Identification of Cardiovascular Baroreflex for Probing Homeostatic Stability

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Abstract

This paper presents a method to identify the cardiovascular baroreflex parameters that are useful for probing homeostatic stability. The work is built upon a physiology-based model of the closed-loop cardiovascular and baroreflex feedback system describing the regulation of heart rate and blood pressure. Parametric sensitivity analysis is conducted on the model to classify the model parameters into high-sensitivity, low-sensitivity, and invariant groups based on their relative impacts on the system outputs. The baroreflex identification is formulated as a nonlinear optimization problem in which only high-sensitivity model parameters are identified whereas low-sensitivity and invariant parameters are fixed at their typical values. The advantage of the method is its computational efficiency without significant compromise in performance and accuracy. The method was applied to the experimental data of 10 individuals in the MIMIC Database in the PhysioBank. The promising results suggest potential of the proposed method in probing homeostasis based on the estimates of sympathetic and parasympathetic tones.

1. Introduction

Homeostasis is the ability of a system to maintain its stability against varying external stimulation [1]. In the cardiovascular system, multiple short-term and long-term regulatory mechanisms have evolved to guarantee adequate blood perfusion to organs by compensating for diverse physiologic changes due to external stimulations [2–5].

Short-term blood pressure regulation (STBPR) is an important homeostatic mechanism for controlling blood pressure (BP) in the human body by maintaining BP at a desired set point using a set of sensors and effectors [6]. In STBPR, perturbations in BP which are sensed by the arterial baroreceptors, are processed by the autonomic nervous system (ANS) to send control commands to the effectors such as sympathetic and parasympathetic reflexes on heart rate (HR) and total peripheral resistance (TPR) to regulate HR and BP [2].

The characteristics of STBPR such as sympathetic and parasympathetic tones vary in time to maintain BP in an appropriate range [7, 8]. Besides, its response characteristics also play an important role in deducing the ANS activity. In particular, it is well known [9] that inappropriate baroreflex response to external stimulation such as stressful tasks may result in oscillation and even instability of HR and BP regulation in the closed-loop cardiovascular and baroreflex systems. Therefore, identification of STBPR characteristics is very useful in probing the stability and performance of homeostasis in the context of the cardiovascular system.

The objective of this study is to develop a computationally efficient method for characterizing STBPR-related parameters using routine measurements: HR, BP, and cardiac output (CO). The method is based on a physiology-based model of the closed-loop cardiovascular and baroreflex feedback systems. Instead of attempting to characterize overwhelming number of parameters in the model, this paper proposes to identify only high-sensitivity model parameters whereas low-sensitivity and invariant (constant within individual) parameters are fixed at their typical values. High-sensitivity parameters are identified by applying a parametric sensitivity analysis to the model. Representative results from idealized simulations and experimental studies are presented and discussed.

2. Methods

2.1. Model

A variety of cardiovascular and baroreflex models with different levels of complexity have been developed [7–9]. Based on our compromise between a model's physiologic transparency (i.e. consistency with brain-cardio physiology) and its simplicity for identification purposes, we used a physiology-based model proposed by Fowler et al. [10]. The model consists of two differential equations, each of

Table 1. Parameters in the Fowler's model.

Parameter	Definition	Value
C_a	arterial compliance	1.55 $mlmmHg^{-1}$
R_a^0	min arteriole resistance	0.6 $mmHgsml^{-1}$
ΔV	stroke volume	50 ml
H_0	intrinsic heart rate	100 min^{-1}
τ	sympathetic delay	3 s
V_H	vagal tone	1.17 s^{-2}
β_H	sympathetic control of HR	0.84 s^{-2}
α	sympathetic effect on R_a	1.3
γ	vagal damping of β_H	0.2
δ_H	relaxation time	1.7 s^{-1}

which describing the dynamics of HR and BP regulation:

$$\dot{H(t)} = \frac{\beta_H T_s}{1+\gamma\, T_p} - V_H T_p + \delta_H\big(H_0 - H(t)\big) \quad (1)$$

$$\dot{P(t)} = -\frac{P(t)}{R_a^0(1+\alpha T_s)C_a} + \frac{H(t)\Delta V}{C_a}, \quad (2)$$

where $T_s = g(p(t-\tau))$ is the sympathetic tone, and $T_p = 1 - g(p(t))$ is the parasympathetic tone with $g(p) = \frac{1}{1+p^4}$. The definitions of the parameters in (1)-(2) are summarized in Table 1 together with their typical values. It has been shown that the baroreflex characteristics are very well represented by a sigmoidal function [9]. Therefore, the Hill equation $g(P)$ in (1)-(2) was replaced by $1 - f(p)$ in an effort to better describe the behavior of sympathetic and parasympathetic tones. $f(p)$ is defined as follows:

$$f(p) = T_{min} + \frac{T_{max} - T_{min}}{1 + e^{-\alpha_{sp}(P - P_{sp})}} \qquad 50 \le P \le 200. \quad (3)$$

where T_{min} and T_{max} are minimum and maximum values of inter-beat interval (H^{-1}), P_{sp} the BP setpoint, and α_{sp} the saturation constant.

2.2. Parametric sensitivity analysis

Although relatively simple, the model (1)-(2) still includes 12 parameters, and it may not be easy to fully characterize the model based only on HR, BP, and CO measurements. Our strategy is to identify those parameters which have significant impact on the system response while fixing the remaining low-sensitivity parameters at their respective typical values. To this aim, a parametric sensitivity analysis was conducted on the model (1)-(2).

Since the system has two outputs (HR and BP), the parametric sensitivity has to be evaluated for both HR and BP. Besides, due to the nonlinearity of the model, traditional frequency-domain sensitivity functions for linear systems cannot be used. To resolve these difficulties, the following

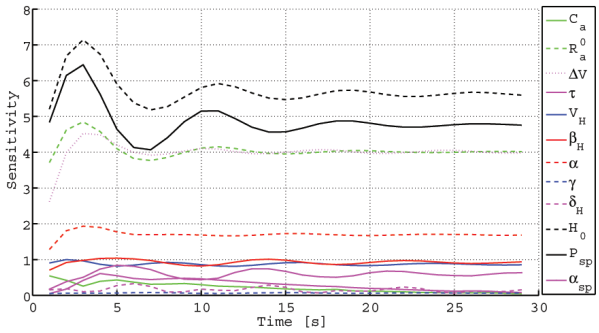


Figure 1. Typical Parametric Sensitivity function $S_j(t)$ for a normal individual.

time-domain sensitivity function was devised:

$$S(t_i, \mu_j) = \frac{S^H(t_i, \mu_j) + S^P(t_i, \mu_j)}{2} \quad (4)$$

where $S(t_i, \mu_j)$ is the total sensitivity at time t_i due to perturbation of parameter μ_j. Sensitivity functions for HR and BP are defined as:

$$S^H(t_i, \mu_j) = \frac{H(t_i, \mu_j) - H(t_i, \mu_{j,0})}{\mu_j - \mu_{j,0}} \times \frac{\mu_j}{H(t_i, \mu_j)} \quad (5)$$

$$S^P(t_i, \mu_j) = \frac{P(t_i, \mu_j) - P(t_i, \mu_{j,0})}{\mu_j - \mu_{j,0}} \times \frac{\mu_j}{P(t_i, \mu_j)} \quad (6)$$

where H and P denote HR and BP, respectively. These quantities represent the percent change in output at time t_i due to percent perturbation of parameter μ_j. To make the sensitivity metric robust against variation in the amplitude of parametric perturbations, (4) was further processed using +/- 50% (1 % increment) parametric perturbation to yield $S_j(t)$:

$$S_j(t) = \sqrt{\sum_{\mu_j = \frac{1}{2}\mu_{j,0}}^{\frac{3}{2}\mu_{j,0}} S^2\left(t_i, \mu_j\right)} \quad (7)$$

Fig. 1 shows an example of $S_j(t)$ for a normal individual with typical parameter values (Table 1). Finally, the metric S_j in (8) was obtained to aggregate different sensitivity values in time into a scalar metric, based on which the overall sensitivity of a particular parameter on the system response can be evaluated:

$$S_j = \sqrt{\sum_{\mu_j = \frac{1}{2}\mu_{j,0}}^{\frac{3}{2}\mu_{j,0}} \sum_{t_{initial}}^{t_{final}} S^2(t_i, \mu_j)} \quad (8)$$

The parameters were classified into high-sensitivity, low-sensitivity, and invariant groups based on S_j.

2.3. Idealized simulation

To assess the validity of our reduced-order identification strategy, a set of 500 Monte-Carlo identifications were run on a simulation model of (1)-(2). In each identification run, only the high-sensitivity parameters were identified with the low-sensitivity and invariant parameters fixed at their typical values, whereas all the parameters in the simulation model were randomly assigned in a neighborhood of their typical values to replicate realistic inter-subject variability. The identification was conducted using HR, BP and CO measurements. The time series sequences of HR, BP, and CO data were divided into 30s-long segments, each of which was used to identify the high-sensitivity parameters representative of the associated data segment using the MATLAB Optimization Toolbox. The sum of absolute normalized errors of HR and BP (9) was used as cost function for optimization:

$$J = \frac{E_P + E_H}{2}; \quad E_X = \sum_{t=0}^{n} \left| \frac{X_p(t) - X_m(t)}{X_m(t)} \right| \qquad (9)$$

where X_m and X_p are measured and predicted outputs ($X = H, P$). The distribution of the resulting 500 sets of parameter estimates was analyzed with respect to their true counterparts using the index (10) :

$$I_{\mu_j}^{Eval} = \frac{\mu_j^{Est}}{\mu_j^{Nom}}, \quad 1 \le j \le 12 \qquad (10)$$

2.4. Identification using experimental data

To assess the feasibility of the proposed method of cardiovascular baroreflex identification, it was applied to experimental data from 10 individuals. The data were taken from the MIMIC Database (PhysioBank), which include continuous recordings of HR, BP and CO at 1Hz. The low-sensitivity and invariant parameters were fixed at their typical values (Table 1). The parameters were identified in the same fashion as described for idealized simulations.

3. Results

The sensitivity metric S_j's of the model parameters are illustrated in Fig. 2, based on which the parameters were classified into 5 high-sensitivity, 5 low-sensitivity, and 2 invariant groups (Table 2). Fig. 3 shows the distribution of index (10) for the high-sensitivity parameters obtained from the 500 Monte-Carlo identification trials. Fig. 4 presents a representative result obtained from applying the method to the experimental data.

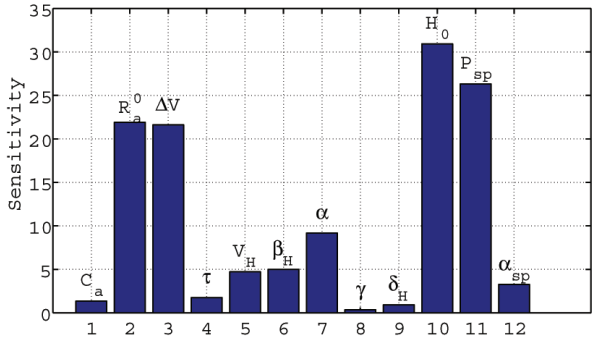


Figure 2. Typical parametric sensitivity function S_j for a normal individual.

Table 2. Sensitivity-based parameter classification.

High-sensitivity	Low-sensitivity	Invariant
P_{sp}	γ	H_0
ΔV	C_a	R_a^0
V_H	τ	
β_H	α_{sp}	
α	δ_H	

4. Discussion and conclusions

4.1. Sensitivity analysis

We classified P_{sp}, ΔV, V_H, β_H, and α as high-sensitivity parameters, and γ, C_a, τ, α_{sp} and δ_H as low-sensitivity parameters. H_0 and R_a^0 were classified into invariant parameters since they are assumed to be constant in an individual, although their sensitivity values are significant. Essentially, the fact that V_H and β_H are included in the high-sensitivity parameters supports our strategy of reduced-order identification for characterizing sympathetic and parasympathetic tones in STBPR.

4.2. Idealized simulation

The distributions of the high-sensitivity parameters are mostly centered at 1 (Fig.3), suggesting that accurate identification of high-sensitivity parameters is possible even if the low-sensitivity and invariant parameters are fixed at their typical values. The same 500 Monte-Carlo identification runs without CO yielded acceptable results, but not as good as Fig. 3. This suggests that the proposed method will benefit from non-invasive measurements of CO.

4.3. Experimental results

Due to unavailability of true parameters, our focus in interpreting the experimental results was on whether the identified parameters are reasonable based on a priori

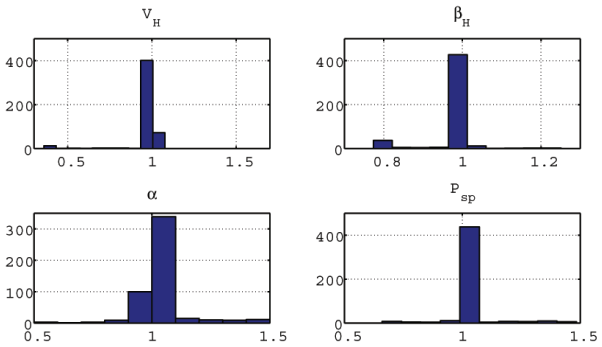
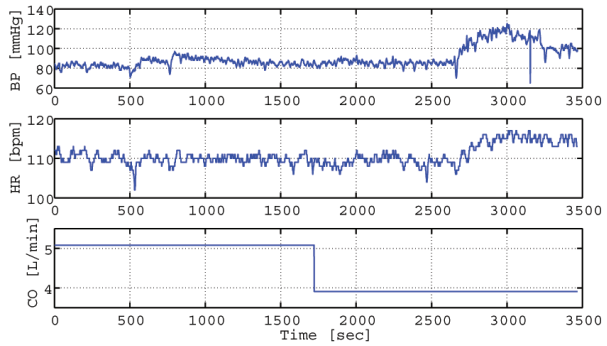
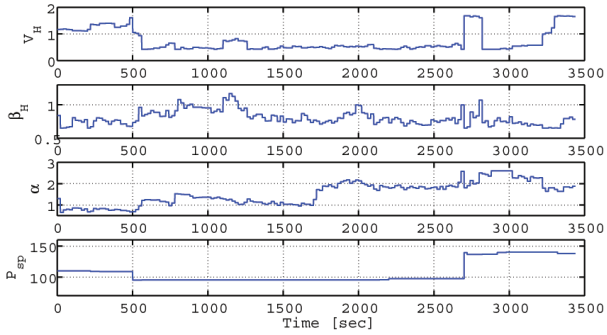


Figure 3. Distribution of identified parameters (normalized by true values).



(a)Measured BP, HR, and CO



(b)Estimated parameters variation versus time

Figure 4. A representative result from a MIMIC data.

knowledge on the behavior of the STBPRS. Consider Fig. 4. Fist, abrupt BP decrease at $t = 500s$ (Fig. 4(a)) results in increase of β_H and α as well as decrease of V_H (Fig. 4(b)), and BP is eventually recovered by increase of HR and TPR. Similar behavior can be observed at $t = 750s$. Besides, sudden drop of CO at $t = 1720s$ is compensated by increase of α, by virtue of which HR and BP are stably maintained. During $t = 2700 - 2850s$, V_H initially responds (Fig. 4(b)) to compensate for BP increase (Fig. 4(a)). However, the system decides to change its state to a new equilibrium at $t = 3250s$ and afterwards (Fig. 4(a); note that this change is beyond usual BP changes observed for $t < 2700s$), for which P_{sp} is increased and the associated re-adjustments of β_H, V_H and α follows (Fig.4(b)). Overall, the result in Fig. 4 suggests, to large extent, the physiologic relevance of the identified high-sensitivity parameters. Similar interpretation could be made for the remaining data to which the method was applied.

In conclusion, this paper presented the feasibility and potential of a computationally efficient method for characterizing STBPRS. Future work will be the application of this method for probing homeostatic stability.

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