Confronting a Cardiovascular System Model with Heart Rate and Blood Pressure Data

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Abstract

The cardiovascular system may be investigated by observing fluctuations in the heart rate, blood pressure and rate of respiration. Its time evolution is governed by the baroreflex control mechanism, where the sympathetic and vagal nerves compete to increase and decrease the heart rate respectively. A nonlinear delay-differential equation model is constructed to describe this control mechanism and to explore the interactions between the heart rate and blood pressure. In this model, a time delay gives rise to the oscillations in the blood pressure known as Mayer waves. The model maintains an intrinsically stable heart rate in the absence of nervous control, and features baroreflex influence on both heart rate and peripheral resistance. The effect of respiratory sinus arrhythmia (RSA) is introduced using a sinusoidal driving component. Clinical recordings obtained by carefully controlling the rate and depth of respiration are used to test the suitability of the model for representing the complicated physiology of the cardiovascular system. The model is shown to be able to reproduce many of the empirical characteristics observed in these biomedical signals, including RSA, Mayer waves and synchronization. Key physiological parameters in the model, including the time delay and levels of sympathetic and vagal activity, could provide useful diagnostic information about the state of the cardiovascular system.

1. Introduction

The human body relies on adequate control of blood pressure as the heart pumps blood to all the vital organs. Increased blood pressure, hypertension, indicates an increased presupposition to a range of disorders including congestive heart failure, stroke, myocardial infarction and kidney failure. A better understanding of the dynamics underlying the control mechanisms used to regulate blood pressure may be used to facilitate improved diagnosis of these disorders using non-invasive clinical techniques.

The electrocardiogram (ECG) can be used to extract a time series of inter-beat time intervals, which reflect the cardiac activity. The human cardiac system displays a number of bio-rhythms such as (i) respiratory sinus arrhythmia (RSA) whereby the heart rate increases during inspiration [1] and (ii) Mayer waves, slow oscillations in blood pressure with an approximate 10-second period [2]. There has been some debate about the exact source of these Mayer waves [3]. While the most widely accepted theory suggests that these waves are caused by the sympathetic (delayed) feedback control of the blood pressure through the baroreflex [2], others cite an oscillator in the central nervous system [4].

A variety of approaches have been employed to describe the short-term control of blood pressure. Ottesen *et al.* [5, 6] provide an excellent review of attempts at modelling the physiology of the cardiovascular system. Grodins [7] used algebraic equations for the steady controlled heart which can be rearranged to model mean arterial pressure by a sixth order polynomial. DeBoer *et al.* [2] proposed a beat-to-beat difference model where each heart beat is considered as a discrete event and the sympathetic feedback from the baroreceptors is distributed over the following 2-6 beats. Madwed *et al.* [8] provided a descriptive model using feedback control. Ursino *et al.* have produced a series of differential delay equation models to allow for changes in the venous capacity and cardiac pulsatility (see [9] and references therein). Seidel & Herzel [10] developed a hybrid model with continuous variables and an integrate and fire mechanism to generate a discrete heart rate.

In this paper, we present a model that is capable of describing the interactions between heart rate, blood pressure and respiration. The aim is that this model is (i) sufficiently simple to allow for a mathematical analysis of the dynamics, (ii) sufficiently complex to provide a faithful representation of the underlying physiology and (iii) provides output signals for heart rate, blood pressure and respiration that resemble real biomedical signals.

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2. Methods

First we briefly summarise the primary control mechanisms that regulate the cardiovascular system and affect the heart rate, blood pressure and respiration. Second we introduce the delay recruitment model that is used to describe the interaction between these signals. Third we describe the biomedical signals used for assessing the model.

2.1. Control mechanisms

In the absence of feedback from the central nervous system, the heart is known to continue beating at a rate given by the firing of the sino-atrial node [11]. Within the cardiovascular system of a healthy human subject, there is an intricate relationship between blood pressure and heart rate. The heart rate may be increased by slow acting sympathetic activity or decreased by fast acting parasympathetic (vagal) activity. This competition between the sympathetic and parasympathetic systems, the two opposite acting branches of the autonomic nervous system, is referred to as the sympathovagal balance. Evidence of these competing mechanisms is present in the beat-to-beat changes of the cardiac cycle [12]. A spectral analysis of the inter-beat time intervals may be employed to quantify the effects of the sympathetic and parasympathetic modulation of the inter-beat intervals. The two main frequency bands of interest are referred to as the Low-Frequency (LF) band (0.04 to 0.15 Hz) and the High-Frequency (HF) band (0.15 to 0.4 Hz) [13]. Sympathetic tone is believed to influence the LF component whereas both sympathetic and parasympathetic activity have an effect on the HF component [14].

The major effect of respiration on the cardiac control system is understood to be via the sympathetic and vagal efferents from the medulla, which are modulated by a respiratory signal. This corresponds in our model to modifying the dependence on pressure, adding a sinusoidal term to the pressure to imitate respiration. This respiratory forcing is then fed back to the cardiac control system through the baroreceptor response to blood pressure, consistent with the physiology. A number of other modellers have adopted this approach, adding a sinusoid to directly modify the effective arterial pressure [2, 10].

2.2. The model

Following Ottesen [5], we have developed a non-pulsatile lumped-parameter model of the systemic loop. This loop consists of the left ventricle which pumps blood to the arteries, capillaries, veins and back to the left ventricle. The heart and pulmonary system are effectively combined into one cardiac output term. We assume (i) a closed system with incompressible blood, thereby conserving blood volume, (ii) compliant arteries and veins, and (iii) the capillary system is like a resistance vessel [15].

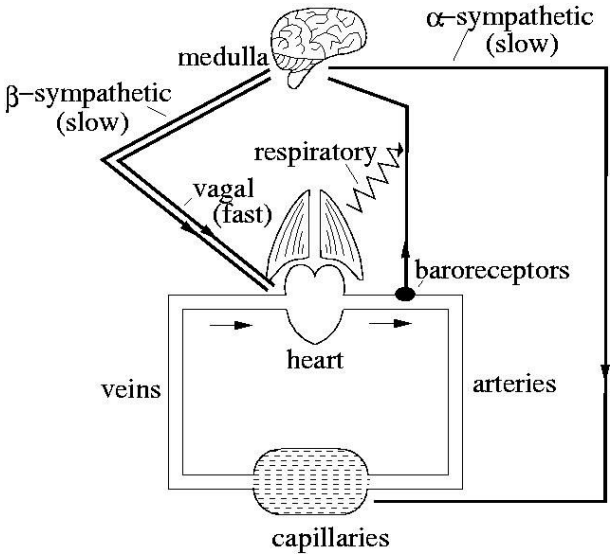

Figure 1. Schematic diagram of the short-term baroreflex cardiac control system.

The baroreflex system (Fig. 1) acts by detecting arterial pressure and sending signals to the brainstem or medulla, which responds via either parasympathetic (fast) and sympathetic (slow) signals that change the heart rate and peripheral resistance of the arterioles and capillaries. In the model, the fast-acting parasympathetic system is assumed to be instantaneous and the slow-acting sympathetic system is modelled as depending on the blood pressure with a delay of $\tau = 3$ seconds. The model also includes the intrinsic controlled behaviour that would be present with no central nervous system. Indeed the resulting natural frequency affects the response dynamics of the cardiac system to baroreflex feedback.

In the absence of nervous control the sino-atrial node will pulse at approximately $h_0 = 100$ beats per minute. The mean arterial blood pressure is approximately $p_0 = 100$ mm Hg. Our model for heart rate h and mean blood pressure p is given by the dimensionless system

$$\begin{aligned} \varepsilon_h \dot{h}^* &= \frac{\beta g_1}{1+\gamma g_2} - \nu g_2 + \delta(1-h^*), \\ \varepsilon_p \dot{p}^* &= \mu h^* - \frac{p^*}{1+\alpha g_1}, \end{aligned} \tag{1}$$

in which $h^* = h/h_0$ and $p^* = p/p_0$ are dimensionless heart rate and blood pressure, respectively, and an overdot denotes differentiation with respect to dimensionless time $t^* = t/\tau$. The functions g_1 and g_2 are defined by

$$\begin{aligned} g_1 &= g(p_1^* + r_1), \\ g_2 &= 1 - g(p^* + r_2), \end{aligned} \tag{2}$$

where

$$\begin{aligned} g(p) &= \frac{1}{1+p^n}, \\ r_1 &= A_1 \sin\{2\pi f_r \tau(t^* - 1) - \phi\}, \\ r_2 &= A_2 \sin\{2\pi f_r \tau t^* - \phi\}, \end{aligned} \tag{3}$$

and the notation p_1^* denotes the delayed function $p^*(t^*-1)$.

Equations (1) may be viewed as follows: for $\dot{h}^*$, the terms represent β-sympathetic, vagal, and intrinsic (sinoatrial) response; for $\dot{p}^*$, the terms represent mechanical inflation by the heart pump action, and the α-sympathetic response. The Hill function $g(p)$ represents the pressure-dependent baroreceptor control. The default values used by Fowler and McGuinness [15] were $\alpha = 1.3$, $\beta = 0.3$, $\varepsilon_h = 0.18$, $\varepsilon_p = 0.3$, $\nu = 0.4$, $\delta = 1$, $\mu = 0.5$, $\gamma = 0.2$, $n = 3$. The influence of respiration is controlled by the amplitudes A_1 and A_2 (dimensionless), frequency f_r (s^{-1}), and phase lag ϕ (dimensionless) of the response; we take $\phi = \pi$.

2.3. Biomedical signals

An electrocardiogram (ECG) signal was used to measure the electrical activity of the heart. By detecting the R peaks of the ECG, a time series of interbeat intervals RR was obtained. These were then used to determine the instantaneous heart rate, $h = 60/RR$ beats per minute (bpm). The respiration rate was carefully controlled by the subject breathing at rates of 6, 10 and 20 bpm corresponding to frequencies of 0.1, 0.17 and 0.33 Hz respectively. A thermistor recording of airflow temperature was also used to measure and confirm the rate of respiration.

3. Results

Figure 2 shows the evolution of the heart rate and blood pressure with time for the paced breathing experiments. The contributions of RSA and Mayer waves can be seen in these time series. Certain features are evident in the experimental results, and it is with these that we wish to confront the model. The principal features are that the mean blood pressure stays close to 100 mm Hg and the mean heart rate stays close to 65 beats per minute. Additionally, heart rate responds directly to ventilation, but the blood pressure is hardly affected. The heart rate shows Mayer waves, particularly at the high forcing frequency, but the blood pressure shows little in the way of oscillation, except at low forcing frequency, where there is some effect of resonance. In fact, the blood pressure shows symptoms of longer term variation which we cannot hope to simulate with this model.

Our strategy in confronting the data in Figure 3 is to mimic these features. We have done so by hand, choosing parameter values by searching manually. To produce

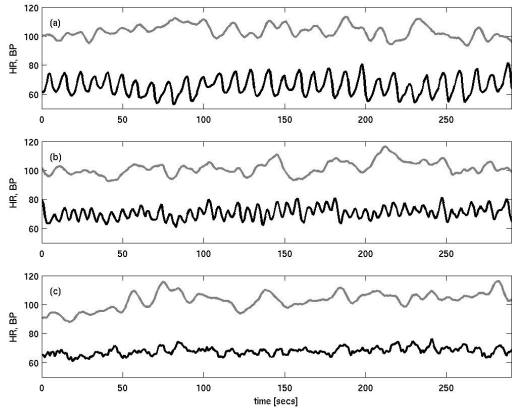

Figure 2. Clinical recordings of heart rate (lower signals) and blood pressure (upper signals) during paced breathing at (a) 6, (b) 10 and (c) 20 breaths per minute.

the figures shown in Figure 3 took less than a day, but the practice indicates that it is very far from optimal. It is less obvious how to find a useful automated procedure.

With $h_0 = 100$ bpm and $p_0 = 100$ mm Hg, a steady heart rate of 67 beats per minute and blood pressure of 100 mm Hg corresponds to values $p^* = 1$ and $h^* \approx \frac{2}{3}$. We have thus chosen μ and ν in order that these steady states are fixed, thus

$$\mu \approx \frac{3}{2+\alpha}, \quad \nu \approx \frac{2\beta}{2+\gamma} + \frac{2\delta}{3}. \tag{4}$$

With μ and ν fixed in this way, we vary the other parameters as follows. The fact that p does not respond to the respiratory forcing suggests that (bearing in mind that $\mu \sim 1/\alpha$) we need to have $\alpha\varepsilon_p$ large. We also tighten control of p by increasing the Hill exponent n. In order to be close to the instability threshold where Mayer waves are generated, we need β (and thus also $\nu \sim \beta$) to be large. Fine tuning of the forcing amplitudes to mimic the amplitude of both forced and resonant Mayer waves can be done by altering δ and A_2. Figure 3 shows the results of simulations of the model using parameter values $\varepsilon_h = 3$, $\varepsilon_h = 1$, $\alpha = 15$, $\beta = 10$, $\gamma = 0.2$, $\mu = 0.18$, $\nu = 9.63$, $n = 8$, $A_1 = 0$, $\phi = \pi$, $\tau = 3$ s, for values $f_r = 6,\ 10,\ 20\ \mathrm{min}^{-1}$, in which respectively we also put $A_2 = 0.005,\ 0.005$ and 0.003, and $\delta = 0.85,\ 0.85$ and 0.8. The simulations show a reasonable resemblance to the heart rate, and also indicate a lack of response of blood pressure. Note that the parameters are very different from the default values.

4. Conclusion

The exercise of confronting a model with real data is an illuminating one. It appears possible to begin to approach

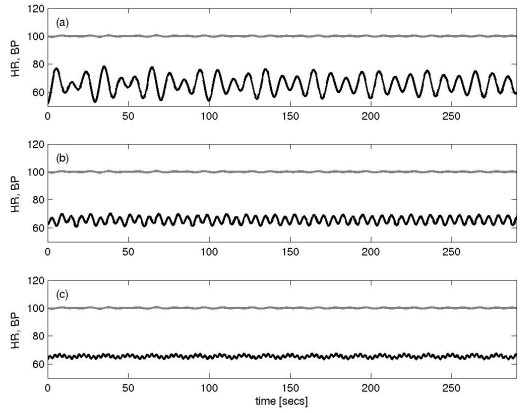

Figure 3. Blood pressure (top curves) and heart rate (lower curves) obtained by solving the model equations (1) for (a) $f_r = 6$ bpm, (b) $f_r = 10$ bpm and (c) $f_r = 20$ bpm. See text for model parameter values.

the calibration of a model with real physiological data, but although we think the agreement of the model with the data is reasonable, it requires stretching of the parameters beyond their acceptable boundaries. It is also the case that in such extreme parameter régimes, the model is liable to undergo large oscillations (which we have not shown) and to be very sensitive to the precise choice of parameter values. For model validation, this raises serious issues of compatibility with real physiological constraints, and provides a compelling challenge for the future.

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