

QUALITATIVE FEATURES OF A NOVEL BARORECEPTOR MODEL

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ABSTRACT

Blood pressure regulation by the cardiovascular system is a complex physiological process. Cardiovascular modeling can offer a valuable insight often beyond the reach of experiments. In this study we provide a new mathematical model of the afferent component of the baroreflex feedback system. The model takes advantage of the so-called quasi-linear viscoelastic theory, which has been widely used to describe the nonlinear viscoelastic response of living tissue. It also uses a simple integrate-and-fire model to predict the baroreceptor response and therefore takes into account the conceptual structure of the baroreceptor. Our objective is to test our new baroreceptor model for its ability to reproduce experimental data qualitatively and demonstrate known pressure-response relationships. We also highlight that the model can be coupled with an existing model of the efferent pathways, eventually predicting heart rate.

Keywords: heart rate regulation, baroreflex, blood pressure dynamics, mathematical modeling

1. INTRODUCTION

Understanding the cardiovascular control system is crucial for gaining more insight into the physiology not only for the healthy individual, but also in order to detect pathologies. Its main role is to provide adequate perfusion of all tissues, which is achieved by maintaining blood flow and pressure at a fairly constant level. To accomplish this, a number of control mechanisms are imposed regulating vascular resistance, compliance, pumping efficiency and frequency. An important contributor to this control system is the *baroreflex* (or *baroreceptor reflex*), which uses specialized neurons called *baroreceptors* for signaling. The baroreceptor neurons are activated via mechano-sensitive channels located in the aortic arch and carotid sinuses. It is believed that the baroreceptor nerves are the main contributor to the short-term regulation of vascular efferents including: heart rate, cardiac contractility, and vascular resistance and vessel tone (Levick 2010).

Prediction of heart rate from blood pressure involves two main pathways: afferent and efferent. *Afferent* pathways integrate firing of the baroreceptors in the nucleus solitarius tract. *Efferent* pathways modulate sympathetic and parasympathetic signals, which lead to release or inhibition of the neuro-transmitters: acetylcho-

line and noradrenaline, which in turn modulate the effectors. In this study, we focus on regulation of heart rate. See Figure 1 for overall, conceptual division of the model predicting heart rate.

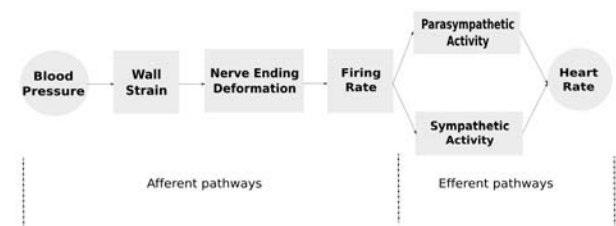


Figure 1: Conceptual division of the mathematical model for the baroreflex feedback control of heart rate.

This study focuses on analyzing qualitative aspects of a new model for the afferent signaling, whereas the efferent dynamics can be predicted using either the existing model developed by Olufsen et al. [2006], or any other model. In Section 2, after reviewing the main qualitative characteristics of the baroreceptor dynamics we introduce our model, which will be analyzed and discussed in Section 3.

2. METHODS

In this section we describe the principal physiological elements of the baroreceptors; identify the most prominent qualitative features of their discharge observed in experiments; and introduce a mathematical model that reflects all those characteristics.

2.1. Basic physiological facts and experiments

For most mammals baroreceptors are found in the aortic arch and the carotid sinuses (Sharwood 2001). These neurons are stimulated via activation of stretch receptors, which are able to detect changes in the wall strain induced by changes in blood pressure. Besides water, which makes up to 70% of arterial wall, it consists of: muscles, elastin, collagen and ground substance. The wall is commonly divided into three layers: the *tunica intima*, a thin layer of endothelial cells lining the arterial wall; the *tunica media* (the middle layer), the primary contributor to the arterial wall deformation; and the *tunica adventitia* (the outer layer) connecting the vessels to their surrounding tissue. Understanding the mechanics and the viscoelastic properties of the arterial wall is essential for modeling the baroreceptor response.

Although some characteristics of the baroreceptor response depend on their type, e.g., whether they have myelinated or unmyelinated axons (Brown 1978), it is possible to identify a number of common signaling patterns. The most prominent static and dynamic characteristics include: saturation, threshold (Seagard et al. 1990), adaptation (Brown 1980), hysteresis, post-excitatory depression (PED) (Brown 1980) and sensitivity to the rate of change of the stimulus (Landgren 1952). It is clear that any complete, baroreceptor model should be able to reflect these important features. Therefore, we first review them in more detail.

Adaptation: If the pressure changes and resets at a new constant value, the baroreceptor-firing rate follows, reaching a new steady state (Landgren 1952). The frequency of the steady discharge is the same whether the new pressure level is reached from a higher or a lower pressure (Brown et al. 1976, Sleight 1980).

Saturation: As pressure increases so does the firing rate, but after a certain increase no further firing rate increase is observed with the increase of the input (Landgren 1952). A constant decrease of the pressure results in a decrease of the firing rate, first in an almost linear and then in a hyperbolic manner tending toward some limiting value (Coleridge et. al. 1981). It has also been observed that the saturation level strongly depends on the type of the baroreceptor (Seagard et. al. 1990, Van Brederode et al. 1990).

Threshold: The increase of pressure from zero does not result in an immediate response. The nerves do not start to fire until the pressure crosses a certain threshold value.

Asymmetry: A difference in the response to a rising and falling pressure is referred to, in general, as asymmetry or hysteresis (Bronk and Stella 1932). In particular, periodic inputs (such as a triangular or sinusoidal wave) produce loops in the pressure-frequency response causing asymmetry also referred to as hysteresis (Coleridge et al. 1981).

Post-Excitatory Depression (PED): After a step decrease in pressure, firing may cease for some seconds, followed by a recovery to the steady state firing rate, commensurating with the new established pressure level (Brown 1980). It has been observed that the length of the pause (also denoted the refractory period) depends on the depth of the pressure drop (Wang et al. 1991).

2.2. Afferent dynamics – the model

One of the first attempts to quantitatively describe the activity of baroreceptors goes back to Landgren (Landgren 1952). Since then, a number of models have been proposed. Unfortunately most of them are not able to reflect all of the known qualitative features of the response (Spickler and Kezdi 1967) or have no biological foundations (Taher et al. 1988). Still other models treat the prediction of baroreflex firing purely from the mechanical perspective, and thus offering very superficial or no description of the neural part of the response (Srinivasan and Nudelman 1972, 1973).

In this study, the modeling processes involved with

predicting baroreceptor firing (described later in this section) will reflect the conceptual division of the afferent pathways including: arterial wall deformation (wall strain); nerve ending deformation (nerve strain); and action potential formation (firing rate). To be more precise, given an arterial pressure $p(t)$ we will model the viscoelastic response of the arterial wall $\varepsilon_w(t)$, which will be used as an input to obtain the current generated along the axons $I(t)$, which will be integrated to predict the baroreceptor firing rate $f(t)$. The sections below describe each of these components in detail.

Arterial wall deformation

Most models predicting the viscoelastic response of the arterial wall due to changing pressure are formulated as linear models involving springs and dashpots. It was observed by Fung (Fung 1993), that biological tissues are not elastic, but that the history of the vessel strain affects the stress. Moreover, he observed that there is a difference in stress response between loading and unloading. Generalizing the linear viscoelastic theory, Fung introduced the so-called *quasi-viscoelastic theory* (QLV), which has been successfully used in modeling stress-strain relationship of the arterial wall (Valdez-Jasso et al. 2009-2011). We shall use the QLV theory in order to model the strain of the arterial wall to changes in pressure. We proceed under the assumption the arterial wall can be modeled as a homogeneous and isotropic cylindrical vessel with a thin wall (Fung 1996). For such a vessel, the wall strain can be predicted as a function of pressure given by

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

where following (Valdez-Jasso, 2009) the *creep function* $K(t)$ is given by

$$K(t) = 1 - A_1 e^{-\frac{t}{b_1}},$$

with the *elastic response* $s^{(e)}[p(t)]$ defined by

$$s^{(e)}[p(t)] = 1 - \frac{\sqrt{A_0(p^k(t) + \alpha^k)}}{\sqrt{A_m p^k(t) + A_0 \alpha^k}}.$$

In this equation A_m and A_0 (cm^2) denote the maximal and zero pressure cross-sectional area of the vessel, respectively, α ($mmHg$) denotes the characteristic pressure at which the vessel starts to saturate, and k denotes the steepness of rise of the sigmoid curve.

Nerve ending deformation

The stimulation of baroreceptor firing is probably the least understood element of the afferent pathway and therefore in most models it is either omitted or treated superficially. Our modeling process is based on the observation that the baroreceptor firing rate is sensitive not only to the intrasinus mean pressure, but also to its rate of change (Ursino 1999). Moreover, we assume that the adaptation process is due to the coupling of the baroreceptor nerve with the wall. Thus, we propose to

model the stretch of the baroreceptors by the following simple dynamical system

$$\begin{aligned}\frac{dx_1}{dt} &= -\alpha_1 x_1 + \alpha_2 x_2 + \gamma_1 \varepsilon_w \\ \frac{dx_2}{dt} &= -\alpha_3 x_1 - \alpha_4 x_2 + \gamma_2 \varepsilon_w,\end{aligned}$$

where $\alpha_1, \dots, \alpha_4$ and γ_1, γ_2 are parameters. In particular, if the parameters of this system are written as

$$\begin{aligned}\alpha_1 &= \frac{E_0 + E_1}{\eta_1} + \frac{E_0}{\eta_2}, & \alpha_2 &= \frac{E_1}{\eta_1} - \frac{E_2}{\eta_2}, \\ \alpha_3 &= \frac{E_0}{\eta_2}, & \alpha_4 &= \frac{E_2}{\eta_2}, \\ \gamma_1 &= \frac{E_0(\eta_1 + \eta_2)}{\eta_1 \eta_2}, & \gamma_2 &= \frac{E_0}{\eta_2},\end{aligned}$$

it can be interpreted as a linear viscoelastic model with a spring and two Voigt bodies in parallel, where x_1, x_2 are denote the relative displacement from the rest position. Similar ideas have been used in the context of baroreceptor modeling in (Alfrey 1997, Bugenhagen et al. 2010), and before that for the modeling the muscle spindle dynamics (Houk et al. 1966, Hasan 1983). Following this idea, the strain sensed by the nerve ending of the receptors due to the changing strain of the arterial wall is given by

$$\delta(t) = \varepsilon_w(t) - x_1.$$

We incorporate a simple mechanism for the threshold, predicting the input current $I(t)$ needed to stimulate the neuron by

$$I(t) = \begin{cases} 0 & \text{if } \delta < \delta_{th} \\ s_1(\delta - s_2 \delta_{th}) & \text{if } \delta \geq \delta_{th} \end{cases},$$

where s_1, s_2 and δ_{th} are parameters.

Firing rate

Finally, the neural part of the baroreceptor is predicted using a simple integrate-and-fire model described by the first-order differential equation

$$C \frac{dv(t)}{dt} + Gv(t) = I(t),$$

where G and C represent the neuron's membrane conductance and capacitance, respectively. It is assumed that the neuron fires if the voltage on the membrane reaches the threshold value V_{th} . In other words, when $v(t) = V_{th}$ an action potential is generated and the capacitor voltage is reset to zero. Simple computation shows that for a constant stimulus, the time it takes to integrate the model from 0 to V_{th} is given by

$$T = \frac{C}{G} \log \left(\frac{I(t)}{I(t) - GV_{th}} \right).$$

It is well known that after an action potential has occurred the neuron cannot fire for several milliseconds (Izhikevich 2007). This time is generally referred to as

the *refractory period*, which we denote by t_{ref} . The refractory period t_{ref} , can be added to T giving

$$f = \frac{1}{T} = \frac{1}{\tau \log \left(\frac{I(t)}{I(t) - GV_{th}} \right) + V_{th}},$$

where $\tau = C/G$. We note that for a sufficiently large current $I(t)$, the term involving the *log* function is arbitrary small. Thus because of the refractory period, the maximum firing rate is given by (Chen 2004)

$$f_{sat} = \frac{1}{t_{ref}}.$$

2.3. Efferent responses: heart rate dynamics

For the sake of completeness we point out how the afferent and efferent parts can be used to predict the heart rate. Following (Olufsen et al. 2006) the sympathetic and parasympathetic tone can be predicted as

$$T_{par} = \frac{f}{N}, \quad T_{sym} = \frac{1 - f(t - \tau_d)}{N},$$

where N is the baseline firing rate and τ_d is a delay for sympathetic stimulation. Stimulation of sympathetic and parasympathetic outflow modulate the concentration of the neurotransmitters acetylcholine C_{ach} and noradrenaline C_{nor} , which can be predicted from the differential equations

$$\frac{dC_{ach}}{dt} = \frac{T_{par} - C_{ach}}{\tau_{ach}}, \quad \frac{dC_{nor}}{dt} = \frac{T_{sym} - C_{nor}}{\tau_{nor}},$$

where τ_i denotes characteristic timescales. Finally, heart rate H can be computed as

$$H = H_0(1 - M_{nor}C_{nor} + M_{nor}C_{nor}),$$

where H_0 is the baseline firing rate and M_i are constants weighting each of the neurotransmitters.

3. QUALITATIVE ANALYSIS

To test the ability of the baroreceptor model, introduced in Section 2 to reflect the qualitative features of the baroreceptor firing rates observed in experiments, we study the response to the following pressure inputs: a step-increase and decrease, a sine wave, and a continuous ramp. With these stimuli, it is possible to show that the model under investigation is able to reflect all the main static and dynamics features listed in Section 2.1. Figure 2 shows data (adapted from previous studies by Brown [1978, 1980] and Seagard [1990]) from the three pressure input types and Figure 3 shows similar responses obtained with the proposed model.

We begin the testing the model's response to a pressure step increase and decrease (Figures 2 and 3, top panels). A step change (either an increase or a decrease) is one of the most commonly used pressure stimuli for studying the activity of the afferent baroreceptor nerves. The response to this stimulus has been discussed in several previous studies (Franz 1971, Clarke 1968, Brown 1978, Brown 1980, Taher et al. 1988).

Figure 2 (top panel) shows a typical experimental result (from Brown 1980). For comparison, our model shows similar dynamics including overshoot, threshold, adaptation, post-excitatory depression, and saturation. It should be noted that similar to the experiments, the adaptation occurs with different time-scales in response to a step increase or decrease, respectively. One aspect, not shown here, is that the steady-state discharge depends only on the level of the stimulus, which is in accordance with the experimental observations by Brown et al. [1976].

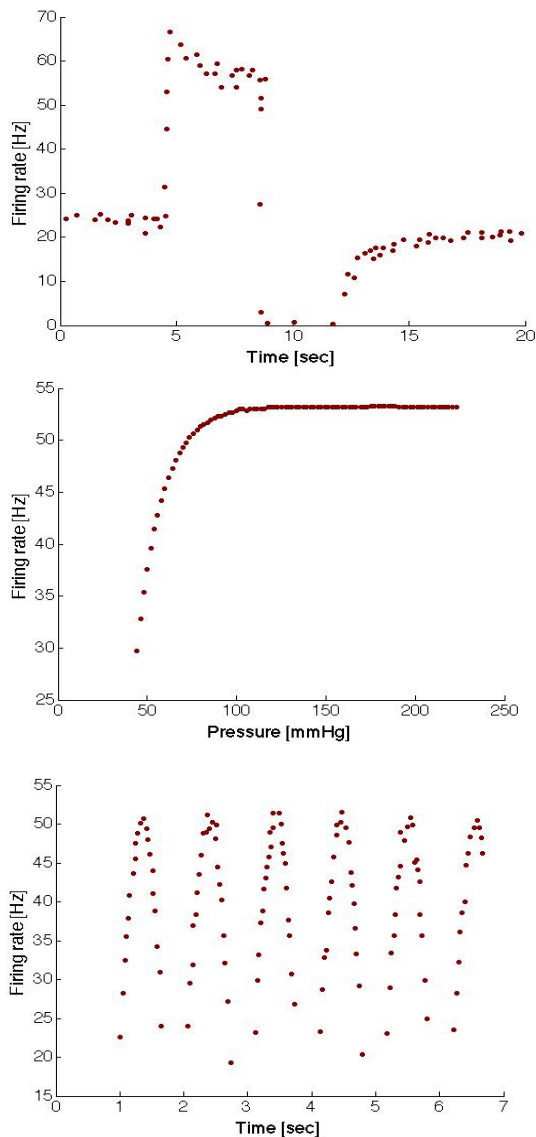


Figure 2: Typical baroreceptor response to a step (top; from Brown 1980), ramp (center; from Brown 1978), and sinusoidal (bottom; from Seagard 1990) pressure stimulus. The response to a step change (either a step increase or decrease) shows that the baroreceptor exhibits threshold, overshoot, adaptation and post-excitatory depression. The ramp response shows that the firing discharge saturates, and the sinusoidal response shows that in the lower frequencies discharge to disappear.

The model also predicts a *threshold pressure with steady discharge*, i.e., the minimum pressure value needed for obtaining a steady nonzero discharge. This feature has been observed by (Landgren 1952). Most of the model's dynamics stems from the equations predicting viscoelasticity of the nerve endings, and therefore it is typically assumed that the firing rate modulation is mediated by the coupling of the nerve ending with the arterial wall. Next we test the model's ability to predict the response to a ramp pressure profile (Figures 2 and 3, center panel).

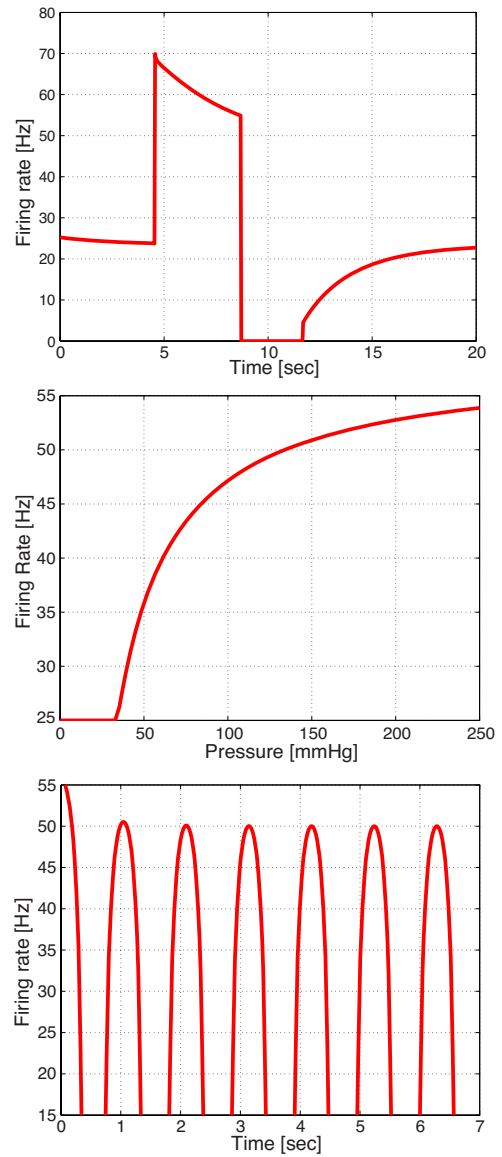


Figure 3: Baroreceptor responses obtained with the proposed model. Model responses shown here are designed to qualitatively predict similar dynamics as those observed experimentally (see Figure 2). Top shows results to a step increase and decrease; the center panel shows results to a ramped pressure stimulus, and the bottom panel shows the response to a sinusoidal stimulus.

The continuous ramped up pressure input is another commonly used stimulus, see previous studies by Clarke [1968], Coleridge et al. [1981, 1987], and Seagard et al. [1990].

As noted in the introduction, two physiological arguments can be used to explain why saturation occurs. First, the arterial wall can only deform finitely, baroreceptors are imbedded in the arterial wall, and thus, beyond a certain pressure stimuli the wall will no longer expand and neither will the baroreceptor nerve endings. This property can be incorporated, by imposing *nonlinear elastic response* within the viscoelastic model predicting arterial wall strain. Saturation has been described in previous studies, see (Kalita and Schaefer 2008, Valdez-Jasso 2009). Second, as described in the methods section, the refractory period following the firing of the neuron causes saturation. This phenomenon has also been observed previously; see (Koch and Segev 1998, Izhikevich 2007). As illustrated on Figure 3, we noted that both elements are well reflected in the modeling proposed model. This figure also shows threshold, as the discharge does not take place until the minimum value of the stimulus is reached.

Finally, we tested the dynamic response using a sine wave pressure profile as the stimulus. Comparison of Figures 2 and 3 (bottom panels), show that the model is in qualitatively agreement with experimental observations (Brown et al. 1978, Franz et al. 1971). The model predicts a time-varying firing rate that ceases when the pressure is below a given threshold. In addition to the result depicted here we tested the model using pressure waves with varying amplitudes, results showed that the firing rate is sensitive to the rate of change of the stimulus. This observation is in agreement with observations by Landgren [1952], Spickler and Kezdi [1967].

4. CONCLUSION

In this study we introduced and analyzed a new model predicting dynamics within the afferent pathways of baroreflex regulation. The main focus was on predicting firing of the afferent baroreceptor nerves. By using various pressure profiles we tested our model's ability to reproduce the main qualitative features reported in the literature, and we observed that our model is able to reproduce all known observed features including: threshold, saturation, overshoot, adaptation, post-excitatory depression, and sensitivity to the rate of change of the stimulus. We also showed that the firing rate model has potential to be coupled with an efferent model allowing prediction of heart rate. The efferent model can either be the existing model presented in section 2.3 (Olufsen et al. 2006), or any model that utilizes the afferent firing rate to predict heart rate. In future studies, we will test this model's ability to predict heart rate observed in both rat and human data.

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