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A Systematic Approach to Local Stability Analysis of Cardiovascular Baroreflex

Pedram Ataee, Jin-Oh Hahn, Guy A. Dumont, and W. Thomas Boyce

Abstract— **This paper presents a novel systematic approach to the stability analysis of the cardiovascular (CV) baroreflex. The proposed approach determines the equilibrium state and the system stability in its neighbourhood with computational efficiency, once the parameters of the CV baroreflex model are specified for an individual. We first propose a linearization-based analytical method for determining the equilibrium state of the CV baroreflex. We then present a Lyapunov-based systematic approach to analyze the system stability in the neighbourhood of the equilibrium state. The results of simulation experiments suggest that the performance of the proposed approach is encouraging: it was able to accurately determine the equilibrium state and quantify the stability of the CV baroreflex. The proposed approach is also powerful in exploring the relationship between the CV baroreflex stability and its parameter configurations.**

I. INTRODUCTION

In the cardiovascular (CV) baroreflex, the autonomic nervous system (ANS) regulates blood pressure and heart rate in the neighbourhood of a desired setpoint using a set of receptors and effectors [1], [2]. In this context, perturbations in blood pressure, such as orthostatic hypotension and exercise, are measured by the arterial baroreceptors and transmitted to the ANS. Then, the ANS acts against these perturbations by sending control commands to a set of effectors, including sympathetic and parasympathetic reflexes on heart rate and peripheral resistance, in order to maintain homeostasis [3]–[5].

For a group of patients such as individuals with treatment-resistant hypertension, it is crucial to maintain a certain degree of stability margin in their cardiovascular system [6]. To make it possible to actively control the stability of the CV system, it is important to predict the system's transition to instability in order to provide the patients with appropriate preventive interventions. In order to determine appropriate and effective interventions, it is desirable to identify the root cause of the instability by unveiling the influence of the CV baroreflex parameters on its stability.

The complex dynamic interactions among nonlinearities and delays in the CV baroreflex may cause unstable behaviour that is not relevant to its normal regulatory task [5]. For instance, it may incur an onset of oscillations in blood pressure and heart rate. Indeed, it has been shown that changes in the CV baroreflex parameters such as time delay in afferent and/or efferent pathways may result in limit cycle behaviour or even instability in the CV system [4].

In this paper, we present a novel systematic approach to the stability analysis of the CV baroreflex. A unique strength of the proposed approach is its capability to determine the equilibrium states and the system stability in their neighbourhood with computational efficiency. We first propose a linearization-based analytical method for determining the equilibrium states of the CV baroreflex. We then present a Lyapunov-based systematic approach to analyze the system stability in the neighbourhood of the equilibrium state. It is demonstrated that the proposed approach can determine the equilibrium state and quantify its stability very accurately. This approach is also very powerful in identifying the root cause of possible instability in the CV baroreflex, by virtue of its capability to characterize the relationship between the CV baroreflex stability and its parameter configurations.

II. ALGORITHM DEVELOPMENT

We first present a mathematical model of the CV baroreflex described by a set of coupled nonlinear delay-differential equations. Then a linearization-based analytical method to estimate an equilibrium state (heart rate and blood pressure) for a given CV baroreflex parameters (i.e. parameter configuration) is presented, followed by a novel Lyapunov-based approach to analyze the stability of the CV baroreflex in the neighbourhood of the estimated equilibrium state.

A. Mathematical Model

A large number of models have been developed to describe the physiological behaviour of the CV baroreflex [5], [7], [8]. Recently [9], we proposed an improved model of the closed-loop CV baroreflex based on the work of Fowler et al [8]. This model is a physiology-based model that is made up of a set of coupled differential equations having nonlinear and delayed dynamic interactions:

$$\dot{H}(t) = \beta_H T_s - V_H T_p + \delta_H \big[H_0 - H(t)\big] \quad (1a)$$

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

where H is heart rate, P is mean blood pressure, $T_s = 1-\sigma\big(P(t-\tau)\big)$ is the sympathetic tone, and $T_p = \sigma\big(P(t)\big)$ is the parasympathetic tone with

$$\sigma(P) = T_{min} + \frac{T_{max} - T_{min}}{1+e^{-\alpha_{sp}(P-P_{sp})}} \qquad 50 \leq P \leq 200. \quad (2)$$

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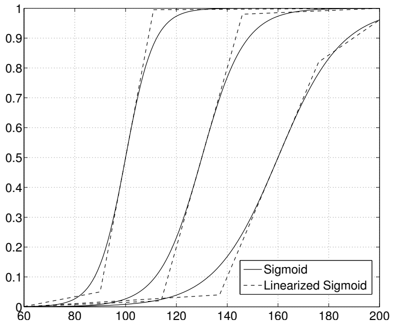


Fig. 1. Linearization-based approximation of sigmoid function: examples;

and τ is the time delay associated with sympathetic pathway. The definitions of the parameters, as well as a systematic method to identify these parameters, can be found in our previous work [9]. By substituting (2) into (1), it yields

$$\begin{aligned}\dot{H}(t) &= \beta_H\Big[1-\sigma\big(P(t-\tau)\big)\Big] - V_H\sigma\big(P(t)\big)\\ &+ \delta_H\big[H_0 - H(t)\big] \qquad (3a)\\ \dot{P}(t) &= -\frac{P(t)}{R_a^0\Big(1+\alpha\Big[1-\sigma\big(P(t-\tau)\big)\Big]\Big)C_a}\\ &+ \frac{H(t)\Delta V}{C_a} \qquad (3b)\end{aligned}$$

In this study, we focus on the impacts of the high-sensitivity parameters ($P_{sp}, V_H, \beta_H, \alpha$, and ΔV; see Ataee et al. [9]) on the stability of the CV baroreflex.

B. Estimation of Equilibrium States

$\dot{H}(t) = 0$ and $\dot{P}(t) = 0$ are satisfied at an equilibrium state. By putting $P(t) = P(t-\tau) = P_f$ and $H(t) = H_f$ into (3), the following coupled algebraic equations are obtained:

$$H_f = \frac{1}{\delta_H}\Big(\beta_H\big[1-\sigma(P_f)\big] - V_H\ \sigma(P_f) + \delta_H H_0\Big) \qquad (4a)$$

$$P_f = H_f \Delta V\ R_a^0\Big(1+\alpha\big[1-\sigma(P_f)\big]\Big) \qquad (4b)$$

Deriving closed-form solutions of the equilibrium state (H_f and P_f) from these nonlinear equations is not trivial. Employing a numerical optimization technique can be an easy remedy. However, it has two potential drawbacks: relatively expensive computational load and local minima. In order to avoid these problems, we propose a method to derive an analytic solution for the equilibrium states by approximating the sigmoid function (2) to a piece-wise linear function. As illustrated in the multiple examples in Fig. 1, the sigmoid function can be approximated to a combination of three linear functions, each of which describes the behaviour of the sigmoid function within the associated region, as follows:

$$\sigma(P) \simeq \begin{cases} k_1P + c_1; & 50 \le P \le P_1\\ k_2P + c_2; & P_1 \le P \le P_2\\ k_3P + c_3; & P_2 \le P \le 200\end{cases} \qquad (5)$$

Since the equilibrium state (P_f and H_f) is unknown a priori, the "candidate" equilibrium states are first estimated by using (4) and each of the three linear approximations in (5). Each obtained candidate P_f is then validated for consistency with its corresponding region which is pre-assumed to contain the calculated P_f. For each linearization (4) can be rewritten as follows:

$$H_f = \frac{1}{\delta_H}\Big(\beta_H + \delta_H H_0 - (kP_f + c)(V_H + \beta_H)\Big) \qquad (6a)$$

$$P_f = H_f\Delta V\ R_a^0\Big(1 + \alpha - \alpha(kP_f + c)\Big) \qquad (6b)$$

Denoting $A_1 = \beta_H + \delta_H H_0 - cV_H - c\beta_H$, $A_2 = k(V_H + \beta_H)$, $A_3 = 1 + \alpha - \alpha c$, $A_4 = \alpha k$, $A_5 = \Delta V\ R_a^0$, and $A_6 = \frac{1}{\delta_H}$; it yields:

$$H_f = A_6\Big(A_1 - A_2P_f\Big) \qquad (7a)$$

$$P_f = A_5\Big(A_3 - A_4P_f\Big)H_f \qquad (7b)$$

which can be reformulated into a quadratic equation of P_f, where $a = -A_4A_2A_5A_6$, $b = A_4A_1A_5A_6 + A_3A_2A_5A_6 + 1$, and $c = -A_1A_3A_5A_6$:

$$aP_f^2 + bP_f + c = 0, \qquad (8)$$

which finally results in the following closed-form solution for P_f:

$$P_{f_{1,2}} = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a} \qquad (9)$$

Once P_f is determined, H_f can be easily calculated as a function of P_f using (7a).

C. Stability Analysis

Depending on the CV baroreflex parameter values, the heart rate and blood pressure responses may converge to an equilibrium state (stable), attracted to a limit cycle or diverge (unstable). There is no simple method to analyze global stability of nonlinear dynamic systems with delays. However, the system stability in the neighbourhood of an equilibrium state can be analyzed relatively easily based on their linearized dynamics with respect to the equilibrium state [10].

In order to apply a linear system framework to the present analysis, the delayed state variable $P(t-\tau)$ in (3) needs to be approximated. For this purpose, a new state variable, X, is defined according to (10)-(14), using a first-order Pade approximation (11) in this derivation process:

$$\begin{aligned}P_\tau(t) &= P(t-\tau) && (10)\\ &\overset{\mathcal{L}}{\Rightarrow}\ P_\tau(s) = P(s)e^{-\tau s} = P(s)\frac{1-\frac{\tau}{2}s}{1+\frac{\tau}{2}s} && (11)\\ &\Rightarrow\ P_\tau(s) = P(s)(-1 + \frac{2}{1+\frac{\tau}{2}s}) && (12)\\ &\Rightarrow\ \underbrace{P_\tau(s) + P(s)}_{X(s)} = \frac{2P(s)}{1+\frac{\tau}{2}s} && (13)\\ &\overset{\mathcal{L}^{-1}}{\Rightarrow}\ X(t) = P(t-\tau) + P(t) && (14)\end{aligned}$$

According to (13), the dynamic equation of X is obtained as follows:

$$\dot{X}(t) = \frac{2}{\tau}\big[2P(t) - X(t)\big] \tag{15}$$

The delay-free realization of the CV baroreflex model (3) is given by (18)-(20) where $P(t-\tau)$ has been replaced by $X(t) - P(t)$.

Finally, taking partial derivatives of the delay-free realization at a given equilibrium state (H_f, P_f, X_f) yields the "Jacobian matrix" (J) or "State matrix" linearized at the given state as follows:

$$\boldsymbol{J} = \frac{\partial F}{\partial Z} \tag{16}$$

where $Z = [H\ P\ X]^T$, and $F = \{\boldsymbol{f_1}, \boldsymbol{f_2}, \boldsymbol{f_3}\}$. Based on the Lyapunov's Linearization Theorem [10], the CV baroreflex is stable at an equilibrium state if all the eigenvalues λ_i $(i = 1, 2, 3)$ of the Jacobian matrix have negative real parts, whereas it is unstable if at least one of its eigenvalues has a positive real part. To investigate this condition, M_s is defined as follows:

$$M_s = \max_{i=1,2,3}\big[real(\lambda_i)\big] \tag{17}$$

where $real(\cdot)$ denotes the real part of its argument, and λ_i is the i-th eigenvalue.

According to the Hartman-Grobman Theorem [11], stability properties of a nonlinear system in the vicinity of an isolated equilibrium can be determined by its linearization if the linearized system has no eigenvalues on the imaginary axis. The equilibrium state obtained by our analysis is isolated in the sense that it is uniquely determined for a given CV baroreflex parameter configuration. Therefore, M_s can be used as a quantitative metric to describe the CV baroreflex stability as long as λ_i $(i = 1, 2, 3)$ have negative real parts. Indeed, M_s can be used as a stability margin of the CV baroreflex which measures the distance between the dominant system pole and the imaginary axis. The system forfeits its stability margin, i.e. approaches to instability, as M_s become closer to imaginary axis.

The impact of a specific parameter configuration on the stability of the CV baroreflex can be examined by analyzing the value of M_s over a parameter space of interest. For instance, a 2-D contour plot can be used to graphically illustrate how the configuration of two CV baroreflex parameters relates to the system stability.

III. Method

To evaluate the proposed approach, we conducted a series of simulation experiments on the CV baroreflex models with different parameter configurations corresponding to a wide-ranging degree of CV baroreflex stability. For each parameter configuration, the equilibrium state was estimated using a very low-computational load method (9). The model was then linearized using (16), and the stability was determined by the Lyapunovs Linearization Theorem. The stability margin was quantified using (17).

To assess the proposed approach, we conducted numerical analysis on estimating equilibrium state as well as analyzing stability. For each parameter configuration, we used a numerical minimization technique [12] on (4) to find the equilibrium state, which was compared with the one estimated using the proposed approach. We also performed a numerical simulation with the original nonlinear model (3) to obtain time series sequences of $H(t)$ and $P(t)$ for different parameter configurations. The steady-state value was then compared with the estimated equilibrium state (P_f and H_f) using the proposed approach.

In order to demonstrate how the metric M_s from the proposed approach can be used to examine the effect of parameter configuration on the CV baroreflex stability, M_s was calculated for a wide range of P_{sp} versus the remaining high-sensitivity parameters. We perturbed every two parameters by +/- 50% of their typical values in 4% increments, and computed M_s in order to present in a filled 2-D contour plot with 25 contour levels afterward. The quantitative stability margin metric M_s of the CV baroreflex at each point of the 2-dimensional parameter space is mapped into a pixel-intensity level. In Fig. 3, higher pixel-intensity levels are related to lower stability margin, and vice versa. In addition, an empirical metric for stability margin was defined as the absolute amount of the fluctuation of $P(t)$ around its average value for the full nonlinear system. The fidelity of M_s was then tested against this numerical metric to demonstrate the accuracy of the proposed metric. It was observed that both metrics are highly consistent.

IV. Results and Discussion

The equilibrium states estimated by the proposed approach were highly consistent with those estimated by numerical minimization and nonlinear simulation (Fig. 2). Over 100 randomly generated CV baroreflex parameter configurations, bias and confidence interval obtained from the Bland-Altman analysis, with respect to nonlinear simulation, were only 1.2 mmHg and 4.3 mmHg, respectively. Fig. 2 shows that the proposed approach is very accurate in normal blood pressure range, whereas its accuracy deteriorates in hypertensive and hypotensive conditions.

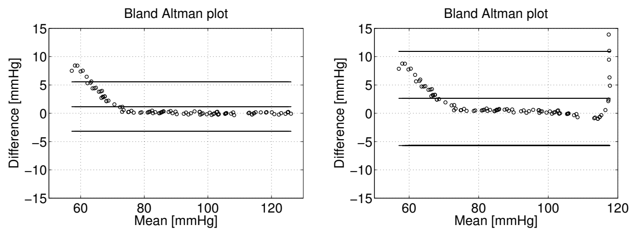
We also verified that the proposed approach was computationally efficient in calculating the profile of stability margin with respect to CV baroreflex parameter configurations compared with direct nonlinear simulation. The proposed approach (Fig. 3) not only was in good agreement with the nonlinear simulation (Fig. 4) but also was validated against some a priori knowledge of the CV physiology. For instance, Fig. 3 is consistent with the well-known fact that the stability margin of CV baroreflex decreases as the vagal (V_H) and sympathetic (β_H) tones on the heart rate decreases and increases, respectively. Overall, the results obtained strongly supported the feasibility and initial proof-of-concept of the proposed approach to CV baroreflex stability analysis.

The ability to determine the stability of the CV baroreflex for a given parameter configuration is very important for CV monitoring and treatment purposes. With our proposed

$$\dot{H}(t) = \boldsymbol{f_1}\big(H(t), P(t), X(t)\big) = \beta_H \Big[1 - \boldsymbol{\sigma}\big(X(t) - P(t)\big)\Big] - V_H\ \boldsymbol{\sigma}\big(P(t)\big) + \delta_H\big(H_0 - H(t)\big) \tag{18}$$

$$\dot{P}(t) = \boldsymbol{f_2}\big(H(t), P(t), X(t)\big) = -\frac{P(t)}{R_a^0\Big(1 + \alpha\big[1 - \boldsymbol{\sigma}(X(t) - P(t))\big]\Big)C_a} + \frac{H(t)\Delta V}{C_a} \tag{19}$$

$$\dot{X}(t) = \boldsymbol{f_3}\big(H(t), P(t), X(t)\big) = \frac{2}{\tau}\big[2P(t) - X(t)\big] \tag{20}$$



(a) (b)

Fig. 2. Comparison equilibrium blood pressures estimated using the proposed approach with (a) numerical minimization and (b) nonlinear simulation.

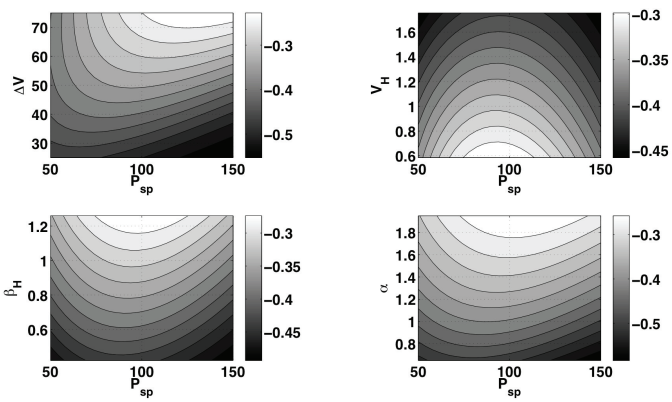


Fig. 3. Stability profiles of P_{sp} versus other high-sensitivity parameters using Lyapunov-based index (M_s)

approach, it is possible to probe the system stability by knowing that the CV baroreflex will loose its stability margin by approaching to the regions with higher pixel-intensity level in the parameter space shown in Fig. 3. For instance, it is observed that very large and small P_{sp} rather than moderate P_{sp} is advantageous for the CV baroreflex system to achieve greater stability margin.

V. CONCLUSIONS AND FUTURE WORKS

In this paper, we proposed a novel systematic approach to the stability analysis of the CV baroreflex. The initial proof-of-principle was performed using a series of simulation experiments, in which the approach was able to accurately estimate the equilibrium states and determine the stability margin. Future work will include the extension of the proposed approach to global stability analysis and the development of computationally efficient strategies for studying the CV baroreflex stability in a multi-dimensional parameter space.

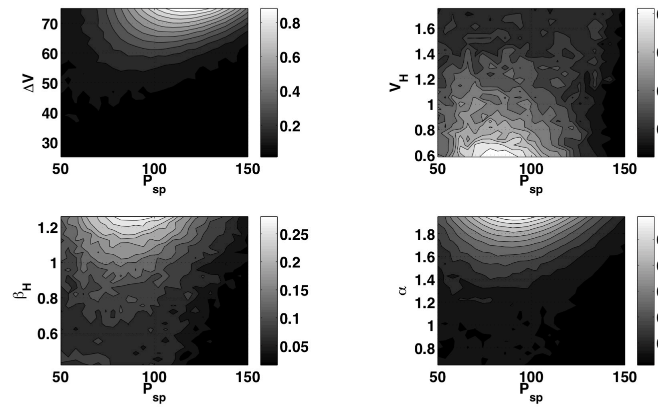


Fig. 4. Stability profiles of P_{sp} versus other high-sensitivity parameters using nonlinear simulation

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