecting the axial deformation, the wall strain \(\varepsilon_w\) can be computed using *Laplace’s law*,

\[
\varepsilon_w = \frac{r - r_0}{r} = k_{wall} p, \quad k_{wall} = \frac{r_0}{Eh},
\]

where \(E \text{ (mmHg)}\) denotes Young’s modulus, \(r \text{ (mm)}\) the vessel radius, \(r_0 \text{ (mm)}\) the unstressed radius at zero transmural pressure, and \(h \text{ (mm)}\) the wall thickness.

**Nonlinear elastic wall model** \((W_{ne})\). It is well known that the area-pressure response curve is nonlinear and can be modeled using a sigmoidal function, accounting for saturation of the vessel wall deformation at both high and low pressures. Following \[104, 106\] the pressure-area relationship can be modeled as

\[
A(p) = (A_m - A_0)\frac{p^k}{\alpha^k + p^k} + A_0,
\]

where \(A_0\) and \(A_m \text{ (mm}^2\) are the unstressed and maximum cross-sectional area; \(\alpha \text{ (mmHg)}\) is the characteristic pressure at which the vessel starts to saturate; and \(k\) determines the steepness of rise of the sigmoidal curve, representing the stiffness in the lumen distention due to changes in pressure.
Using (3.4) as a definition of wall strain $\epsilon_w$, we obtain

$$\epsilon_w = 1 - \sqrt{\frac{A_0(a^k + p^k)}{A_0a^k + A_mp^k}}. \quad (3.5)$$

Viscoelastic wall models ($W_{ve}$). While the main contribution to arterial wall deformation is elastic, as mentioned above, the arterial wall is composed of tissue that has viscoelastic properties. Viscoelastic models encompass both elastic deformation and viscoelastic creep, and thus can be described using either linear or nonlinear elastic responses.

Linear viscoelastic response of the arterial wall is typically, although not solely, described using a number of springs (elastic elements) and dashpots (viscous elements) in various configurations. The so-called standard linear solid (SLS), is one of the most commonly used examples of such configurations. It involves a Maxwell element (a spring $E_1$ (mmHg) and dashpot $\eta_1$ (mmHg·s) in series) in parallel with a spring $E_0$ (mmHg). It is easy to establish that the total stress-strain relationship is given by

$$\epsilon + \tau_a \frac{d\epsilon}{dt} = \frac{1}{E_0} \left( \sigma + \tau_b \frac{d\sigma}{dt} \right), \quad \tau_a = \frac{\eta_1}{E_0} \left( 1 + \frac{E_0}{E_1} \right), \quad \tau_b = \frac{\eta_1}{E_1}. \quad (3.6)$$

To apply the SLS model to the arterial wall, we think of $\epsilon$ as vessel distention $\epsilon_w$ and the stress as the blood pressure $p$ (mmHg). Moreover, assuming the arterial wall is a thin-walled elastic tube we can substitute $E_0 = Eh/\rho_0$ (mmHg) and obtain

$$\epsilon_w + \tau_a \frac{d\epsilon_w}{dt} = k_{wall} \left( p + \tau_b \frac{dp}{dt} \right), \quad k_{wall} = \frac{r_0}{Eh}.$$ 

In order to avoid numerical differentiation of the data, following $[106]$ we apply the integrating factor and transform this equation to

$$\epsilon_w = \left( \epsilon_w(t_0) - \frac{k_{wall} \tau_b}{\tau_a} p(t_0) \right)e^{-\tau_a \frac{d\gamma}{dp}} + \frac{k_{wall} \tau_b}{\tau_a} p(t) + k_{wall} \frac{\tau_a - \tau_b}{\tau_b} \int_{t_0}^{t} e^{-\tau_a \frac{d\gamma}{dp}} p(\gamma) d\gamma. \quad (3.7)$$

QLV framework. Formulated as linear elements in series and parallel, the above model cannot directly be extended to account for nonlinear elastic response; moreover, it is limited to models described using a finite number of components. It was noted by Fung [39], that biological tissues are not elastic and that strain history affects the stress. These tissues also exhibit a difference in the stress response between loading and unloading. Generalizing linear viscoelastic theory, Fung [39], introduced the so-called quasi-linear viscoelastic theory (QLV), which has been used successfully to model stress-strain relationships involving living tissues [79, 114]. The QLV theory is a flexible framework that includes linear viscoelastic theory and provides a more accurate description of the pressure-strain curve, especially in living tissues. We proceed with the assumption that the arterial wall can be modeled as homogeneous and isotropic thin walled cylindrical vessel [38]. Therefore the
wall strain as a function of pressure can be determined as

$$\epsilon_w = \int_{\infty}^{t} K(t - \gamma) \frac{\partial s^e[p(\gamma)]}{\partial \gamma} d\gamma,$$

(3.8)

where $K(t)$ is a creep function, and $s^e[p(\gamma)]$ is the elastic response [39, 106]. Finally, it should be noted that all the linear and nonlinear arterial wall models described above can be expressed within the unified framework of the QLV theory, see Table 3.1.

Table 3.1: Elastic and viscoelastic models of arterial wall strain. The unified QLV formulation in (3.8) encompasses all models studied here. The first column lists the model, the second the elastic response, the third the creep, and the fourth states if the model is linear or nonlinear.

<table>
<thead>
<tr>
<th>Model</th>
<th>Elastic response $s^e[\cdot]$</th>
<th>Creep $K(\cdot)$</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>$W_e$</td>
<td>$\frac{r_0}{Eh}p$</td>
<td>1</td>
<td>elastic</td>
</tr>
<tr>
<td>$W_{ve}$</td>
<td>$\frac{r_0}{Eh}p$</td>
<td>$1 - A_1 e^{-t/b_1}$</td>
<td>viscoelastic</td>
</tr>
<tr>
<td>$W_{ne}$</td>
<td>$1 - \frac{A_0(a^k + p^k)}{A_0a^k + A_mp^k}$</td>
<td>1</td>
<td>nonlinear elastic</td>
</tr>
</tbody>
</table>

**Mechanoreceptor stimulation**

The BR nerves emanating in the adventitial layer of the aortic arch and carotid arteries form a complex branching network [59]. In rats electron microscopy studies have revealed that BR aortic nerve fibers form bundles, usually containing one myelinated and five unmyelinated fibers of different sizes [59, p.401]. Each bundle is surrounded by a protective sheath, perineurium. Both unmyelinated and myelinated fibers are sheathed in Schwann cells and are embedded in collagen, see [59, p.404] and [74, 75]. Because these nerve endings are embedded in the arterial wall, deformations of the arterial wall also deform the nerve endings. This stimulates stretch sensitive, non-selective cation channels that serve to transduce the changes in the nerve ending structure into an electrical signal, which is encoded into the firing pattern of the BR neuron [12].

We propose a model specifying the strain effected specifically at the nerve endings as a result of a given arterial wall strain. Thus our model seeks to capture the stimulation of the mechanoreceptive nerve endings by capturing the stretching dynamics of the nerve endings as the arterial wall expands or contracts in response to changes in pressure. We propose models with the assumption...
Figure 3.4: A schematic illustration of the strain sensed by the mechanoreceptors. The spring and $n$ Voigt bodies (a parallel spring and dashpot) in series shown here describes the strain sensed by the mechanoreceptors relative to the deformation of the arterial wall. The spring $E_0$ represents the elasticity of the BR nerve endings, whereas the $n$ Voigt bodies reflect the viscoelastic properties of the surrounding connective tissue. Each element $n$ provides a timescale adaptation of BRs firing rate in response to a step increase in pressure observed in experiments. This study compares the cases $n = 1, 2, 3$.

that viscoelastic properties of BR nerve ending connective tissue are the key factor in the transduction process [29, 41]. Following the ideas used in previous BR modeling studies [2, 21]; and before in the modeling of the muscle spindle dynamics [44, 47] we describe the coupling of the strain sensed by the mechanoreceptors to the wall deformation using $n$ Voigt bodies in series with a spring (Figure 3.4). Following this idea, the strain sensed by the mechanoreceptors in response to the arterial wall deformation is given by

$$\epsilon_{ne} = \epsilon_w - \epsilon_1,$$

where $\epsilon_w$ denotes the strain of the wall, and $\epsilon_1$ denotes the strain of the first Voigt body. Choosing the parameters $a_{ij}$ and $b_1, \ldots, b_n$, determined by the spring, $E$, and dashpot, $\eta_i$, constants, the model given in Figure 3.4 can be described using the dynamical system

$$\frac{d\epsilon_j}{dt} = a_{j1}\epsilon_1 + \ldots + a_{jn}\epsilon_n + b_j\epsilon_w \quad j = 1, 2, \ldots, n$$

where $\epsilon_j, (j = 1, \ldots, n)$ is the relative displacement within each Voigt body. Consequently, our model assumes a declining afferent sensory activity during constant intensity stimulation, a fundamental property of mechanoreceptors that can be described in terms of viscoelastic relaxation processes in the vessel wall [36, 101]. Below we describe, in more detail, the computational aspects of this element of the BR model, analyzing model components including one, two, and three Voigt bodies. Since the strain is calculated using Voigt bodies, we have denoted this model component as $V_i$ where $i = 1, 2, 3$ indicates the number of Voigt bodies included.

One Voigt body model ($V_1$). We start with the simplest model, consisting of one Voigt body in series with a spring (Figure 3.4 for $n = 1$). The governing equation used for determining the nerve ending
deformation is given by
\[
\frac{d\epsilon_1}{dt} = -(\alpha_1 + \beta_1)\epsilon_1 + \alpha_1\epsilon_w, \tag{3.10}
\]
where \(\beta_1\) and \(\alpha_1\) depend on the spring constants \(E_0, E_1\) and viscous element \(\eta_1\) as stated in Table 3.6. Since equation (3.10) is a first-order linear ODE, the total strain sensed by the mechanoreceptor is equivalent to the strain on the Voigt body, thus this model component only exhibit one time-scale \(\tau_{v_1} \, (s^{-1})\) associated with the strain \(\epsilon_w\). This time-scale is given by
\[
\tau_{v_1} = \alpha_1 + \beta_1. \tag{3.11}
\]

Two Voigt body model \((V_2)\). The model with two Voigt bodies and a spring in series (Figure 3.4 for \(n = 2\)) can be described by the following system of equations
\[
\frac{d\epsilon_1}{dt} = -(\alpha_1 + \alpha_2 + \beta_1)\epsilon_1 + (\beta_1 - \beta_2)\epsilon_2 + (\alpha_1 + \alpha_2)\epsilon_w, \tag{3.12}
\]
\[
\frac{d\epsilon_2}{dt} = -\alpha_2\epsilon_1 - \beta_2\epsilon_2 + \alpha_2\epsilon_w,
\]
where \(\alpha_1, \alpha_2, \beta_1\) and \(\beta_2\) are defined in Table 3.6. There are two timescales \(\tau_{v_2}^a\) and \(\tau_{v_2}^b\) associated with the nerve ending relaxation, thus one expects the BR firing rate to observe adaptation more closely. For this model represented by two Voigt bodies \((E_j, \eta_j), j = 1, 2\), in series with a spring \(E_0\), those two time-scales can be computed as follows. The total strain-stress relationship is given by
\[
a_2\epsilon_{w''} + a_1\epsilon_{w'} + a_0\epsilon_w = b_2\sigma'' + b_1\sigma' + b_0\sigma, \tag{3.13}
\]
where the coefficients are
\[
a_0 = E_0 E_1 E_2 \quad b_0 = E_0 E_1 + E_0 E_2 + E_1 E_2
\]
\[
a_1 = E_0 (E_1 \eta_2 + E_2 \eta_1) \quad b_1 = E_0 \eta_1 + E_0 \eta_2 + E_1 \eta_2 + E_2 \eta_1
\]
\[
a_2 = E_0 \eta_1 \eta_2 \quad b_2 = \eta_1 \eta_2.
\]
For the step-increase in pressure (and thus wall stain \(\epsilon_w\)) we obtain \(\epsilon_{w'} = \epsilon_{w''} = 0\). Therefore the two timescales \(\tau_{v_2}^a \, (s^{-1})\) and \(\tau_{v_2}^b \, (s^{-1})\) are given by the roots of
\[
x (x) = [a_2 \beta_1 + a_1 \beta_2 + \beta_1 \beta_2] + [a_1 + a_2 + \beta_1 + \beta_2] x + x^2. \tag{3.14}
\]

Three Voigt body model \((V_3)\). For model with three Voigt bodies in series with a spring (Figure 3.4...
for $n = 3$) we obtain the following system of equations

\[
\begin{align*}
\frac{d\varepsilon_1}{dt} &= -(a_1 + a_2 + a_3 - \beta_1)\varepsilon_1 + (\beta_1 - \beta_2)\varepsilon_2 + (\beta_2 - \beta_3)\varepsilon_3 + (a_1 + a_2 + a_3)\varepsilon_w, \\
\frac{d\varepsilon_2}{dt} &= -(a_2 + a_3)\varepsilon_1 + \beta_2\varepsilon_2 + (\beta_2 - \beta_3)\varepsilon_3 + (a_2 + a_3)\varepsilon_w, \\
\frac{d\varepsilon_3}{dt} &= -a_3\varepsilon_1 - \beta_3\varepsilon_3 + a_3\varepsilon_w,
\end{align*}
\]

(3.15)

where as in the previous case the coefficients $a_j, \beta_j, j = 1, 2, 3$ are provided in Table 3.6. This model has three time-scales $\tau_{\varepsilon_1}^a (s^{-1}), \tau_{\varepsilon_2}^b (s^{-1}),$ and $\tau_{\varepsilon_3}^c (s^{-1})$ associated with the nerve ending relaxation. Again, the total strain-stress relationship for our model is given by

\[
a_3 \varepsilon_w^{(3)} + a_2 \varepsilon''_w + a_1 \varepsilon'_w + a_0 \varepsilon_w = b_3 \sigma^{(3)} + b_2 \sigma'' + b_1 \sigma' + b_0 \sigma,
\]

(3.16)

where the coefficients are given by

\[
\begin{align*}
a_0 &= E_0 E_1 E_2 E_3 & b_0 &= E_0 E_1 E_2 + E_0 E_1 E_3 + E_0 E_2 E_3 + E_1 E_2 E_3 \\
a_1 &= E_0(E_2 E_3 \eta_1 + E_1 E_3 \eta_2 + E_1 E_2 \eta_3) & b_1 &= E_0 E_2 \eta_1 + E_0 E_3 \eta_1 + E_2 E_3 \eta_1 + E_0 E_1 \eta_2 + E_0 E_3 \eta_2 + \\
& & & & + E_1 E_3 \eta_2 + E_0 E_1 \eta_3 + E_0 E_2 \eta_3 + E_1 E_2 \eta_3 \\
a_2 &= E_0(E_3 \eta_1 \eta_2 + E_2 \eta_1 \eta_3 + E_1 \eta_2 \eta_3) & b_2 &= E_3 \eta_1 \eta_2 + E_0 \eta_1 \eta_2 + E_0 \eta_1 \eta_3 + E_2 \eta_1 \eta_3 + E_0 \eta_2 \eta_3 + \\
& & & & + E_1 \eta_2 \eta_3 \\
a_3 &= E_0 \eta_1 \eta_2 \eta_3 & b_3 &= \eta_1 \eta_2 \eta_3.
\end{align*}
\]

For the step-increase in pressure (and thus wall stain $\varepsilon_w$) we obtain $\varepsilon'_w = \varepsilon''_w = \varepsilon^{(3)}_w = 0.$ Thus the timescales are the roots of

\[
\xi_{V_3}(x) = A_0 + A_1 x + A_2 x^2 + x^3,
\]

(3.17)

where

\[
\begin{align*}
A_0 &= a_1 \beta_2 \beta_3 + a_2 \beta_1 \beta_3 + a_3 \beta_1 \beta_2 + \beta_1 \beta_2 \beta_3, \\
A_1 &= a_1(\beta_2 + \beta_3) + a_2(\beta_1 + \beta_3) + a_3(\beta_1 + \beta_2) + \beta_1 \beta_2 + \beta_1 \beta_3 + \beta_2 \beta_3, \\
A_2 &= a_1 + a_2 + a_3 + \beta_1 + \beta_2 + \beta_3,
\end{align*}
\]

where again $a_j, \beta_j (j = 1, 3)$ are given in Table 3.6.

**BR Firing rate**

The final model component requires a description of the generation of action potentials in response to stimulation of the mechanoreceptors. The generation of action potentials is often described using the Hodgkin-Huxley (HH) model representing the biophysical characteristic of cell membranes, in-
Figure 3.5: **Diagram for leaky integrate-and-fire model.** The circuit diagram (left) represents the schematic layout of the integrate-and-fire components. The graph (right) depicts voltage vs time for a neuron stimulated by a constant current.

including a lipid bilayer represented by a capacitance and membrane channel proteins represented as nonlinear resistors. Action potentials are initiated when the neuron receives sufficient electrical current stimulus, in case of BRs, this stimulus is typically via pressure dependent stimulation of stretch sensitive ion channels. These detailed models are fairly complex and contain numerous parameters; moreover, they describe the dynamics of membrane voltage instead of directly modeling firing rate. In this study, we proceed by considering two models: a simple model, that predicts firing rate linearly from the mechanoreceptor stimulation, and using a leaky integrate-and-fire model. The linear model simply amplifying the strain is denoted by $N_a$, and the integrate-and-fire model is denoted by $N_{IF}$.

**Simple amplifier ($N_a$).** For the simplest possible model, we assume that action potential generation, and thus nerve firing rate, can be obtained by considering a simple linear amplifier described by

$$ f = s_1 e_{ne} - s_2, \quad (3.18) $$

where $s_1$ is the gain, and $s_2$ is the shift. The underlying assumption of this model is that the change in firing is proportional to the mechanical stimulation, $e_{ne}$, of the nerve ending.

**Leaky integrate-and-fire model ($N_{IF}$).** A more realistic description can be obtained using a leaky integrate-and-fire model, which considers the BR neuron as a simple electrically excitable membrane stimulated by a current generated by the mechanoreceptors. We assume that the generated current is proportional to the strain sensed by the nerve endings $e_{ne}$. The leaky integrate-and-fire model originally proposed by Lapicque [65], but also discussed in [1, 56], describes the excitation of the voltage across the BR membrane as equivalent to the capacitor voltage in an RC circuit (Figure 3.5). The circuit consists of a stimulus current source (given as a function of $e_{ne}$), an Ohmic leakage conductance, $g_{leak}$, and a capacitor, $C_m$, all three elements in parallel.
The change in voltage generated by a leaky integrate-and-fire model is given by

$$C_m \frac{dV_m}{dt} = I_{ne} - g_{leak} V_m,$$

(3.19)

where $I_{ne}$ (pA) denotes the current stimulus, $g_{leak}$ ($\mu$S) is a leakage conductance, and $C_m$ (nF) denotes the membrane capacitance. In the equation above, the voltage $V_m$ (mV) is relative to the equilibrium potential. To model the firing rate of the neuron we assume that to form an action potential, the BR neuron has to charge the membrane voltage above a given voltage threshold, which we denote $V_{th}$ (mV). Applying this assumption to (3.19), allows calculation of $T$ (s), i.e., time required for the voltage to increase from equilibrium to the threshold, for a given stimulus current, $I_{ne}$. We can calculate $T$ integrating (3.19) giving

$$\int_{0}^{V_{th}} \frac{dV_m}{I_{ne} - g_{leak} V_m} = \int_{0}^{T} \frac{dt}{C_m}.$$

(3.20)

For constant $I_{ne}$ this equation can be solved analytically, yielding

$$T = \frac{C_m}{g_{leak}} \left[ \ln \left( I_{ne} - g_{leak} V_{th} \right) - \ln(I_{ne}) \right],$$

where, as stated above, $T$ represents the time required to generate an action potential given a constant current stimulus $I_{ne}$. We propose to model $I_{ne}$ as a linear function of $\epsilon_{ne}$

$$I_{ne} = \tilde{s}_1 \epsilon_{ne} + \tilde{s}_2,$$

(3.21)

where $\tilde{s}_1$ and $\tilde{s}_2$, both of units (s), are the gain and shift of the stimulus current. Finally, the absolute refractory period, $t_{ref}$ (s), denotes the time following an action potential, during which a subsequent action potential cannot be generated [51]. We account for this by letting the rate (frequency) $f = \left( T + t_{ref} \right)^{-1}$ (Hz). With these simplifying assumptions the BR firing rate can be computed as a function of the instantaneous strain of the nerve ending sensed by the BR as

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

(3.22)

We propose to interpret the BR firing rate as that given by (3.22) for $I_{ne}$ at a given instant. The piecewise definition of the frequency is necessary as (3.20) does not have a solution when the stimulus current is less than the leak current at threshold voltage. This is a consistent interpretation of the
instantaneous frequency as we do not expect any firing events to occur for a sub-threshold stimulus (less than the base current). In general, for a sub-threshold current stimulus the firing rate, $f$, is expected to cease until $I_{ne}$ is increased above the threshold level. The parameters $C_m$, $g_{leak}$, $t_{ref}$, and $V_{th}$ of this model are expected to approximately correspond to the electrophysiologically observable characteristics of the BR neuron, membrane capacitance, leakage conductance, refractory period and threshold, respectively. The membrane capacitance can be measured using electrophysiological techniques [90]. Leakage conductance can be approximated as the net inward conductance near equilibrium potential. The true refractory period and threshold voltage of a neuron are not absolute and are typically somewhat dynamic and thus difficult to measure. One may roughly estimate these values for BRs from the results of experimental studies of the membrane excitability of nodose neurons, a neuron family including BRs [90]. The observation of BR firing rates up to 140 Hz leads to a refractory period of $t_{ref} \approx 7\,\text{ms}$ [16, 17].

**Composite BR models**

In the previous sections we developed a framework to model the three main components involved with description of the BR firing. To develop a composite model, one component must be chosen from each category. There are various options one may select from in order to construct a BR model. The choice depends on a number of factors including the type of species (e.g., rats, dogs, sheep, humans, etc.) and the type of data (e.g., steady, step-change, dynamic, *in vivo*, etc.). We propose a total of six linear and nonlinear models, summarized in Table 3.2, which we will carefully analyze and test using aortic baroreceptor rat data. These models can be formulated as a system of algebraic and differential equations of the form

$$\epsilon_w = g_1(p, t; \theta)$$
$$\frac{dx}{dt} = g_2(x, \epsilon_w, t; \theta)$$
$$f(x, t; \theta) = g_3(x, t; \theta),$$

(3.23)

where $p$ (mmHg) is the blood pressure (model input); $\epsilon_w$ denotes the vessel strain; $x = (\epsilon_1, \epsilon_2, \ldots, \epsilon_n)$; $t$ time (s); $\theta$ the model parameters; and $f$ (Hz) the BR firing rate. Models can be classified as one of two basic types: linear and nonlinear models. It should be noted that differential equations only enter via the model component describing mechanoreceptor strain. To ensure that model simulation began from a relaxed state, we computed the initial conditions by solving $g_2(x, g_1(p, t; \theta), t; \theta) = 0$. To be more precise for the four linear BR models $W_c V_1 N_a$, $W_c V_2 N_a$, $W_c V_3 N_a$, and $W_c e V_3 N_a$ the initial conditions are respectively

36
\[ x_{V1}^* = -a_1 k_w p_M / (a_1 + \beta_1) \]

\[ x_{V2}^* = \frac{k_w p_M}{a_2 \beta_1 + (a_1 + \beta_1) \beta_2} \left[ a_2 \beta_1 + a_1 \beta_2, \quad a_2 \beta_1 \right]^T \]

\[ x_{V3}^* = \frac{k_w p_M}{a_3 \beta_1 \beta_2 + (a_2 \beta_1 + (a_1 + \beta_1) \beta_2) \beta_3} \left[ a_3 \beta_1 \beta_2 + a_2 \beta_1 \beta_3 + a_1 \beta_2 \beta_3, \quad \beta_1 (a_3 \beta_2 + a_2 \beta_3), \quad a_3 \beta_1 \beta_2 \right]^T \]

\[ x_{ve}^* = \frac{k_w (p_M + \tau_b p_D)}{a_2 \beta_1 + (a_1 + \beta_1) \beta_2} \left[ a_2 \beta_1 + a_1 \beta_2, \quad a_2 \beta_1 \right]^T \]

where \( p_M \) and \( p_D \) (mmHg) are the initial values of the pressure stimulus and its derivative, respectively, and \( \tau_b \) (s), \( \alpha_j \) (mmHg), \( \beta_j \) s\(^{-1} \), for \( j = 1, 2, 3 \) are given in Table 3.6. For the nonlinear model \( W_{ne} V_2 N_a \) we used the following initial condition

\[ x_{ne}^* = \frac{I_n}{a_2 \beta_1 + (a_1 + \beta_1) \beta_2} \left[ a_2 \beta_1 + a_1 \beta_2, \quad a_2 \beta_1 \right]^T, \quad I_n = 1 - \left[ A_0 (\alpha^k + p_M^k) / (A_0 \alpha^k + A_m p_M^k) \right]. \]

Table 3.2: Summary of the BR models. The table defines six BR models that are tested against previously recorded BR data from rats [19]. Each model is denoted by a three-element name referring to a corresponding part of its component (arterial wall \( W \), mechanoreceptor stimulation \( V \), neuron \( N \)). The cross-reference indicates what equation is included in a given model.

<table>
<thead>
<tr>
<th>Model</th>
<th>Wall</th>
<th>Nerve ending</th>
<th>Neuron</th>
<th>Parameters</th>
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<td>Eq (3.4)</td>
<td>Eq (3.10) &amp; (3.9)</td>
<td>Eq (3.18)</td>
<td>( k_{wall}, a_1, \beta_1, s_1, s_2 )</td>
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<td>Eq (3.4)</td>
<td>Eq (3.12) &amp; (3.9)</td>
<td>Eq (3.18)</td>
<td>( k_{wall}, a_1, a_2, \beta_1, \beta_2, s_1, s_2 )</td>
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<tr>
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<td>Eq (3.15) &amp; (3.9)</td>
<td>Eq (3.18)</td>
<td>( k_{wall}, a_1, a_2, a_3, \beta_1, \beta_2, \beta_3, s_1, s_2 )</td>
</tr>
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<td>Eq (3.18)</td>
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</tr>
<tr>
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<td>Eq (3.15) &amp; (3.9)</td>
<td>Eq (3.18)</td>
<td>( A_0, A_m, \alpha, \kappa, a_1, a_2, \beta_1, \beta_2, s_1, s_2 )</td>
</tr>
<tr>
<td>( W_{ne} V_2 N_{IF} )</td>
<td>Eq (3.5)</td>
<td>Eq (3.15) &amp; (3.9)</td>
<td>Eq (3.22)</td>
<td>( A_0, A_m, \alpha, \kappa, a_1, a_2, \beta_1, \beta_2, s_1, s_2, C_m, g_{rec}, V_{th}, i_{ref} )</td>
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### 3.3 Results

In this section we present results obtained with the models introduced in the Method section and summarized in Table 3.2. First, we test the models’ abilities to quantitatively fit experimental data with sinusoidal and step-increase stimuli. Second, we discuss the models ability to show qualitative features not encompassed by the quantitative data. Quantitative simulations allow us to identify the components necessary to fit observed data, whereas qualitative simulations allows us to test the model further in response to stimuli not detailed by experimental measurements.
3.3.1 Quantitative results

Models will be tested quantitatively using three types of pressure stimuli: sinusoidal at a fixed frequency, a step-increase, and a step-increase followed by a step decrease (Figure 3.2A-C). We investigated six linear and nonlinear models summarized in Table 3.2. For the wall strain three models were investigated, the simplest assumes the wall strain $\epsilon_w$ has a spring-like response (denoted $W_s$). The second model (denoted $W_{ne}$) accounts sigmoidally for increased stiffening with increased pressure, and finally we investigate a viscoelastic model ($W_{ve}$). The mechanoreceptor strain $\epsilon_{ne}$, is modeled using one, two, and three Voigt bodies, respectively, in series with the spring ($V_1$, $V_2$, $V_3$). Finally, two models were used for determining the BR firing rate, a linear model ($N_a$) and an integrate-and-fire model ($N_{IF}$). As mentioned above, these models can all be described as a system of algebraic and differential equations. For all models the model input is pressure $p$ and the model output is BR firing rate $f$, initial conditions were computed to ensure that model solutions start at steady state. The objective was to estimate model parameters minimizing the least squares error between the model and data. This is calculated from the point wise residual error between model and data

$$R_i = \frac{f_{data}(t_i) - f_{model}(t_i, \theta)}{\bar{f}_{data}},$$

where $\bar{f}_{data}$ is the average firing rate of the specific data set considered and $\theta$ denotes the parameter vector. To estimate the parameters we minimize the sum of squares cost function (referred to as RMSE in Tables 3.3, 3.4, and 3.5)

$$J(\theta) = \frac{R^T R}{N} = \frac{\sum_{i=1}^{N} \left[ f_{data}(t_i) - f_{model}(t_i, \theta) / \bar{f}_{data} \right]^2}{N}.$$

Since data is only available for the BR firing rate and the pressure stimuli, for most models not all parameters are identifiable. We denote as identifiable parameters, those that are sensitive and not correlated, given the model output and the associated available data [77]. In this study, identifiability of parameters was determined using sensitivity based methods [80]. Subsequently, for models completely characterized by smooth functions, the Levenberg-Marquardt method was used to estimate model parameters, while for models not fulfilling this requirement (the integrate-and-fire models), parameters were estimated using the Nelder-Mead method. Both used optimization algorithms from Kelley [54].

Below we first describe the methodology used for sensitivity analysis and parameter identification and subsequently we discuss results obtained using nonlinear optimization, the latter is separated according to the input stimulus.

Sensitivity analysis: For any smooth model of the form (3.23), the sensitivities [30, 31, 35] can be
computed as

$$S_k = \frac{\partial f}{\partial \theta_k}.$$ 

Following Pope et al. [87], we use a finite difference approximation to compute $S_k$

$$S_k = \frac{f(t, \theta + he_k) - f(t, \theta)}{h}, \quad e_k = \begin{bmatrix} k \\ 0 \ldots 0 \end{bmatrix},$$

where $e_k$ is the unit vector in the $k^{th}$ component direction and $h$ is a small number. The BR firing rate $f$ is obtained computationally, with an integration tolerance of $\chi = 10^{-6}$ imposed on solution of the differential equations, thus $h$ is bounded by $\sqrt{\chi}$. To satisfy this requirement we let $h = 0.01$.

Sensitivities are ranked by averaging time-varying functions using the two-norm. For each model, this ranking was used to separate parameters into two groups: one group consisted of parameters to which the model output was sensitive, and the other group consisted of parameters to which the model output was insensitive. Estimating only sensitive parameters allows more reliable estimation of parameters [48].

Not all sensitive parameters are practically identifiable [77, 80]. To identify parameter correlations, we used the QR-SVD subset selection method [22, 49, 87]. We also used a method based on covariance analysis to identify pairs of correlated parameters [80]. For each pair of correlated parameters the least sensitive parameter was kept fixed at its nominal value while the other was included in the subset. Parameter correlations were computed from

$$c_{i,j} = \frac{C_{i,j}}{\sqrt{C_{i,i}C_{j,j}}}, \quad C = \sigma(S^T S)^{-1},$$

where $\sigma$ is the variance of the assumed noise in the data, $C$ is the covariance matrix, and is $c_{i,j}$ the correlation coefficient. Parameters for which $|c_{i,j}| > \gamma$ are labeled as correlated. For the models studied in this work we let $\gamma = 0.8$. Once a set of uncorrelated sensitive parameters were identified, we used either the Levenberg-Marquardt or the Nelder-Mead method to estimate the subset of practically identifiable model parameters [54]. The Levenberg-Marquardt method was used for models that can be described using smooth functions, while the Nelder-Mead method was used for models including the leaky integrate-and-fire component. Since this model contains a discontinuity the gradient based Levenberg-Marquardt method is not applicable.

**Sinusoidal stimulus:** Now we present results obtained using sinusoidal forcing allowing us investigate asymmetry of the model response. Results (Figure 3.6) show BR firing rate as a function of time and BR firing rate as a function of stimulus. For both graphs model results are marked with red lines and data with black. The associated pressure stimulus is depicted in Figure 3.2A. For this stimulus we analyzed five models. We first describe results obtained with the three linear models, analyzing...
Figure 3.6: The optimized response of linear BR models (left), and the corresponding hysteresis loop (right). We present the fits for three linear BR models $W_c V_1 N_a$, $W_c V_2 N_a$ and $W_c V_3 N_a$ (denoted in the legend as V1, V2, and V3, respectively), listed in Table 3.2. The optimized parameter values, the $R^2$ and the RMSE errors are reported in Table 3.3.

The three linear models include a component determining the wall strain, described using a linear elastic function of pressure, a component representing mechanoreceptor stimulation, described using one, two, and three Voigt bodies, and a component predicting the BR firing rate. The three models have 5, 7, and 9 parameters, respectively, as well as two additional parameters $p_1$ and $p_2$ associated with the sinusoidal stimulus. In [20, p. 695] the authors indicated that phase measurements are less accurate than amplitude measurements due to the inaccuracies associated with assigning interspike intervals to bins. Thus, the parameters $p_1$ and $p_2$ were added to the parameter set. Sensitivity analysis together with subset selection allowed us to identify four uncorrelated parameters including $s_1, s_2, p_1$, and $p_2$, which were estimated for all three models.

The nominal values for the model parameters (listed in Table 3.3) were computed as follows. The parameter $k_{wall} = r_0/Eh$ (mmHg$^{-1}$), where $E$ is Young's modulus (mmHg), $h$ (mm) is the wall thickness, and $r_0$ (mm) is the zero pressure radius as described in the Methods section (see also Table 3.6). We use $E = 1050$mmHg approximating a lower bound to values observed in a previous study [73]. In [34, Figure 1] Feng et al. provide detailed measurements of the external diameter $D$ and thickness $h$ for the rat aortic arch, measured in adult male Sprague-Dawley rats. They found that in the region with aortic BR endings the average values of $D = 2.27 \pm 0.17$ (mm) and $h = 0.17 \pm 0.02$ (mm). Using these values we compute $k_{wall} = 0.0063$ (mmHg$^{-1}$). We note this parameter and $s_1$ were highly correlated indicating equivalent fits could be achieved through adjustment of either parameter.
Figure 3.7: The optimized response of linear BR models. We show the ability of three linear models $W_1 V_1 N_a$, $W_2 V_2 N_a$ and $W_3 V_3 N_a$ (denoted in the legend as V1, V2, and V3, respectively) to reproduce four types of increases in pressure: (A) 128 mmHg, (B) 134 mmHg, (C) 137 mmHg, and (D) 143 mmHg) published by Brown [20]. The parameters of each model have been optimized for each data set individually and are listed in Table 3.3 together with the $R^2$ and the RMSE errors.

direct experiments exist allowing estimation of nominal values for the elastic $E_1, E_2, E_3$ and viscous constants $\eta_1, \eta_2, \eta_3$ associated with mechanoreceptor strain. These parameters appear only in the dynamic part of the model and determine the adaptation time-scales. To ensure that the three models are distinct, it is essential that parameters representing time-scales are separated, otherwise the models would essentially reduce to one. This knowledge, along with values chosen in the study by Bugenhagen et al. [21] motivated our choice for nominal parameter values. To avoid the problem of structural nonidentifiability [77] we rescaled the parameters as follows $\alpha_j = E_0/\eta_j$ and $\beta_j = E_j/\eta_j$ for $j = 1, 2, 3$. The full list of the model parameters together with their initial conditions, units and literature reference is provided in Table 3.6. As for the stimulus, the average pressure (127 mmHg) and the amplitude (5 mmHg) was provided in [20]. To compute the frequency $p_1$ and the shift $p_2$ of the pressure, we digitized the stimulus provided in [20, Figure 2A], and then fitted to a sinusoidal function $p(t) = -2.5 \sin(-p_1 t + p_2) + 127$, obtaining $p_1 = 6.45$ and $p_2 = 46.75$ (Hz). As noted in
Figure 3.6, results of parameter estimation with each of the three models were indistinguishable, though estimated parameter values varied significantly, the latter is due to added complexity associated with adding more Voigt bodies. The fact that graphs were almost identical was also reflected by the least squares cost RMSE (and the coefficient of determination $R^2$) for models $W_{e1}V_{1}N_{a}$, $W_{e2}V_{2}N_{a}$ and $W_{e3}V_{3}N_{a}$ we obtained 2.522 (0.949), 2.507 (0.950), and 2.495 (0.951), respectively, see Table 3.3.
Table 3.3: Optimized values of parameters for the linear models of BR response. For the three linear models $W_e V_i N_a$, $W_e V_i V_i N_a$ and $W_e V_i N_a$ of BR response we present the initial and optimized values of their parameters. We used the BR firing data published by Brown \[20\] for two different stimuli: the sinusoidal-like pressure profile, and step pressure increase with different magnitude.

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Next, we investigated the impact of including more complex wall models. Additionally, we incorporated a nonlinear response wall model $W_{ne}$, and a viscous wall model $W_{ve}$. To be more precise we compare the BR response of the following three models $W_e V_2 N_a$, $W_{ve} V_2 N_a$ and $W_{ne} V_2 N_a$ described using 7, 8, 9 parameters plus the two parameters associated with the stimulus. We examined the ability of each of these models to fit the sinusoidal stimulus. Sensitivity analysis and subset selection allowed us to estimate 4-6 parameters. All models allowed us to estimate $s_1$, $s_2$, $p_1$, and $p_2$. In addition, for the nonlinear elastic model $A_m$ was added to the subset and for the viscoelastic model $\tau_a$ and $\tau_b$ were added to the subset. Given that the more complex nonlinear models allows estimation of more parameters, one should anticipate better results. But due to the limited dynamics embedded within the pressure stimulus, adding more complex wall models did not improve results as reflected by the least squares cost RMSE (and the coefficient of determination $R^2$), which for $W_e V_2 N_a$, $W_{ve} V_2 N_a$ and $W_{ne} V_2 N_a$ gave 2.507 (0.950), 2.517 (0.950), and 2.458 (0.952), respectively; see Table 3.4.
Table 3.4: **Optimized nonlinear models of BR response: wall strain models** For the three models, $W_e V_2 N_a$, $W_{ee} V_2 N_a$, and $W_{ne} V_2 N_a$, of BR response, we present the initial and optimized values of their parameters. We used the BR firing data published by Brown [20] for a sinusoidal-like pressure profile.

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Figure 3.8: The optimized response of (A) $W_eV_2Na$, and (B) $W_eV_3NI_F$ to a PED profile of BR firing rate. The parameters of each model have been optimized for each data set individually and are given in Table 3.3 together with the $R^2$ and the RMSE errors.

*Step-increase stimulus:* This section presents results with the same five models previously used for prediction of the BR response with the sinusoidal pressure stimulus. As with the sinusoidal stimulus we do not test the integrate-and-fire model, due to the nature of the input stimulus. Again, we first discuss results obtained with the three linear models $W_eV_1Na$, $W_eV_2Na$ and $W_eV_3Na$ followed by results obtained using the more complex nonlinear and viscoelastic wall models.

Studies were done to capture the effect of overshoot and adaptation in response to four input stimuli varying in the magnitude of the pressure step. All stimuli start at the same baseline pressure, and the step-increase was imposed at the same time $t_0$. As before the three models have 5, 7, and 9 parameters, respectively, but functions describing the “smooth” step pressure increase (3.2) only involve one additional parameter $\delta_u$, representing the onset of the step-increase. This parameter was not provided in [20]. Subset selection together with efforts to make model comparison possible resulted in $\theta_{step} = \{a_1, b_1, s_1, s_2, \delta_u\}$. As reported in [20, Figure 5] the baseline pressure associated with the step-increase stimulus was set to 115 mmHg, and the step-increases (from the baseline) to 128, 134, 137, 143 mmHg, respectively. Figure 3.7(A-D) shows the ability of the three linear BR models to reflect observed overshoot and adaptation. Each panel shows the optimized firing rate. The least squares cost RMSE (and the coefficient of determination $R^2$) of model $W_eV_1Na$ for the optimized values of its parameters with respect to the four step-increases 128, 134, 137, and 143 mmHg were: 1.860 (0.899), 2.677 (0.919), 2.420 (0.969), and 1.832 (0.983). Marginal improvements were obtained with $W_eV_2Na$, which gave: 1.800 (0.905), 2.702 (0.917), 2.390 (0.970), and 1.823 (0.983), and finally, for $W_eV_3Na$ the values were: 1.764 (0.909), 2.700 (0.918), 2.390 (0.970), and 1.809 (0.983), see Table 3.3. Similar to the sigmoidal stimulus, no improvements (results not shown) were obtained with the more advanced nonlinear and viscoelastic wall models.

*Square stimulus:* The square stimulus is characterized by a constant pressure input followed by
a step-increase after which the pressure is decreased to its baseline value. This type of stimulus primarily tested the models’ ability to reflect PED followed by recovery, although other features including adaptation and overshoot are also shown. Similar to previous studies we first investigated the simpler linear models including one, two and three Voigt bodies. For the square input stimulus, in Figure 3.8A, we plot BR firing rate data extracted from Saum et al. [88] (circles) and the corresponding optimized fit using $W_2N_a$ (solid line), changing the number of Voigt bodies did not improve the model response. This model has 7 parameters and additional two $\delta_u$ and $\delta_d$ related with the input stimulus (3.3). Subset selection together with our effort to make model comparisons possible made us estimate the parameters $\theta_{square} = \{s_1, s_2, \delta_u, \delta_d\}$. The least squares cost RMSE (and the coefficient $R^2$) with optimized parameters was 7.384 (0.862 for $R^2$), see Table 3.5. While the model, as anticipated, was able to produce overshoot and adaptation, this model was not able to capture PED accurately.

We hypothesize that the inability to show PED is due to the simple linear firing rate model, which does not allow the BR firing rate to cease for sub-threshold stimuli. Thus, we first investigated the impact of exchanging the linear BR firing rate model with the integrate-and-fire model. Including the integrate-and-fire model clearly improved results (not shown) though with the linear wall model it was difficult to accurately fit the data both during adaptation and recovery. Subsequently, we analyzed the impact of exchanging the linear wall model with the nonlinear wall model, keeping the integrate-and-fire model. Results with this model ($W_{ne}V_2N_{IF}$) is shown in Figure 3.8B. This figure shows the recorded BR firing rate (circles) and the model fit (solid line) in response to the square pulse stimulus. Model parameters estimated include $A_0, \vec{s}_1, \vec{s}_2, \text{leak}, \vec{V}_{th}, \text{ref}, p_u, p_d$. Optimized parameter values and units are given in Table 3.5 together with the $R^2$ and RMSE errors. Finally, we investigated the impact of adding a viscoelastic wall model, which did not provide any additional improvements.
Table 3.5: Optimized linear and nonlinear models of BR response: Post-excitatory depression. For the three models $W_c V_2 N_a$, $W_{ne} V_2 N_a$ and $W_{ne} V_2 N_{IF}$ of BR response we present the initial and optimized values of their parameters. We used the BR firing data published by Brown [20] for a square pressure profile. For $W_{ne} V_2 N_{IF}$ values for $\delta_u, \delta_d, \alpha, \kappa$ were 4.663, 8.788, 145 and 5 respectively. These are not listed as they were not part of the optimization process for this model.

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|             | $W_{ne} V_2 N_a$ IC | 0.0063 | 0.5 | 0.4 | 0.5 | 2 | 480 | 100 | 4.60 | 8.70 |       |       |
|             | $W_{ne} V_2 N_a$ opt | 0.0063 | 0.5 | 0.4 | 0.5 | 2 | 1076 | 375 | 4.59 | 8.59 | 0.883 | 6.795 |

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<th>$G$</th>
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Figure 3.9: **Simultaneous response with a linear and a nonlinear BR model.** (A) Predictions obtained estimating one parameter set for all four pressure step-increases using the linear model with two Voigt bodies $W_e V_2 N_a$. Note, that the overshoot is diminished for responses to smaller step-increases in pressure, and that the baseline firing rate is not reproduced accurately. (B) Predictions obtained with the nonlinear model $W_{ne} V_2 N_a$ accounting for nonlinear stiffening with increased pressure allowed us to accurately fit all four responses using one set of parameter values.

**Simultaneous fits:** Figure 3.7 showed that linear models can exhibit overshoot, adaptation, and can fit the firing rate data for all four step-increases, though as reported in Table 3.3, each step-increase resulted in significantly different parameter estimates. However, data are extracted from experiments done within the same fiber, thus we expected only small variation in parameter values. We performed additional optimizations to investigate if the observed differences in the parameter estimates, were simply a result of performing optimizations for one stimulus at the time. To remedy this problem, we estimated one set of parameters for all four step-increases. Results of this simulation are shown in Figure 3.9A (computed with the model $W_e V_2 N_a$). This simulation confirms that the simple linear model cannot estimate one set of parameters that allows *simultaneous* fit of the response to all four pressure stimuli. Similar results were obtained with the other models. In particular, it should be noted that the overshoot is diminished for the smaller step-increases, and that the model was unable to capture the correct baseline firing rate. In contrast, when including a nonlinear elastic wall $W_{ne} V_2 N_a$ we were able to estimate one set of parameters that allowed us to simultaneous fit the response to all four pressure stimuli. This model accurately reproduced the baseline firing rate as well as the overshoot and adaptation observed in response to the step-increase (Figure 3.9B). We hypothesize that this difference is due to larger range of pressure within the applied stimuli, where the known nonlinear behavior of the arterial wall deformation plays an important role. It is known that arteries appear stiffer at higher pressures than at lower pressure. Thus the nonlinear wall model significantly improves the fit.
Figure 3.10: Qualitative responses. We present a qualitative response of the two Voigt body BR model $W_n e V_2 N_{IF}$ to various pressure stimuli including sinusoidal (A), ramp up (B), step-increase (C), and triangular (D) showing the model's ability to reflect rectification (A), saturation (B), two time-scale adaptation (C), and asymmetry (D).

3.3.2 Qualitative results

In the previous section we showed the ability of our proposed linear and nonlinear BR models to fit the firing rate data measured from rats. It is well known (see section Methods) that the BR firing rate can exhibit a number of qualitative characteristics including saturation, threshold, adaptation, overshoot, PED and rectification. The quantitative data used to test the model in the previous section showed adaptation, overshoot, and PED, in response to a sinusoidal (with fixed amplitude) and step changes (increase/decrease) in blood pressure. However, these stimuli did not test saturation, threshold, or rectification. Although the models show adaptation, no clear conclusion could be drawn to determine how many Voigt elements (time-scales) were needed to reflect known BR firing rate obser-
vations.

Now we show our preferred model $W_{ne}V_2N_{IF}$ with estimated parameters, including nonlinear deformation of the elastic wall, two Voigt bodies for computing nerve ending stimulation, and a leaky integrate-and-fire model for predicting firing rate, exhibits the features not yet studied experimentally. This was done using ramp and sinusoidal (with varied amplitude and frequency) pressure stimuli.

**Rectification:** Figure 3.10A presents the model’s response to a sinusoidal wave pressure stimulus with various amplitude. This simulation is motivated by the observation of Brown et al. [20, Figure 6] that a 2.5 increase in amplitude of the sinusoidal stimulus resulted in an increased amplitude of the firing rate, with a lower mean firing rate. Moreover, it was noted that for large amplitude stimulation the firing rate ceases during the trough of the pressure wave. These two observations are referred to as rectification. One could question if the simpler linear model is able to display this phenomena. The linear wall model would certainly be able to reproduce the increased amplitude for a single stimulus, but again, if multiple stimuli were tested, correct predictions require the nonlinear wall model. Moreover, the ability of the firing rate to cease requires the threshold built into the integrate-and-fire model. With the simple linear neuron model, the firing rate would become negative, which does not represent what happens physiologically.

**Threshold and saturation:** Two other prominent firing characteristics are threshold and saturation. In [92, Figure 5] Seagard et al. noted that BRs with a higher threshold pressure were less sensitive, had lower discharge rates, and had higher values for saturation. Receptors with higher discharge rates were also more sensitive and were found to have afferent fibers with greater conduction velocities. In Figure 3.10 B we show that our model $W_{ne}V_2N_{IF}$ is able to reproduce qualitatively similar saturation features.

**Adaptation:** Even though our quantitative models were able to capture adaptation, it was noted that results with one, two, or three Voigt bodies were similar, in other words, the models could not clearly distinguish if the adaptation process included one or three time-scales. Yet, several authors (e.g., [18, 82, 89, 99]) have hypothesized that adaptation occurs with more then one time constant. It is also known that the muscle spindle can produce a response of this kind to a clipped-off ramp stretch [84]. Figure 3.10 C shows that the studied model $W_{ne}V_2N_{IF}$ admits the fast adaptation and the slow adaptation in agreement with experiments. We also plot an exponential fit and show that a similar adaptation is not possible by only one exponential function. This qualitative feature made us include two Voigt bodies in our preferred model, a conclusion that could not have been made strictly from quantitative simulations presented in the previous section.

**Asymmetry:** In Figure 3.10 D we show that our preferred model $W_{ne}V_2N_{IF}$ clearly exhibits asymmetry when exposed to a ramp-up followed by a ramp-down pressure stimulus, which agrees with experiments (see e.g., [25]).
3.4 Discussion

The objective of this study was to develop a mathematical framework for constructing computationally efficient and accurate BR models, which in contrast to the existent models, are able to reflect all known qualitative BR firing features as well as fit quantitative data. Our overall aim was not to focus on a concrete experimental species but rather to formulate a family of BR models, which could potentially be included in a more comprehensive model of CV system. Quantitative computations were done comparing our models to experimental measurements by Brown et al. [20] and Saum et al. [88]; while qualitative studies were performed to show that our preferred generic model $W_{ne} V_{2} N_{IF}$ is able to exhibit all known firing rate responses. All models used blood pressure as an input and computed the BR firing rate as an output. Although our procedure was designed to be generically applicable to various species and multiple types of baroreceptors, we tested our models using only quantitative data from experiments performed using aortic baroreceptors from rats.

We believe that this is the first work that offers a systematic approach to building and evaluating BR models with the objective to provide the simplest possible family of generic models. Our modeling framework first analyzed the known physiology and common features of the firing rate observed in the BRs of various species. Second we generated submodels describing each stage of the physiological response: arterial wall deformation, stimulation of mechanosensitive channels found in the BR nerve endings, and generation of action potentials. Finally we modeled the BR system by combining the submodels in various configurations (summarized in Table 3.2). Each of these configurations was tested in order to determine the contributions of each component to the transduction of the BR signal. This process allowed identification of the importance of nonlinear effects of two critical subsystems in the BR response, the arterial wall and the neuron itself. This framework advanced the state of BR modeling by first evaluating models comparatively with respect to the same data and features, second by generating a model which fits all known characteristics of BR firing qualitatively, and third by developing a model which is capable of fitting multiple data sets of BR firing rates quantitatively.

A particular insight was revealed by consideration of BR models with various descriptions of the arterial wall. Applying our framework demonstrated the insufficiency of linear wall models’ representations of the response of a single BR neuron to multiple step-pressure inputs (see Figure 3.9A). A nonlinear elastic wall model was required to implement a model capable of accurately fitting the BR response to multiple pressure levels with one set of parameter values (see Figure 3.9B). The choice of this model is further motivated by the well known fact that arteries exhibit nonlinear deformation with saturation at both high and low pressures [25, 92]. Additionally by applying our framework and considering the effects of including the viscoelastic wall model, we found that the additional complexity did not contribute to better definition of BR dynamics, despite previous studies having shown wall deformation does have viscous components [39, 45]. This is likely due to our modeling choice for nerve ending stimulation. This portion was modeled using two Voigt bodies in series to allow
adaptation at multiple time-scales. Data is not available to separate the viscoelastic part of the wall-deformation with the viscoelastic deformation associated with stimulation of the mechanosensitive channels, thus indirectly our model exhibits both features. One explanation would consider the first Voigt body to be associated with wall deformation while the second is associated with nerve ending deformation. Moreover, it should be emphasized qualitative simulations were needed to show that the two Voigt bodies allow multiple time-scales, a feature we were not able to extract from simulations alone. These considerations, and our studies, affirm the importance of viscoelastic effects; however, in terms of simplicity it is advantageous to isolate the viscoelastic components within the model, and further we note linear viscoelastic effects are sufficient to capture the dynamics of BR firing when coupled with a nonlinear elastic total deformation of the arterial wall.

To our knowledge, this study provides the first direct measure of the importance of incorporating various time-scales in BR models. It is believed that various time-scales in the adaptation process are due to the viscoelastic coupling of the nerve ending to the arterial wall. We chose to emphasize this in our modeling process by considering different numbers of Voigt bodies in series with a spring. In Table 3.3 we show the results of testing three models $W_e V_1 N_a$, $W_e V_2 N_a$, and $W_e V_3 N_a$ differing only with respect to their nerve ending models $V_1$, $V_2$, and $V_3$, respectively. Our findings indicate that no more then two timescales in the adaptation process are needed in order to achieve a very precise fit to the data. This conclusion is closely related to the fact that we tested our models using rat data with fairly limited pressure-stimulus response as only this type of experiments are currently available. To test this component more carefully, it is essential to analyze data recorded over longer time-scales.

Another insight afforded by this investigation highlights the importance of nonlinearities in the neural response to mechanoreceptor strain. As hypothesized previously [18], our study affirms the nonlinearities of action potential generation, even for the leaky integrate-and-fire model $N_{IF}$ are sufficient to produce the hysteretic phenomenon of PED. In contrast the simple linear model $N_a$ of firing in response to mechanoreceptor strain does not allow for the asymmetric responses seen in PED as well as in the response to sinusoidal stimulus with high amplitude. The nonlinear-elastic wall in combination with two Voigt bodies modeling mechanoreceptor stimulation responds in an equal but opposite manner to rising and falling pressure, thus the change in firing rate with the linear model is symmetric to step-increase and step-decrease, which is not reflective of the data. We affirm the hypothesis that the neuron itself is responsible for generating PED, as this feature was robustly represented by the leaky integrate-and-fire model regardless of the mathematical description for arterial wall strain. This would provide a good explanation for the observation of PED in multiple species, many of which have a high degree of variability in the viscoelasticity in their respective arterial walls.

The results and insights generated through application of our proposed modeling framework are not limited to those presented in this study. In addition it provides a means to identify which features and what level of detail of the underlying physiological systems are of greatest significance.
in generating BR dynamics. This ability is useful in developing experiments which may be able to isolate physiology responsible for a given phenomenon, such as the responsibility of the neuron in generating PED. Further this approach provides evaluative power to make design decisions when developing a model for a specific data interpretation or simulation task. An example of this follows from our insights into the role of the arterial wall in BR signal transduction. Although the arterial wall may best be modeled using viscoelastic theory, our framework allows a modeling decision to be made in favor of simplicity if only the output dynamics are of interested.

This investigation further suggests a methodology for integrating a model generated in this manner into a model of larger scope. Suppose a mathematical representation of an overall baroreflex system (see Figure 3.1) is desired to reflect only normal physiological conditions, then it may be sufficient to use only simplified description of the BR signal. For example a simple linear firing rate model may be adequate for simulations operating in the range above the firing rate threshold. However, to reflect heart rate at various abnormal physiological conditions a more complex model combining nonlinear deformation with the leaky integrate-and-fire model may be necessary. Additionally, application of our modeling approach to a larger CV model might reveal features of the BR subsystem with importance in maintaining homeostasis. We hypothesize that overshoot, adaptation and recovery, features of the BR firing in response the extremes of pressure waves, are critical for regulation of blood pressure during stressful situations, such as a head-up-tilt experiment.

### 3.5 Acknowledgments

We would like to thank Alison Margolskee, Manchester Pharmacy School, University of Manchester, for drawing Figure 3.1.
Table 3.6: The state variables and parameters of the BR models. The models considered in this work and defined in Table 3.2 contain between three and six state variables listed here. Additionally, the parameters for the whole family of BR models together with their nominal values, units and literature references are provided.

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<td>s$^{-1}$</td>
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Chapter 4

Modeling differentiation between A- and C-type baroreceptor firing patterns

4.1 Introduction

The cardiovascular system (CVS) continuously provides and regulates the supply of oxygen and nutrients to the body as well as removes waste products from tissues. The CVS is kept at homeostasis via negative feedback control, which actively restores the system state in response to perturbations. An important contributor to the control are the baroreceptor nerves emanating within the wall of the aorta and carotid sinuses (depicted in Figure 4.1). These nerves sense changes in arterial wall strain induced by changes in blood pressure. Signals generated by these nerves are integrated in the nucleus solitary tract from which efferent signals transmitted via the sympathetic and parasympathetic systems modulate heart rate, cardiac contractility, and vascular tone.

The baroreceptor cell bodies are located in the nodose ganglion in the brainstem. They have stretch sensitive nerve endings, which terminate in the arterial wall and in the nucleus solitary tract. These neurons are typically divided into two types (A-type and C-type) separated in part by their function (their distinct firing patterns), but primarily according to the myelination of their axons: A-type neurons are myelinated, while C-type are not. Both neuron types are activated via stimulation of mechanosensitive ion channels (MSC), which respond to changes in wall strain associated with changes in blood pressure, thereby transducing changes in blood pressure into an electrically coded neural signal.

Although many details associated with baroreflex regulation are known, some components of this mechanism are still not understood [10], in part due to difficulties in studying their function experimentally, in particular it is difficult to extract a complete nerve with its nerve-endings still intact. This is due to the fact that if the transduction site is disturbed by the process of isolating the nerve,
Figure 4.1: The baroreflex response to a drop in blood pressure includes a decrease in the aortic baroreceptors firing rate, which encodes the detected change in arterial wall strain. This signal propagates along vagal fibers to the nucleus solitary tract, which transfers the signal to the sympathetic and parasympathetic nervous systems upregulating heart rate, cardiac contractility, and vascular tone.
and the structure coupling the nerve ending to the mechanical deformation of the artery is lost [58]. As a result, to our knowledge no data exist showing simultaneous recordings of wall and neural deformation, as well as the signal encoded by the ensemble of ion channels. However, studies of nerve cells without stretch sensitive endings have identified a number of ion channels and characterized their dynamics. The primary include a TTX-sensitive fast sodium current ($I_{Na,F}$), a TTX-insensitive slow sodium current ($I_{Na,S}$), a sodium background current ($I_{Na,B}$), a sodium-potassium pump current ($I_{Na,Ca}$), a delayed rectifier potassium current ($I_{K,DR}$), and a 4-AP sensitive potassium current ($I_A, I_D$) [90].

One way to explore baroreceptor firing further is using mathematical modeling. Several modeling approaches have been used including phenomenological models predicting firing rate as a function of blood pressure [72, 82, 83, 98] and biophysical models using a Hodgkin-Huxley type approach describing the electrical behavior of the isolated neurons [90]. Some of the biophysical models were designed to predict the differences in firing patterns between A- and C-type neurons [15, 90]. However, since these studies focused on predicting dynamics in isolated neurons, they were not able to examine how changes in vessel strain stimulate the stretch-sensitive channels. Another study by Alfrey added in mechanosensitivity, but focused only on reproducing A-type firing patterns [2]. In contrast, the phenomenological models have put much effort into describing the firing rate as a function of wall-strain, but to our knowledge no phenomenological models have attempted to differentiate between A- and C-type firing [26, 69, 90, 92].

This study aims to combine previous efforts building an exhaustive biophysical model that can distinguish between A- and C-type firing. To do so we designed an anatomically and physiologically motivated model including three components: arterial wall deformation, mechanoreceptor stimulation, and action potential generation. This model was shown to effectively reproduce experimentally observed responses of afferent baroreceptor nerves to various pressure stimuli.

More specifically, the arterial wall strain is modeled as a nonlinear function of pressure accounting for increased stiffening with increased pressure. This model was designed to agree with experimental studies of the rat aorta [23, 34], as well as general results common across species [105, 107]. Modulation of wall strain causes deformation of baroreceptor nerve endings though little experimental knowledge exists to characterize the coupling of the nerve ending deformation to the wall strain. This study follow ideas proposed by Alfrey [2] and Mahdi et al. [72] describing nerve ending deformation using a viscoelastic model with two relaxation timescales of approximately 1 and 3 seconds.

The nerve ending deformation stimulates mechanosensitive channels, which are modeled using a sigmoidal function of strain to describe the probability that the channel opens in response to a given neuron deformation. Finally the afferent baroreflex firing rate is calculated from the action potentials generated by a Hodgkin Huxley type model incorporating the major ion channels identified in patch clamp studies of baroreceptor cell bodies [90].

Model simulations were carried out to demonstrate that our model is able to reproduce observed
differences between A- and C-type firing patterns. This was done by showing that the proposed model can qualitatively fit data reported in literature.

![Block diagram of the model components needed to represent the biophysical basis of BR firing in response to an applied blood pressure stimulus.](image)

**Figure 4.2**: Block diagram of the model components needed to represent the biophysical basis of BR firing in response to an applied blood pressure stimulus.

### 4.2 Methods

This section first describes experimental data used for model simulations followed by a discussion of each model component shown in Figure 4.2.

#### 4.2.1 Experimental data

Data used for this study, extracted from literature [20, 34, 92], were chosen to show four differences between A- and C-type firing patterns associated with threshold, saturation, overshoot, and adaptation. These features were identified by comparing model predictions to data extracted from rats and dogs using ramp, step and sinusoidal stimuli [20, 92]. It should be noted that these experiments considered *in situ* functioning of baroreceptors in excised arterial walls, which do not necessarily represent normal perturbations of pressure, though they are necessary to test if the model displays adequate behavior. Below we discuss each firing rate response followed by a detailed description of the stimuli necessary to elicit these responses.

**Threshold**

characterizes the pressure at which the firing rate frequency changes. As shown in figure 4.3, A-type neurons fires when the ramp stimulus reaches a particular threshold, whereas C-type neurons fire for all pressures (over the ramp) but at a distinct threshold C-type neurons increase their firing rate [92].

**Saturation**

refers to the pressure range over which the firing rate remains constant, i.e. when an increase ramp pressure no longer lead to an increase in firing rate. While both A- and C-type neurons show satu-
ration, A-type neurons saturate at a higher frequency but lower pressure than C-type neurons (see Fig. 4.3).

**Overshoot and adaptation**

refer to the response to a step change in pressure. A-type neurons dramatically increase firing at the onset of the increase and then slowly decay toward a new steady firing rate corresponding to the new pressure, while C-Type neurons dramatically increase firing in response to the pressure step change, then rapidly adapt, and subsequently cease firing [19] (See Fig. 4.4).

**Frequency response**

refers to the dependence of baroreceptor firing rate on the frequency of a sinusoidal pressure stimulus with a given amplitude. As shown in Figure Fig. 4.5 A-type neurons exhibit a gain with increasing firing rate for increased stimulus frequency, up to a certain stimulus frequency. Beyond this point the firing rate drops with further increases in stimulus frequency, while the firing rate of C-type decrease rapidly with any increase in stimulus frequency.

**Ramp stimulus**

refers to stimulation obtained by applying a slowly increasing blood pressure (see Figure 4.3). The response to this type of stimulus have been studied in many species [40, 64, 92]. While the response characteristics clearly differ between A-type and C-type neurons the frequency range differs among species. For consistency with data for the other stimuli, this study uses data from [92]. Generally, A-type neurons exhibit a hyperbolic firing pattern with no firing below the threshold and an relatively high firing rate above the threshold. In contrast C-type neurons fire at all frequencies in a sigmoidal pattern, exhibiting a low firing rate until a given pressure threshold after which the firing rate is increased until saturation occurs.

Typical ramp stimuli are slow, this study uses a stimulus with a slope of 2 mmHg/sec. In this study the ramp stimulus is modeled using the linear function

\[ p(t) = a t + b, \]  

where \( a \) is the rate of increase in pressure in mmHg, and \( b \) is the initial pressure used in/for the stimulation.
Step pressure stimulus

refers to stimulation by blood pressure that is changed in a step from one value to another (see Figure 4.4). Generally, both A- and C-type neurons respond with an overshoot followed by adaptation, though C-type neurons exhibit more irregular firing patterns [62] than A-type neurons. However, another study [19] it was found that C-type neurons response with overshoot followed by rapid adaptation after which the neuron cease to fire.

In addition to the dataset used in this study, extracted from [20]), similar responses mostly in A-type neurons have been observed in multiple studies [88, 108]. The step change was modeled using the function

\[ p(t) = \begin{cases} p_b & \text{if } t < t_{\text{step}} \\ p_b + \Delta p & \text{otherwise} \end{cases} \]  

(4.2)

where \( p_b \) denotes the baseline pressure and \( \Delta p \) the step change.

Sinusoidal pressure stimulus

refers to stimulation with a sinusoidal varying pressure (see Figure 4.5). This type of stimulus was used to analyze firing rate dynamics in a setting mimicking in vivo conditions. Brown et al. [20] characterized the frequency dependent response for both A- and C-type neurons in a series of experiments in which they varied the frequency of the sinusoidal wave [20].

For stimulations varying frequency with fixed amplitude A-type neurons exhibited amplitude
gain for frequency increases between 1-9 Hz, after which the amplitude dropped, while for C-type neurons the amplitude dropped for all frequencies.

The sinusoidal stimulus was modeled as

\[ p(t) = p_b + p_A \sin(2\pi \omega t), \] (4.3)

where \( p_b \) denotes the baseline pressure, \( p_A \) the amplitude, and \( \omega \) the stimulus frequency.

For a given stimulus, the amplitude gain was defined by

\[ g(\omega, p_A) = \log(A/p_b), \quad \text{where} \quad f(t) = A \sin(2\pi \omega t + \theta) + C, \] (4.4)

where \( A \) was defined by fitting (in the least squares sense) the firing rate response to the function \( f \) in which \( \omega \) is the stimulus frequency and \( \theta \) a phase shift parameter.

### 4.2.2 Modeling

As shown in Figure 4.2, baroreflex firing rate was modeled using three components describing arterial wall deformation, neural deformation and mechanoreceptor stimulation, as well as action potential generation. A summary of variables and parameters is given in the appendix in Tables 4.5 and 4.6.
Figure 4.5: Left panel shows example firing rate response to a sinusoidal pressure stimulus for an A-type neuron. Right panel shows the gain and phase response for both A- and C-type neurons from Brown et al. [20]. The gain was normalized by setting the gain for the lowest stimulus frequency to 0.

Wall Models

The arterial walls of larger animals exhibit nonlinear elastic and viscoelastic response to changes in blood pressure [107]. However, by Brown et al. [20] showed that viscoelasticity plays a minor role in rat arterial wall deformation. Moreover, since arteries are fixed in their longitudinal direction due to attachment to various tissues wall deformations in the axial direction is negligible and thus the axial stress, \( \sigma_{zz} = 0 \).

Assuming arteries can be modeled as homogeneous and isotropic thin walled straight cylindrical vessels where \( \sigma_{zz}, \sigma_{rr} \ll \sigma_{\theta\theta} \). Under equilibrium conditions in such vessels, Laplace’s law relates the circumferential stress in the vessel wall to the fluid pressure \( p \), and the geometry of the vessel as \( \sigma_{\theta\theta} = pr/h \), where \( r \) is the cross-sectional radius and \( h \) is the vessel wall thickness.

For such vessels, the circumferential strain \( \sigma_{\theta\theta} \) can be expressed relative to the zero-pressure state as the normalized change in the vessel radius so that \( \epsilon_{\theta\theta} = (r - r_0)/r_0 \), where \( r_0 \) represents the radius at zero pressure. Using the thin wall assumption \( (r_0 >> h) \) we obtain a simplified stress-strain law \( \epsilon = pr/Eh \), where \( E \) is the elastic modulus.

These equations can be combined obtain a strain measure, \( \epsilon_w \), defined as

\[
\frac{pr}{Eh} = \frac{r - r_0}{r_0} \iff \frac{pr_0}{Eh} = \epsilon_w, \quad \text{where} \quad \epsilon_w = \frac{r - r_0}{r}.
\]

It is well known that arteries exhibit increased stiffening for high pressures. Similar to Valdez et al. [107], we assume that area saturates at high and low pressure following the sigmoidal relation

\[
A(p) = (A_m - A_0) \frac{p^k}{\alpha^k + p^k} + A_0,
\]
where $A_0$ and $A_m$ (mm$^2$) are the unstressed and maximum cross-sectional area, $\alpha$ (mmHg) represents the approximate saturation pressure, and $k$ determines the steepness of the response. The corresponding wall strain is given by

$$\epsilon_w = 1 - \sqrt{\frac{(\alpha^k + p^k)}{\alpha^k + R_A p^k}}, \quad (4.5)$$

where $R_A = \frac{A_m}{A_0}$.

**Nerve ending deformation and mechanoreceptor stimulation**

The aortic baroreceptor nerve endings form a complex network emanating from the adventitia, merging into the afferent vagal (cranial nerve X) nerve [6]. The nerve endings are sensitive to stretch, however, the mechanisms explaining how changes in stretch stimulate mechanosensitive ion channels are not well understood [58]. This study follow ideas by Alfrey [2] predicting mechanosensitive stimulation as a function of the relative displacement of the nerve endings, which respond to changes in wall strain.

This mechanism is described in two subsections describing A) the stretch of the nerve endings relative to the arterial wall strain, and B) stimulation of the mechanosensitive ion channel. A linear viscoelastic system of springs and dashpots is used to model A, while B is represented as a sigmoidal function of the nerve-ending strain described in A.

**Mechanical coupling**

The nerve endings have been observed to exist with and without connective fibers to the arterial wall and typically in the connective tissue between elastic laminae of the adventitia [59]. It is well known that connective tissues are viscoelastic [39], though the origins of viscoelasticity and mechanisms for how forces are transferred from the constitutive material to the overall structure of the arterial wall tissue are not fully understood.

In this study, we based our wall strain model on observations by Brown et al. [20] that showed arterial wall deformation was mainly elastic. But account for viscoelasticity in the model predicting nerve-ending deformation. To do so, similar to previous studies [2, 21, 72], we model the nerve-ending deformation using two Voigt bodies in series with a spring all in parallel with the wall deformation, $\epsilon_w$, as presented in Fig. 4.6.

For this model, spring elements have a stress-strain relation $\sigma = E\epsilon$, while dashpot elements follow $\sigma = n \frac{d\epsilon}{dt}$. The strain across elements in parallel is equal, while the stress of elements in series must be equal. Applying these relations to the first Voigt body gives the stress-strain equation $\sigma_2 = E_2\epsilon_2 + \eta_2 \frac{d\epsilon_2}{dt}$, where $\epsilon_2$ is the strain across the Voigt body. The second Voigt body has total
strain $\epsilon_1 - \epsilon_w$ giving $\sigma_1 = E_1(\epsilon_1 - \epsilon_2) + \eta_2 \frac{d}{dt}(\epsilon_1 - \epsilon_2)$. Both $\sigma_1$ and $\sigma_2$ must be equal to the stress in the final spring element $\sigma_{ne} = E_{ne}(\epsilon_w - \epsilon_1)$. By substituting the derived expressions in $\sigma_2 = \sigma_{ne}$ gives a following differential equation for $\epsilon_2$ of the form

$$\frac{d \epsilon_2}{dt} = -\frac{E_2}{\eta_2} \epsilon_2 + \frac{E_{ne}}{\eta_2} (\epsilon_w - \epsilon_1).$$

Similarly solving $\sigma_1 = \sigma_{ne}$ yields

$$\frac{d \epsilon_1}{dt} = -\left( \frac{E_{ne}}{\eta_1} + \frac{E_{ne}}{\eta_2} + \frac{E_1}{\eta_1} \right) \epsilon_1 + \left( \frac{E_1}{\eta_1} - \frac{E_2}{\eta_2} \right) \epsilon_2 + \left( \frac{E_{ne}}{\eta_1} - \frac{E_{ne}}{\eta_2} \right) \epsilon_w.$$ 

![Figure 4.6: Schematic showing the linear mechanical model predicting the transfer of wall strain to nerve ending strain. The strain across the coupling system is assumed to equal the circumferential wall strain, $\epsilon_w$. The strain experienced by the spring labeled $E_n$ corresponds to the strain transferred from the wall to the nerve endings, $\epsilon_{ne}$.](image)

One parameter can be eliminated by re-parameterization this system using $\beta_i = E_i/\eta_i$ and $\alpha_i = E_{ne}/\eta_i$ giving

$$\frac{d \epsilon_1}{dt} = -(\alpha_1 + \alpha_2 + \beta_1) \epsilon_1 + (\beta_1 - \beta_2) \epsilon_2 + (\alpha_1 + \alpha_2) \epsilon_w$$

$$\frac{d \epsilon_2}{dt} = -\alpha_2 \epsilon_1 - \beta_2 \epsilon_2 + \alpha_2 \epsilon_w,$$

where, the total strain $\epsilon_{ne}$ experienced by the mechanoreceptor is given by

$$\epsilon_{ne} = \epsilon_w - \epsilon_1$$

(4.6)
This system has a unique steady state for a given $\epsilon_w$ given by

$$
\begin{pmatrix}
\varepsilon_1 \\
\varepsilon_2
\end{pmatrix} = \left( \begin{array}{cc} 
\alpha_1 \beta_2 + \alpha_2 \beta_1 \\
\alpha_2 \beta_1 
\end{array} \right) \epsilon_w(\alpha_1 \beta_2 + \alpha_2 \beta_1 + \beta_1 \beta_2)^{-1}.
$$

(4.8)

**Ionic currents**

Previous studies have shown that the mechanosensitive current (MSC) is a nonspecific cation current, which can be modeled as a simple ohmic current with zero reversal potential

$$
I_{MSC} = p_o(\epsilon_{ne}) g_m V,
$$

(4.9)

where $g_m$ represents the maximal whole cell conductance of the mechanosensitive channels, and $p_o(\epsilon_{ne})$ represents the fraction of channels open for a given strain.

Following observations by Kraske et al. [58, Figure 2B], we assume that the fraction of open channels $p_o$ depend sigmoidally on the nerve ending deformation $\epsilon_{ne}$. This is quantified using a Boltzmann relationship

$$
p_o(\epsilon_{ne}) = \left(1 + \exp \left( \frac{\epsilon_{1/2} - \epsilon_{ne}}{S_{1/2}} \right) \right)^{-1}.
$$

(4.10)

where $S_{1/2}$ determines the steepness of the transition mostly closed to open, and $\epsilon_{1/2}$ corresponds to the strain associated with an open probability of 50%. This basic approximation assumes instantaneous dynamics, which is reasonable since the channel’s dynamics are fast compared to the electrical activity [58].

**Neural model**

The baroreceptor neuron activity is modeled using a simplified conductance based approach describing action potential generation using voltage gated channel dynamics. The approach presented here follows previous studies by Schild et al. [90], though simplified to only include the basic currents including:

- Mechanosensitive stretch channel ($I_m$).
- TTX-sensitive fast sodium current ($I_{Na,F}$) voltage gated, inward).
- Sodium background current ($I_{B,Na}$, inward).
- Sodium-potassium pump current ($I_{Na,K}$)
- Delayed rectifier current ($I_{K,DR}$, voltage gated, outward).
Figure 4.7: Schematic showing the channels included in the reduced neural model, a mechanosensitive channel, an inward current NaF (Nav1.7), a 4AP sensitive potassium current KA + KD, a delayed rectifier current K,DR (Kv2.3), a linear leakage current Na,B, and a sodium-potassium exchanger current Na,K.

- 4-AP sensitive potassium current (IKA + IK,D, two independent voltage gated currents, outward).

As is typically done, we use a Hodgkin-Huxley type neuron model, describing the whole-cell voltage using an equivalent circuit consisting of a capacitor in series with conductance representing specific ways the current can flow through the cell membrane. The transmembrane voltage potential \( V \) is given by

\[
\frac{dV}{dt} = \frac{\sum I_i - I_{stim}}{C_m},
\]

where \( I_i \) corresponds to the total current through a particular ion channel, \( I_{stim} \) denotes the applied current, and \( C_m \) denote the membrane capacitance. An equivalent circuit representation of the model is shown in Fig. 4.7.

According to this technique, the current through a particular channel can be predicted by

\[
I_i = \bar{g}_i a^k b^l (V - E_i),
\]

where \( \bar{g}_i \) (\( \mu S \)) is the maximum whole-cell conductance in the absence of inactivation, \( V \) (mV) is the membrane potential, \( E_i \) (mV) is the reversal potential, and \( a, b \) (dimensionless) denote the activation and inactivation gating variables, with \( k \) and \( l \) (dimensionless) being constant exponents. Each of the gating variables can attain a value between 1 (fully permeable to ions) and 0 (fully non-permeable), the product of these variables denotes the percentage of conducting channels. The inte-
ger power denotes the number of gating particles that must transition to cause the channel to open or close. Assuming the particles are independent, the probability that $k$ activating and $l$ inactivating particles exist in the permeable state is $a^k b^l$.

The dynamics of the ion channel are determined by the gating variables, $a$ and $b$, assumed to display first order kinetics given by differential equations of the form

$$\frac{dz}{dt} = \frac{z_\infty - z}{\tau_z},$$

where $z$ represents the gating variable, $z_\infty$ is the steady state value and $\tau_z$ denotes the time scale. The values of both depend on the membrane voltage. For most currents $z_\infty$ is assumed to exhibit a sigmoidal voltage dependency

$$z_\infty = \left\{1 + \exp\left(\frac{V_{1/2} - V}{S_{1/2}}\right)\right\}^{-1},$$

where $V_{1/2}$ (mV) corresponds to half-activation potential and $S_{1/2}$ (mV) is related to the reciprocal of the slope of the activation curve measured at $V = V_{1/2}$. The time constants $\tau$ follows a simple Gaussian form

$$\tau = A \exp[-B^2(V - V_{peak})^2] + C,$$

where $A$ (msec) corresponds to the peak amplitude $B$ (1/mV) scales the function width, and $V_{peak}$ (mV) corresponds to the membrane potential, at which $\tau$ equals $A$ and $C$ (msec).

The key state variables regulating channel opening and the parameters determining the total Ohmic current are given in Table 4.1).
Table 4.1: Summary of the various currents included in the neuronal model. The conductance based currents are shown in the first section with a summary of the conductance and combination of gating variables determining activation. The current is thus given in general by Eq. 4.11.

<table>
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<tr>
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<td>$p_a$</td>
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<td>$p_a = {1 + \exp {- (\epsilon_{m} - \epsilon_{1/2})/S_{1/2}}}^{-1}$</td>
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<td>$g_{Na,f}$</td>
<td>$m_f h_f$</td>
<td>$E_{Na}$</td>
<td>$m_f = {1 + \exp(- (V + 41.35)/4.75)}^{-1}$ $h_f = {1 + \exp(V + 62.00)/4.50}^{-1}$ $j_f = {1 + \exp(V + 40.00)/1.50}^{-1}$ $\tau_{m,f} = 0.75 \exp(-0.0635^2(V + 40.35)^2) + 0.12$ $\tau_{h,f} = 6.50 \exp(-0.0295^2(V + 75.00)^2) + 0.55$ $\tau_{j,f} = 1.0 \exp(V - 20.00)/4.50 + 0.01$</td>
</tr>
<tr>
<td>Slow sodium</td>
<td>$g_{Na,s}$</td>
<td>$m_s h_s$</td>
<td>$E_{Na}$</td>
<td>$m_s = {1 + \exp(-(V + 20.35)/4.75)}^{-1}$ $h_s = {1 + \exp((V + 18.00)/4.5)}^{-1}$ $\tau_{m,s} = 1.50 \exp(-0.0595^2(V + 20.35)^2) + 0.15$ $\tau_{h,s} = 4.95 \exp(-0.0335^2(V + 20.00)^2) + 0.75$</td>
</tr>
<tr>
<td><strong>Outward currents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed rectifier</td>
<td>$g_K$</td>
<td>$n$</td>
<td>$E_K$</td>
<td>$n_{\infty} = {1 + \exp((V + 14.62)/18.38)}^{-1}$ $\tau_n = \frac{1}{\alpha_n + 1.0}$ $\alpha_n = \frac{1}{\exp((V + 14.275)/10)}$ $\beta_n = 0.0125 \exp\left(\frac{(V + 5.50)^2}{2.5}\right)$</td>
</tr>
<tr>
<td>Fast 4AP Current IA</td>
<td>$g_{K,A}$</td>
<td>$p^4 q$</td>
<td>$E_K$</td>
<td>$p_{\infty} = {1 + \exp(-(V + 28.00)/28.0)}^{-1}$ $q_{\infty} = {1 + \exp((V + 58.00)/7.0)}^{-1}$ $\tau_p = 5.0 \exp(-0.0222^2(V + 65.0)^2) + 2.5$ $\tau_q = 100.0 \exp(-0.0355^2(V + 30.00)^2) + 10.5$</td>
</tr>
<tr>
<td>Slow 4AP Current ID</td>
<td>$g_{K,D}$</td>
<td>$x^3 y$</td>
<td>$E_K$</td>
<td>$x_{\infty} = {1 + \exp(-(V + 39.59)/14.68)}^{-1}$ $y_{\infty} = {1 + \exp((V + 48.00)/7.0)}^{-1}$ $\tau_x = 5.0 \exp(-0.0222^2(V + 65.0)^2) + 2.5$ $\tau_y = 7500.0$</td>
</tr>
<tr>
<td><strong>Background currents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>$g_{K,Na}$</td>
<td></td>
<td>$E_{Na}$</td>
<td>$I_{Na,K} = I_{Na,K} \left(\frac{[Na^+]_o}{[Na^+]<em>o + K</em>{Na,Na}}\right) \left(\frac{[K^+]_o}{[K^+]<em>o + K</em>{Na,K}}\right)$</td>
</tr>
<tr>
<td>Sodium-potassium pump</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4.2: Initial and estimated wall model parameters. The ordinary least squares cost $J$ objective value was 0.0015.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$R_A$</th>
<th>$a_w$</th>
<th>$\kappa_w$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial value</td>
<td>4.4135</td>
<td>125.0000</td>
<td>3.5000</td>
</tr>
<tr>
<td>Optimized value</td>
<td>8.3167</td>
<td>198.0798</td>
<td>2.6478</td>
</tr>
</tbody>
</table>

**Firing rate calculation**

This model predicts the voltage of the neuron as a continuous function of time, thus post processing of the model output is necessary to identify the timing of action potentials and to calculate the firing rate. Traditionally the instantaneous firing rate is defined as the inverse of the interspike interval. It is can be predicted by determining the distance between two successive action potentials. This study used a peak detection algorithm with a predetermined threshold level determining when a spike occurs and a maximum interspike interval corresponding to no firing. Peak times, $t_i$, were identified using the MATLAB `findpeaks` function with the threshold for peaks defined as 40mV. The difference between the time of consecutive spikes, $\Delta t_i = t_i - t_{i-1}$, is used to define the frequency $f_i = 1/\Delta t_i$. Finally, linear interpolation was used to obtain continuous firing rate, which is compared to firing rate data.

4.3 **Results**

4.3.1 **Model calibration**

**Wall model calibration**

Model results predicting wall strain is compared to data extracted from studies by Feng et al. [34] (shown in Fig. 4.8). This data displays wall deformation in the center of the aortic arch over a range of pressures from 0 – 200mmHg (see [34, Figure 4B]). Results shown in Fig. 4.8 were obtained using MATLAB's Levenberg-Marquardt `lsqnonlinear` method to minimize the ordinary least squares cost

$$J(\theta) = \sum_i^n (y_d(t_i) - y_m(t_i, \theta))^2$$  \hspace{1cm} (4.12)

as a function of model parameters, $\theta$, where $y_d(t_i)$ is the data value given for time $t_i$ and $y_m(t_i, \theta)$ is the model value at time $t_i$. Estimated parameter values for fitting (4.5) are given in Table 4.2.
Figure 4.8: Optimized model wall strain as a function of pressure along with data extracted from Feng et al. [34].

Table 4.3: Resulting parameters for fitting Eq. 4.13 to the data for the all pressure step responses, the first row using the reported pressure step reported by Brown et al., the second row show results obtained when shifting the stimulus pressure by 15mmHg corresponding to the active range of the A-type ramp data (see Fig. 4.3).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$a_1$</th>
<th>$a_2$</th>
<th>$\beta_1$</th>
<th>$\beta_2$</th>
<th>$s_1$</th>
<th>$s_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>8.5651e-5</td>
<td>3.4671e-4</td>
<td>4.7159e-4</td>
<td>1.00909e-3</td>
<td>823.38</td>
<td>-182.29</td>
</tr>
<tr>
<td>Rescaled</td>
<td>1.1712e-04</td>
<td>5.2057e-04</td>
<td>2.0641e-04</td>
<td>0.0025</td>
<td>1003.1</td>
<td>-252.71</td>
</tr>
</tbody>
</table>

Voigt body model calibration

Due to the aforementioned obstacles of directly investigating the characteristics of the nerve ending coupling, we attempt to calibrate this portion of the model by attempting to match its shape to the response of firing rate to a step input of pressure. This may be achieved by using a simple model to scale $\epsilon_{ne}$ directly to firing rate using an affine function of the nerve ending strain

$$f_{af}(\epsilon_{ne}) = s_1 \epsilon_{ne} + s_2$$

(4.13)

as proposed by Mahdi et al. [72]. The parameters were estimated using MATLAB’s Levenberg-Marquardt lsqnonlin method to minimize the least squares error between model and measured firing rate. This was done using the step pressure stimulus to elicit changes in firing rate. It should be noted that this calibration is done without accounting for ion channel dynamics. Parameters were estimated both using the pressure step reported by Brown et al. [20], and rescaled to reflect dynamics over active range of A-type ramp data.
Neural model calibration

To calibrate the neural model the parameters for conductances and other currents were taken from Schild et al. \[90\]. The parameters for the mechanosensitive channel were chosen by considering the relationship of $\epsilon_{ne}$ and $p$ so that the sigmoid response curve corresponded to the ramp firing rate response as far as the pressure threshold. Thus $\epsilon_{1/2}$ was chosen visually to correspond to the middle pressure between threshold and saturation. The value for $S_{1/2}$ was similarly chosen so the value of $p_o$ was nearly zero around the pressure threshold. The value for $\bar{g}_m$ was chosen by first stimulating the neuronal model with a ramp conductance $g_m(t)$ and noting the range of conductance values, for which the neuron continuously fired. The values used are present in Table 4.6 in the appendix of this paper.

4.4 Simulation results

Using the parameters resulting from these calibrations, we simulated the model response to ramp, step and sinusoidal pressure stimuli to compare the model’s ability to reproduce features observed using these stimuli experimentally. Parameters were adjusted by hand to reproduce differences observed between A- and C-type responses.

4.4.1 Ramp stimulus

The first set of simulations considers the model’s response to the ramp pressure stimulus Eq. 4.1. For both models with a slope of $a = 2$ mmHg/sec. The initial pressure was $p_b = 120$ for the A-type simulation and $p_b = 0$ for the C-type simulation. Fig. 4.9 shows results using wall and Voigt body parameters from Table 4.4. For the strain response of the mechanosensitive channel, $p_o(\epsilon_{ne})$, the parameters corresponding to half activation strain $\epsilon_{1/2}$ and reciprocal slope $S_{1/2}$ were estimated, while the neuronal model’s max conductances $g_i$ were estimated to predict firing rate responses similar to the two data sets shown in Fig. 4.3.

In addition to estimating parameters to fit the ramp stimuli, the final parameters were used to simulate model response to a step stimulus of the form Eq. 4.2 with base pressure, $p_b = 135$mmHg, step amplitude, $\Delta p = 22$mmHg, and onset time $t_{step} = 1.1$sec to determine the response of these optimized ramp responses to step pressure input. The resulting firing rates are shown in Fig. 4.10.

4.4.2 Step stimulus

A step stimulus following Eq. 4.2 with $p_b = 115$mmHg, $\Delta p = 22$mmHg, and $t_{step} = 1.1$sec was used to simulate the experiments by Brown et al. \[20\]. Similar to the ramp simulations only neuronal conductances were adjusted to predict fits to the data (see Fig. 4.11 and Table 4.4). The resulting parameters were also used to simulate the model response to a ramp stimulus with initial pressure
Figure 4.9: Firing rate responses are shown for model simulation with 2 different parameters sets. One estimated using differential evolution comparing the firing rate output to the A-type data shown in Fig. 4.3, the other to the C-type data.

Table 4.4: Parameters used to fit the various stimuli shown in Fig. 4.9 and Fig. 4.11. Neural parameters not estimated are reported in Table 4.1

<table>
<thead>
<tr>
<th>Neuron</th>
<th>$\alpha_1$</th>
<th>$\alpha_2$</th>
<th>$\beta_1$</th>
<th>$\beta_2$</th>
<th>$\epsilon_{1/2}$</th>
<th>$k_{\text{msc}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-step</td>
<td>0.5000e-03</td>
<td>0.4000e-03</td>
<td>0.5000e-3</td>
<td>0.0020</td>
<td>0.1850</td>
<td>0.0213</td>
</tr>
<tr>
<td>A-ramp</td>
<td>1.1712e-04</td>
<td>5.2057e-04</td>
<td>2.0641e-04</td>
<td>0.0025</td>
<td>0.2794</td>
<td>0.0246</td>
</tr>
<tr>
<td>C-ramp</td>
<td>1.1712e-04</td>
<td>5.2057e-04</td>
<td>2.0641e-04</td>
<td>0.0025</td>
<td>0.2540</td>
<td>0.0246</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neuron</th>
<th>$g_{Na,f}$</th>
<th>$g_{K,dr}$</th>
<th>$g_{K,A}$</th>
<th>$g_{K,D}$</th>
<th>$g_{\text{msc}}$</th>
<th>$C_m$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-step</td>
<td>8.9230</td>
<td>0.009900</td>
<td>0.16800</td>
<td>0.01800</td>
<td>0.0023</td>
<td>0.0325</td>
</tr>
<tr>
<td>A-ramp</td>
<td>2.0500</td>
<td>0.09900</td>
<td>0.06300</td>
<td>0.01800</td>
<td>0.0011</td>
<td>0.0325</td>
</tr>
<tr>
<td>C-ramp</td>
<td>2.0500</td>
<td>0.05500</td>
<td>0.03500</td>
<td>0.01000</td>
<td>0.0001</td>
<td>0.0325</td>
</tr>
</tbody>
</table>

Figure 4.10: Step response with estimated ramp parameters: A-type dark, and C-type light.
Figure 4.11: Step responses for parameters estimated to fit the step data for a slowly adapting (A-type) neuron observed by Brown et al. [20], and shown in Fig. 4.4.

\( p_b = 0 \text{mmHg/sec} \) and slope \( a = 2 \text{mmHg/sec} \) as used in the previous simulations. This was done to ensure the parameters estimated for the step response also reflected an appropriate ramp response (see Fig. 4.12).

### 4.4.3 Frequency Response

Using the ramp parameters from Table 4.4 the neurons were simulated with sinusoidal pressure stimulus of the form Eq. 4.3 with \( p_b = 150 \text{mmHg} \) and \( p_A = 10 \text{mmHg} \). The resulting model firing rate was fit to the function Eq. 4.4 using Matlab's fmincon, ensuring \( A > 0 \) and \( \theta \in [-\pi, \pi] \). The gain was then calculated as defined in Eq. 4.4 with the results plotted in Fig. 4.13.

In addition to characterizing the firing rate frequency response, we were also interested in calculating the same quantities for \( \epsilon_{ne} \) to understand if the frequency response was equivalent to that of the mechanical coupling. Thus using the same pressure stimuli we characterized the frequency response of the nerve ending strain with results shown in Fig. 4.13.

### 4.5 Discussion

The objective of this study was to use a model based on biophysical features to predict differentiated responses from A- and C-type baroreceptor neurons. To do so, we developed a model predicting arterial wall deformation, baroreceptor nerve ending deformation, mechanoreceptor stimulation, and action potential generation. To our knowledge this is the first model including all elements transducing changes in arterial blood pressure to generation of baroreceptor firing rate. Where available, data was extracted from literature to show that each model component accurately reproduced known dynamics.
Figure 4.12: Simulation results corresponding to parameters for the A-type step fit and stimulus corresponding to Eq. 4.1. Parameter values for this fit are given in Table 4.4.

Figure 4.13: On the left we show frequency response of the neuron for the estimated ramp parameters: A-type light, and C-type dark. Note the normalized gain for C-type for $\omega > 20$Hz was $-\infty$. In addition the gain of the nerve ending strain $\epsilon_{ne}$ is shown on the right.
First, arterial wall deformation was compared to data from [34], parameters estimated from this prediction was used in all model simulation. Second, since to our knowledge no data exist showing nerve ending deformation relative to wall deformation, the Voigt body model was calibrated using a previous modeling study [72] that used a simple model for prediction of firing rate. Finally, models predicting mechanosensitive stimulation and the ion channel model were calibrated using firing rate data for a number of stimuli. For the latter model, only maximum conductance was estimated, while all other parameters were taken from previous studies by Schild et al. [90].

Using this model we both quantitatively and qualitatively demonstrate differences in A- and C-type responses changing only the relative expressions of particular ion channels.

The most commonly studied difference between A- and C-type neurons are observed during the ramp response [26, 40, 92]. This difference was reproduced in Fig. 4.9 by changing the relative expression of potassium currents and the strength of the mechanosensitive current. These results agree with observations by Schild et al. [91] who reported different levels of expression of calcium currents. However, no data are available distinguishing mechanosensitive channels between the two neuron types.

To quantitative reproduce the step response data of Brown et al. [20] the overall conductances of the A-type parameters were increased, especially the sodium conductance. In order to accommodate the higher range of firing rate response exhibited by the data. With these adjustments the model still exhibited an A-type ramp response though the initial firing rate was lower than typical.

These quantitative and qualitative results indicate a biophysical approach may indeed account for observed differences between A- and C-type neurons, primarily on the neuronal level due to electrophysiological differences. To our knowledge this is the first study, which has reproduced both A- and C-type neuron response with a single model. In addition to these differences the model successfully reproduces the step response characteristics of the firing rate response of baroreceptors. These results are expected as we have developed a model that attempts to incorporate the characteristics of the underlying systems generating the firing rate response: the arterial wall mechanics and neuronal action potential generation. That the differences in response are attributed to neuronal characteristics supports the hypothesis that even the mechanical coupling of the neurons is not differentiated between A- and C-type neurons.

The data available span a large range of firing rate responses indicating significant variability in the response of individual baroreceptor types, and in fact this lack of consistency has been cited as a reason not to model C-type baroreceptor activity [2]. However recent studies by Li et al.[70] indicate differences in distribution A-, Ah- and C-type neurons may play a role in determining the efficacy of the baroreflex. This study has demonstrated the ability to quantitatively reproduce firing patterns observed in A- and C-type neurons, as well as demonstrating the parameters estimated for a particular stimulus also exhibit consistent behavior for the other stimuli for which the parameters were not estimated.
Using these A- and C-type parameters, we also considered the frequency response of the A- and C-type neurons demonstrating these parameters give differentiated frequency responses, though the frequency sensitivity of the neurons was not on the same order of magnitude as reported by Brown et al. [20]. In particular the A-type parameters exhibited a constant response for low frequencies and then attenuated at higher frequencies, where as C-type parameters showed attenuation for any increase in stimulus frequency, which is in agreement with the qualitative features of the reported frequency response. In both cases the overall response seems to be that of a low pass filter, which is to be expected as the neuronal membrane is modeled as a nonlinear resistance in parallel with a linear capacitance, which works as a simple low pass filter. The response is somewhat more complex due to the nonlinear resistances of the voltage gated ion channels. In contrast the coupling response is acting as a high pass filter, which again is expected as the mechanical analog represents a simple high-pass filter with the dash pots absorbing low frequency components, and ensuring all high frequency components transmit directly to the nerve endings. This suggests that two different filtering mechanisms are present in the system and may separately determine the low and high frequency responses of the system as a whole. These mechanisms may lie in some unmodelled physiological components such as excluded ion channels known to be present in the neurons, or in features of the mechanical coupling to arterial wall, which are not accounted for in the Voigt-Body model 4.6.

Our study has included only the largest inward and outward currents from previous electrophysiology and modeling studies in order to simplify the model. Other ion channels may play a significant role in longer term adaptations and pharmacological sensitivities of the baroreceptor firing patterns. Various studies have identified certain specific ion channels as present through various pharmacological, immunohistochemical and genetic techniques [91, Table 1]. These studies have identified voltage gated and calcium activated ion channels, which carry potassium, sodium, and calcium currents. The most prominent currents in both A- and C-type neurons are sodium and potassium channels with rapid kinetics (Nav1.7 and Kv1.4 or Kv4.3). C-type neurons uniquely express a calcium activated potassium current (KCa1.1) and a TTX insensitive sodium current (Nav1.8), which are not present in A-type neurons, it is possible that including these could improve the frequency response of the neuron model. In addition to these currents the C-type potassium current is distributed through a number of channel types (Kv1.1,Kv1.2,Kv1.6,Kv1.3), whereas the A-type neuron has a large portion of whole cell current dominated by a 4AP sensitive potassium current. The 4AP sensitive current is thought to be separated into two channels, one with rapidly inactivating dynamics ($I_A$) and another with much slower inactivation dynamics ($I_D$) on the scale of 7 seconds. $I_A$ is suspected to correspond to Kv1.4 or Kv4.3, whereas $I_D$ is suspected to a non-inactivating correspond to Kv2.1 or Kv2.2.

It is also known there are calcium channels and non-selective HCN channels present in the baroreceptor neurons, the importance of which is not fully understood, though some studies suggest the calcium channels do not play a significant role in the transduction region [5, 61].
Our study demonstrates the feasibility of a biophysical approach to modeling the differentiation of baroreceptor firing patterns. Further work should develop a comprehensive biophysical representation of the origins of various baroreceptor firing characteristics, allowing for quantitative attribution of emergent firing rate features to particular variations in model parameters. Such an approach would provide a biophysical context for evaluating afferent baroreflex dysfunction.

By attributing baroreceptor firing rate responses to key underlying physiology one may evaluate the emergence of baroreflex dysfunction due to inhibition in A- or C-type neurons, which could correspond to unique etiologies of disorders such as orthostatic intolerance. Thus this study lays the groundwork for developing a comprehensive model of baroreceptor blood pressure transduction which accounts for both phenomenological pressure to firing rate relationships as well as underlying biophysical components.

4.6 Appendix

This appendix contains two tables that summarize the mathematical symbols used throughout this chapter. Table 4.5 describes and defines the state and auxiliary variables of the model. Table 4.6 describes and defines the parameters, as well as providing the nominal values and references to the origins of these values.
Table 4.5: Description of the state variables and auxiliary quantities used in this paper.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$p$</td>
<td>aortic blood pressure</td>
<td>mmHg</td>
</tr>
<tr>
<td>$\epsilon_w$</td>
<td>aortic wall strain</td>
<td>unitless</td>
</tr>
<tr>
<td>$\epsilon_1$</td>
<td>nerve ending coupling strain 1</td>
<td>unitless</td>
</tr>
<tr>
<td>$\epsilon_2$</td>
<td>nerve ending coupling strain 2</td>
<td>unitless</td>
</tr>
<tr>
<td>$\epsilon_{ne}$</td>
<td>nerve ending strain</td>
<td>unitless</td>
</tr>
<tr>
<td>$V$</td>
<td>membrane voltage</td>
<td>mV</td>
</tr>
<tr>
<td>$m$</td>
<td>Nav1.7 Activation</td>
<td>unitless</td>
</tr>
<tr>
<td>$h$</td>
<td>Nav1.7 Inactivation</td>
<td>unitless</td>
</tr>
<tr>
<td>$j$</td>
<td>Nav1.7 Reactivation</td>
<td>unitless</td>
</tr>
<tr>
<td>$n$</td>
<td>Delayed Rectifier activation</td>
<td>unitless</td>
</tr>
<tr>
<td>$p$</td>
<td>K A Activation</td>
<td>unitless</td>
</tr>
<tr>
<td>$q$</td>
<td>K A Inactivation</td>
<td>unitless</td>
</tr>
<tr>
<td>$x$</td>
<td>K D Activation</td>
<td>unitless</td>
</tr>
<tr>
<td>$y$</td>
<td>K D Inactivation</td>
<td>unitless</td>
</tr>
<tr>
<td>$f$</td>
<td>firing rate</td>
<td>Hz</td>
</tr>
</tbody>
</table>

**Auxiliary Quantities**

| $I_{Na,F}$  | Nav1.7 Current | nA          |
| $I_{Na,S}$  | Nav1.8 Current | nA          |
| $I_{K,dr}$  | K-DR current  | nA          |
| $I_{K,A}$   | K-A current   | nA          |
| $I_{K,D}$   | K-D current   | nA          |
| $I_{msc}$   | MSC current   | nA          |
| $p_o$       | open probability of MSC | unitless |
| $I_{Na,B}$  | Sodium background leakage | nA          |
| $I_{Na,K}$  | Sodium-potassium pump current | nA          |
Table 4.6: Description of the parameters used in this paper and their nominal values.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
<th>Units</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_0$</td>
<td>unstressed aortic area</td>
<td>4.01</td>
<td>mm$^2$</td>
<td>[106]</td>
</tr>
<tr>
<td>$A_m$</td>
<td>maximal aortic area</td>
<td>15.708</td>
<td>mm$^2$</td>
<td>[106]</td>
</tr>
<tr>
<td>$a$</td>
<td>saturation pressure</td>
<td>145</td>
<td>mmHg</td>
<td>[106]</td>
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<td>$k$</td>
<td>steepness const</td>
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<td>unitless</td>
<td>[106]</td>
</tr>
<tr>
<td>$R_A$</td>
<td>maximal to minimal area ratio</td>
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<td>unitless</td>
<td></td>
</tr>
<tr>
<td>$E_0$</td>
<td>elastic nerve const</td>
<td>1</td>
<td>mmHg</td>
<td>[21]</td>
</tr>
<tr>
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<td>elastic nerve const</td>
<td>1</td>
<td>mmHg</td>
<td>[21]</td>
</tr>
<tr>
<td>$E_2$</td>
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<td>mmHg</td>
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<td>$\eta_1$</td>
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</tr>
<tr>
<td>$\eta_2$</td>
<td>viscous nerve coupling const</td>
<td>2.5</td>
<td>mmHg·s</td>
<td>[21]</td>
</tr>
<tr>
<td>$\alpha_1$</td>
<td>nerve ending const</td>
<td>$E_0/\eta_1$</td>
<td>s$^{-1}$</td>
<td>[71]</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>nerve ending const</td>
<td>$E_0/\eta_2$</td>
<td>s$^{-1}$</td>
<td>[71]</td>
</tr>
<tr>
<td>$\beta_1$</td>
<td>nerve ending relaxation rate</td>
<td>$E_1/\eta_1$</td>
<td>s$^{-1}$</td>
<td>[71]</td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>nerve ending relaxation rate</td>
<td>$E_2/\eta_2$</td>
<td>s$^{-1}$</td>
<td>[71]</td>
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<tr>
<td>$s_1$</td>
<td>firing constant</td>
<td>480</td>
<td>s$^{-1}$</td>
<td>[72]</td>
</tr>
<tr>
<td>$s_2$</td>
<td>firing constant</td>
<td>100</td>
<td>s$^{-1}$</td>
<td>[72]</td>
</tr>
<tr>
<td>$C_m$</td>
<td>membrane capacitance</td>
<td>32.5</td>
<td>nF</td>
<td>[90]</td>
</tr>
<tr>
<td>$E_{Na}$</td>
<td>sodium reversal potential</td>
<td>84.0</td>
<td>mV</td>
<td>[90]</td>
</tr>
<tr>
<td>$E_K$</td>
<td>Potassium reversal potential</td>
<td>-72.8</td>
<td>mV</td>
<td>[90]</td>
</tr>
<tr>
<td>$E_{Ca}$</td>
<td>Calcium reversal potential</td>
<td>126.7</td>
<td>mV</td>
<td>[90]</td>
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<tr>
<td>$g_{Nav1.7}$</td>
<td>maximal Nav1.7 conductance</td>
<td>2.05</td>
<td>$\mu$S</td>
<td>[90]</td>
</tr>
<tr>
<td>$g_{K,DR}$</td>
<td>maximal delayed rectifier conductance</td>
<td>0.0055</td>
<td>$\mu$S</td>
<td>[90]</td>
</tr>
<tr>
<td>$g_{K,A}$</td>
<td>maximal transient 4AP sensitive conductance</td>
<td>0.035</td>
<td>$\mu$S</td>
<td>[90]</td>
</tr>
<tr>
<td>$g_{K,D}$</td>
<td>maximal persistent 4AP sensitive conductance</td>
<td>0.0100</td>
<td>$\mu$S</td>
<td>[90]</td>
</tr>
<tr>
<td>$g_{Na,B}$</td>
<td>Background sodium conductance</td>
<td>3.25e-4</td>
<td>$\mu$S</td>
<td>[90]</td>
</tr>
<tr>
<td>$g_m$</td>
<td>mechanosensitive channel conductance</td>
<td>1.00e-4</td>
<td>$\mu$S</td>
<td>[90]</td>
</tr>
<tr>
<td>$\epsilon_{1/2}$</td>
<td>half activation nerve strain</td>
<td>0.3048</td>
<td>unitless</td>
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<tr>
<td>$S_{1/2}$</td>
<td>reciprocal slope for $p_o$</td>
<td>0.0246</td>
<td>unitless</td>
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<tr>
<td>$[Na^+]_i$</td>
<td>Intracellular sodium concentration</td>
<td>8.90</td>
<td>mM</td>
<td>[90]</td>
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<tr>
<td>$[Na^+]_o$</td>
<td>Extracellular sodium concentration</td>
<td>154</td>
<td>mM</td>
<td>[90]</td>
</tr>
<tr>
<td>$[K^+]_i$</td>
<td>Intracellular potassium concentration</td>
<td>145</td>
<td>mM</td>
<td>[90]</td>
</tr>
<tr>
<td>$[K^+]_o$</td>
<td>Extracellular potassium concentration</td>
<td>5.40</td>
<td>mM</td>
<td>[90]</td>
</tr>
<tr>
<td>$[Ca^+]_i$</td>
<td>Intracellular calcium concentration</td>
<td>9.70e-05</td>
<td>mM</td>
<td>[90]</td>
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<tr>
<td>$[Ca^+]_o$</td>
<td>Extracellular calcium concentration</td>
<td>2.0</td>
<td>mM</td>
<td>[90]</td>
</tr>
<tr>
<td>$i_{Na,K}$</td>
<td>Maximal sodium-potassium pump current</td>
<td>0.243</td>
<td>nA·mM</td>
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</tbody>
</table>
Chapter 5

Model Extensions and Closing Remarks

5.1 Summary of results so far

The results presented in the previous papers (Chapters 3 and 4) have shown the effectiveness of developing a biophysically motivated baroreceptor firing rate model. This framework has been applied to successful reproduce baroreceptor firing patterns exhibited in response to ramp, step, and sinusoidal stimuli, as well as demonstrating qualitative agreement with all known baroreceptor firing pattern features. In addition, we present the first biophysical model, to our knowledge, that differentiates between the A- and C-type firing rate responses by varying only parameters and not the model structure. These results support the hypothesis that differential expression of ion channels is a key functional feature in baroreceptor neurons.

Though our model does not yet reproduce the frequency dependence of baroreceptor firing patterns, we present in this section a confirmation that the full neuronal model does reproduce the phenomenon of post-excitatory depression (PED) in response to a pulse pressure stimulus. A fact that further validates the suitability of this model in studying the comprehensive response of baroreceptors to any pressure stimulus. A number of open questions remain regarding the origins of various features of the baroreceptor response, which we believe may be investigated using the models developed in this study. First, there are many currents that are known to be present in A- and C-type baroreceptors, which have not been characterized in this mathematical model. These currents should be included in this framework to evaluate their significance in determining response patterns. In addition to improving the fidelity of the electrophysiological representation, the alternative mechanical coupling models which consider the interaction of the nerve membrane and the layers of the arterial wall in more detail need to be investigated. A better characterization, even of the qualitative features of this interaction could better establish the role of this coupling in determining the
dynamic response of the baroreceptors. Third a model should be developed to integrate the unique
A- and C-type responses to produce efferent effects. This model would serve as a tool to hypothesis
about the effects of dysfunction specifically in one or the other neuron types, such as demyelination
caused by multiple sclerosis.

In the remainder of this chapter we present results demonstrating the emergence of PED in this
model, and present preliminary results on the significance of including additional background cur-
rents in the neuronal model.

5.2 Post-Excitatory Depression

The response of baroreceptors to a pressure pulse elicits a response known as PED, which refers to a
cessation in firing observed following a sudden decrease in stimulus pressure. This was first observed
by Bronk and Stella [16] as a cessation of firing during diastole. Saum et al. [88] first termed this
cessation PED, though the response had been studied in some detail by Landgren [64]. In addition
Wang et al. [111] observed the duration of cessation depends on the duration of the higher pressure
level. Saum et al. [88] demonstrated that PED is caused within the neuron itself (as opposed to by
the mechanical features of the neuron coupling) and suggested an electrogenic sodium pump is
contributing to the phenomenon. In that study the firing rate of a baroreceptor was recorded while
the aortic arch was subjected to a pulse in pressure with a four second duration. The data is plotted
along with a model response in Figure 5.1. The step change was modeled using the function

\[ p(t) = \begin{cases} 
 p_b & \text{if } t < t_{\text{up}} \text{ or } t_{\text{down}} < t \\
 p_b + \Delta p & \text{otherwise} \end{cases} \]  

(5.1)

where \( p_b \) denotes the baseline pressure and \( \Delta p \) the step change.

We demonstrate that our model reproduces this phenomenon using the A-type step response
parameters found in the previous chapter (see Table 4.4). To ensure the pressure sensitivity was in
accordance with the neuron used in step experiments the pressure stimulus was shifted down 20
mmHg to begin at roughly the same pressure as the step used in the previous chapter. Results are
shown in Figure 5.1.

The results for the pulse stimulus indicate the general suitability of this biophysical model in cap-
turing baroreceptor firing characteristics observed under static and dynamic stimulation. Without
any additional tuning the model is able to effectively reproduce experimental results with a slight
shift in input pressure. This shift is not unlikely as the experiments were preformed on different
neurons which may well have had significantly different pressure thresholds. Further, these results
demonstrate the emergence of PED as an intrinsic feature of the biophysical model, as opposed to
Figure 5.1: Using parameters estimated from fitting the step response in Chapter 3, we were also able to reproduce the phenomena of PED. The data is from Saum et al. [88] and was elicited in response to a pressure pulse from 140 mmHg to 180 mmHg. We used a pressure pulse from 120 mmHg to 160 mmHg so the stimulus lay in a similar range to the step stimulus of Chapter 3. The data is represented as black circles, the model firing rate is the dark purple curve, and the model membrane potential is plotted as light purple to give a sense of the response (note the units of mV for membrane potential and Hz for firing rate).

a conditional bound on the input to the model as achieved in previous studies [21, 72]. Our initial result does not exhibit the same duration of PED as that of the data. We believe this could be explained by variability within the population of neurons, as only one example data set is shown by Saum et al. [88]. Alternatively it could be due to a failure to include some key neuronal components in the model. This would be in agreement with experimental studies indicating PED may be inhibited using pharmacological channel blockers, something easily described in a biophysical neuron model. PED is thought to be a neural phenomenon and is modulated by a number of pharmacological and environmental factors [88]. This motivates the use of a neuronal model including ionic concentrations and channel blockers. Understanding these modulatory mechanisms could provide insights into treatments that could correct the misinformation propagated by increased stiffening in hypertension [9].

5.3 Background currents

As discussed there are a number of background currents without voltage gating that are known to be present in the baroreceptor cell bodies [90]. We consider the effects of the sodium-calcium exchanger, calcium background, calcium pump and sodium potassium pump currents. These include a background calcium current, a calcium pump, and a sodium-potassium exchanger current. Since these were included in the detailed electrophysiological model of Schild et al. [90], we wanted to
evaluate the significance of each of these currents in determining the firing rate response of the baroreceptor neurons. To do so we varied the conductance or maximal current parameters associated with each channel and evaluated the model’s response to a ramp in pressure for values between 0 and twice the nominal value reported by Schild et al. [90]. The resulting firing rate curves are shown in Figures 5.2-5.5, we also present the equations governing these currents in Table 5.1. The majority of these currents do not seem to have a significant qualitative effect on the firing rate response of the model, though the sodium potassium exchanger does exhibit a qualitative transition from tonic firing to a threshold type firing pattern for appropriate parameters. Thus this current was included in the model used in the previous paper.

Table 5.1: Equations determining the background currents.

<table>
<thead>
<tr>
<th>Background currents</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>$I_{B, Ca} = \tau_{B, Ca}(V - E_{Ca})$</td>
</tr>
<tr>
<td>Sodium-calcium Exchanger</td>
<td>$I_{Na,Ca} = K_{Na,Ca}(D_{in} - D_{out})/S$</td>
</tr>
<tr>
<td></td>
<td>$S = 1 + D_{out,Ca}[\text{Ca}^{2+}]</td>
</tr>
<tr>
<td></td>
<td>$D_{in} =</td>
</tr>
<tr>
<td></td>
<td>$D_{out} =</td>
</tr>
<tr>
<td>Calcium pump</td>
<td>$I_{CaP} = \bar{I}<em>{CaP}\frac{[\text{Ca}^{2+}]}{K</em>{M,CaP}}$</td>
</tr>
<tr>
<td>Sodium-potassium pump</td>
<td>$I_{NaK} = \bar{I}<em>{NaK}\left(\frac{[\text{Na}^{+}]}{K</em>{M,Na}}\right)^{3} \left(\frac{[\text{K}^{+}]}{K_{M,K}}\right)^{2}$</td>
</tr>
</tbody>
</table>
Figure 5.3: Firing rate curves for varying $\bar{I}_{CaP}$, the maximal current of the calcium pump to the values shown in the color bar.

Figure 5.4: Response to varying $\bar{K}_{NaCa}$, the maximal current of the sodium-potassium exchanger, to the values shown in the color bar.
Figure 5.5: Response to varying $\bar{I}_{NaK}$, the maximal current of the sodium-potassium exchanger, to the values shown in color bar.
5.4 Closing Remarks

The models included in this thesis have been shown to be effective at reproducing numerous features of baroreceptor firing patterns. The development of these models has resulted in a framework which explicitly represents the contributions of the subsystems underlying blood pressure transduction as described in Chapter 3. This representation encourages the evaluation of the importance of specific features, such as arterial wall viscoelasticity, in determining the behavior of the whole system of blood pressure transduction. We extended the framework to include a more detailed model of the neuron that allows us to compare the contributions of individual currents to transduction. This study also demonstrated that such an approach is a viable way to reproduce different results between A- and C-type neurons based only on neuronal characteristics, as shown in Chapter 4. These results are significant in two ways: (1) they demonstrate the ability to reproduce all known baroreceptor firing rate responses in a single modeling framework, and (2) the biophysical neuronal model is the first model of its kind reproducing both A- and C-type responses. As accounted in Chapter 4 the baroreceptors have been studied primarily from a phenomenological perspective, which accounts for the relationship between blood pressure and firing rate, but cannot account for the significance of particular subsystems [72, 82, 83, 98].

While this study has successfully applied a biophysical approach to build mechanistic models of blood pressure transduction, there are number of elements which have been ignored and will be the focus of future studies. First among these is the consideration of additional ion channels (Nav1.7 and KvCa1.1) known to be present in the C-type neurons [91], as these additional channels may play a role in determining the frequency response of the C-type neurons, a feature which has not been successfully reproduced by our model. In addition to including these channels, a more rigorous analysis of the firing patterns’ sensitivities to each ion channel type should be preformed to rigorously indicate which channels determine the firing rate response. Further, recent studies have identified a potential third type of baroreceptor (Ah), which is expressed almost exclusively in female rats [70] further indicating the importance of a biophysical modeling framework that is able to describe each of these neuron types and reproduce their firing patterns.

Another goal is to develop a model representing the integration of A- and C-type firing patterns in the efferent response, as it has been shown that selective stimulation of A- and C-type neurons may evoke markedly different efferent responses [33]. Such an investigation is enabled by our development of a neuronal model, which reproduces A- and C-type responses to both static and dynamic response. Understanding the differences in the efferent response due to the signals of A- and C-type neurons may provide a means for better understanding disorders such as orthostatic intolerance and hypertension, which are known to be associated with baroreceptor dysfunction.
BIBLIOGRAPHY


