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A model-based approach to stability analysis of autonomic-cardiac regulation

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ABSTRACT

This paper presents a model-based approach to analyze the stability of autonomic-cardiac regulation. In the proposed approach, a low-order lumped parameter model of autonomic-cardiac regulation is used to derive the system equilibria based on the measurements of heart rate and blood pressure, and then the stability margin associated with the equilibria is quantified via the Lyapunov's stability analysis method. A unique strength of the proposed approach is that it provides a quantitative measure of autonomic-cardiac stability via a computationally efficient analysis. Therefore, by integrating it with system identification techniques to derive autonomic-cardiac regulation model tuned to each individual, the proposed approach is able to assess subject-specific autonomic-cardiac stability. Indeed, our initial in-silico investigation showed that the proposed approach could estimate the system equilibria accurately, and the associated stability margin behaved consistently with widely accepted physiologic knowledge. The proposed approach may be useful in identifying physiological conditions that can lead to instability in autonomic-cardiac regulation, quantifying the margin of stability and distance to instability related to autonomic-cardiac regulation, and developing interventions to prevent autonomic-cardiac instability.

1. Introduction

The autonomic-cardiac regulation operates by the interaction between autonomic nervous system (ANS) and cardiovascular system (CVS). The ANS regulates involuntary organ functions to maintain the homeostasis in the CVS against physical (such as exercise and orthostatic hypotension) and psychological (such as anxiety and fear) disturbances [1–3]. Specifically, the ANS regulates blood pressure (BP) by manipulating cardio-respiratory parameters including heart rate (HR), cardiac contractility, systemic vascular resistance (SVR) and so on to deliver adequate oxygenated blood to organs in different physiologic conditions [4]. The autonomic-cardiac regulation is regarded as stable if BP converges to an equilibrium state when it is perturbed by a disturbance. On the other hand, it is regarded as unstable if BP starts to exhibit non-decaying or slowly decaying oscillations, or even diverges from its nominal state.

Existing literature suggests that certain changes in the characteristics of autonomic-cardiac regulation (such as an excessive increase in the transport delay associated with sensory afferent pathways) may lead to the onset of its instability (as manifested by unstable BP responses) [5,6]. For example, Cavalcanti et al. [5,7] demonstrated that perturbations in the autonomic-cardiac parameters affect the stability of the CVS. Ottesen [6] showed that the delay in the baroreflex feedback mechanism exerts a large influence on the stability property of the CVS. Ottesen [6] also illustrated that complex dynamic interactions between nonlinear behaviors and delays associated with the autonomic-cardiac regulation may cause instability. Besides, Abbiw-Jackson [8] reported that an increase in the gain of the baroreflex feedback responsible for the control of venous volume may incur the onset of oscillations in BP. As well, deBoer et al. [9] showed that the delay in the baroreflex feedback loop may initiate the Mayer waves (low-frequency oscillations in the mean arterial BP). Given multiple root causes possibly responsible for the instability in the autonomic-cardiac regulation, formal analysis of autonomic-cardiac stability may be beneficial in improving our understanding of the physiologic mechanisms underlying the autonomic-cardiac regulation and also in advancing diagnostic and therapeutic methods for the ANS-CVS disorders.

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It has been shown that mathematical analysis based on physics-based models can be a versatile tool in examining the autonomic-cardiac stability (such as its reliance on the autonomic-cardiac parameters). For example, it was revealed that the occurrence of the Mayer waves is closely related to the baroreflex parameters [6,7,10]. It was also indicated that the delays associated with the baroreflex feedback play a critical role in the stability of autonomic-cardiac regulation [6]. In another investigation based on a physics-based model, it was suggested that the stability of autonomic-cardiac regulation is affected by baroreflex parameters other than the delays (such as the gain of baroreflex loop) [8]. In addition to stability, such analysis was also used to better understand transient behaviors and characteristics of the autonomic-cardiac regulation. For example, it was illustrated that postural challenges applied to hypertensive elderly subjects resulted in slow convergence of baroreflex modulation to a steady state [11]. Further, an analysis based on a physics-based model was also used to investigate the reliability of the heart rate variability index in the study of autonomic regulatory mechanisms [12]. In addition to the physics-based models, subject-specific data-driven techniques (often resulting in black-box or empirical transfer function models) have also been widely used to analyze the ANS–CVS behaviors [13–15].

To the best of our knowledge, however, state-of-the-art model-based approaches to stability analysis of autonomic-cardiac regulation appear to suffer from limited capability in quantifying the stability margin, although some previous studies attempted to assess the qualitative impact of the changes in the autonomic-cardiac parameters on the stability margin associated with the ANS–CVS dynamics [6,16]. In addition, many existing approaches lack the ability to analyze autonomic-cardiac regulation under simultaneous perturbation of multiple autonomic-cardiac regulation parameters. Considering that it is crucial to maintain a certain degree of stability margin in the autonomic-cardiac regulation (for example, individuals with treatment-resistant hypertension [17]), it is desired that a model-based stability analysis method for autonomic-cardiac regulation be equipped with the capability to assess and quantify its stability margin under a wide range of physiologic conditions.

In our recent study, we investigated an optimization-based system identification approach to determine subject-specific autonomic-cardiac regulation based on a physiology-based ANS–CVS model [18]. In this study, we expand our previous study to develop a model-based subject-specific approach to analyze the stability of autonomic-cardiac regulation. In the proposed approach, a low-order lumped parameter model of autonomic-cardiac regulation is used to derive the system equilibria using the measurements of HR and BP, and the stability margin associated with the equilibria is quantified via the Lyapunov's stability analysis method. In this regard, the main contributions of this study are (1) an analytic method to derive the equilibria of autonomic-cardiac regulation, and (2) a systematic approach to analyze the stability of autonomic-cardiac regulation in the neighborhood of the equilibria. A unique strength of the proposed approach is that it provides a quantitative measure of autonomic-cardiac stability via a computationally efficient analysis. Thus, by integrating it with system identification techniques to derive autonomic-cardiac regulation model tuned to each individual (such as our previous work [18]), the proposed approach is able to assess subject-specific autonomic-cardiac stability. We examined the proposed approach in two ways. First, we compared the stability results obtained by the proposed approach with widely accepted physiologic knowledge. Second, we employed the proposed approach to explore model parameter configurations that can potentially incur instability in autonomic-cardiac regulation. We demonstrated that the proposed approach could determine the equilibria and quantify the stability margin associated with them reasonably well. In sum, the proposed approach can be a powerful tool to analyze autonomic-cardiac stability and the causes of instability due to its capability to derive stability margin associated with different autonomic-cardiac parameter configurations.

The rest of this paper is organized as follows. Section 2 describes the details of the autonomic-cardiac regulation model employed in this study and its delay-free realization that was employed to develop the proposed approach. In Section 3, we present the proposed approach to determine the autonomic-cardiac equilibria (HR and BP) and their stability margin. Sections 4 and 5 present and discuss the results obtained from the initial in-silico investigation of the proposed approach. This paper is concluded in Section 6 with future directions.

2. Autonomic-cardiac regulation model

In this section, the autonomic-cardiac regulation model used to develop the proposed approach to the analysis of autonomic-cardiac stability is presented. We adopted a physiology-based model developed in a previous work [18]. Then, we modified and improved the model to make it suitable to derive the proposed approach.

2.1. Physiology-based model: delayed differential equations

Numerous mathematical models with different levels of complexity have been proposed in the literature to represent the autonomic-cardiac regulation. Examples include a three-element Windkessel model of CVS with the baroreflex feedback represented as series connection of delayed linear dynamic system and a sigmoid nonlinear function [5], a simple nonlinear feedback control model that incorporates a CVS model represented by a delayed transfer function followed by an amplitude-limiting nonlinearity, and a linear proportional-derivative controller for the ANS [19], coupled nonlinear delayed differential equations describing HR and BP regulation mechanisms [20], and a relatively complex model consisting of hemodynamics as the Windkessel model and the Starling heart, baroreflex as a linear function with saturation, and autonomic control as multiple transfer functions [21].

To develop an analytic, rather than numerical, model-based stability analysis tool for autonomic-cardiac regulation that is reliable and computationally efficient, a low-order, physiology-based and high-fidelity model is desired. In this study, we adopted a model developed by Fowler et al. [20] as one such model (Fig. 1). Based on this model, HR and BP dynamics are described as follows:

$$\dot{H}(t) = \frac{\beta_H T_s}{1+\gamma T_p} - V_H T_p + \delta_H [H_0 - H(t)] \tag{1}$$

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

where H is the HR and P is the mean arterial BP. The definitions and nominal values of the parameters in (1) and (2) are summarized in Table 1. In this model, sympathetic and parasympathetic modulating functions produced by the baroreflex control mechanism are denoted by T_s and T_p, respectively. The sympathetic pathway involves a transport delay τ (i.e., $T_s = T_s(P(t-\tau))$, whereas the parasympathetic delay was assumed to be negligible (i.e., $T_p = T_p(P(t))$ [22]. In this study, we neglected the inhibitory impact of the parasympathetic reflex on the sympathetic reflex by setting $\gamma = 0$ in (1) and (2), since it is well known that its effect on the overall autonomic-cardiac regulation is generally small [6,20]. Then, the model (1) and (2) can be rewritten as follows:

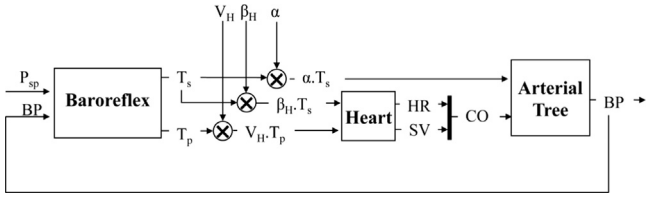

Fig. 1. The autonomic-cardiac regulation model.