2017 International Symposium on Nonlinear Theory and Its Applications,
NOLTA2017, Cancun, Mexico, December 4-7, 2017

Interaction between numerous oscillatory processes in the human cardiovascular system

V.I. Ponomarenko †, A.S. Karavaev †, Yu.A. Ishbulatov †, A.R. Kiselev ‡, M.D. Prokhorov †

† Saratov Branch of Kotel'nikov Institute of Radio Engineering and Electronics of Russian Academy of Sciences
38, Zelyonaya Street, Saratov, 410019, Russia
‡Saratov State Medical University n.a. V. I. Razumovsky
141, Chernyshevskaya Street, Saratov, 410028, Russia
Email: ponomarenkovi@gmail.com, karavaevas@gmail.com, ishbulatov95@mail.ru,
antonkis@list.ru, mdprokhorov@yandex.ru

Abstract– A model of human cardiovascular system is proposed which describes the main heart rhythm and the autonomic regulation of heart function and arterial blood pressure. The model takes into account the influence of respiration on these processes. It is shown that accounting of the autonomous regulation of mean arterial blood pressure allows to obtain the model signals whose statistical and spectral characteristics are qualitatively and quantitatively similar to those for experimental signals. The proposed model demonstrates the phenomenon of synchronization of the mean arterial pressure regulatory system by the signal of respiration with the varying frequency, which is observed in the physiological experiments.

1. Introduction

The modeling of the human cardiovascular system (CVS) is one of the current problems in physiology. Physiological systems are usually complex and nonstationary. They are characterized by a network structure with a number of interacting elements. Currently, many mathematical models of the CVS are known [1-4]. They describe the cardiovascular processes, but some of synchronization effects between slow rhythms are out of their scope. It is because a number of functional elements in the models has been subjected to simplification and linearization.

On the other hand, there are some *in vitro* studies in animals, where the autonomous mathematical model for the system of baroreflex regulation of mean arterial pressure (AP) in mammals has been proposed [5] in the form of a first order nonlinear delay differential equation. The authors have shown that this model can demonstrate stable self-sustained oscillations with a characteristic period of about 10 s in humans.

In the present paper we propose a model of the CVS taking into account the nonlinear properties of the system of mean AP baroreflex regulation. The features of the proposed model are investigated by comparing the results of statistical and spectral analysis of the model heart rate variability (HRV) with the experimental data and a model proposed in [4], which incorporates the systems of CVS regulation. Using the model and experimental signals we investigate the phase synchronization of 0.1 Hz rhythms of mean AP baroreflex regulation system by respiration with the linearly changing frequency.

2. Material and Methods

2.1. Model of cardiovascular system autonomic regulation

The proposed dynamical model includes four first-order differential equations:

$$\begin{cases} \dfrac{d\varphi(t)}{dt} = \dfrac{1}{T_0} f_s(t) f_p(t), & (1) \\ \dfrac{dp_{dia}(t)}{dt} = -\dfrac{p_{dia}(t)}{R(t)C}, & (2) \\ \varepsilon \dfrac{d\bar{p}(t)}{dt} = -\bar{p}(t) + f(\bar{p}(t-\theta)) + k_1 B(t), & (3) \\ \dfrac{dc(t)}{dt} = -\dfrac{c(t)}{\varepsilon_c} + k_2 v_s(t-\theta_c). & (4) \end{cases}$$

The structure of the model is shown in Fig. 1.

The operation of heart sinoatrial (SA) node is described by Eq. (1), where $\varphi(t)$ is the phase of the heartbeat, $T_0 = 0.55$ s is the period of denervated heart rate, and $f_s(t)$ and $f_p(t)$ are the influence of the sympathetic and parasympathetic divisions, respectively. In the absence of regulatory influences (denervation of the heart), $f_s = f_p = 1$ and SA node generates periodic pulses with the period T_0. Under the influence of autonomic nervous system, the frequency of the heart rate (HR) is modulated and variability appears.

The dynamics of blood pressure in the systolic phase is modeled as:

$$p_s(t) = D_{i-1} + S(t)\frac{(t-T_{i-1})}{T_s}\exp\left(1-\frac{(t-T_{i-1})}{T_s}\right) + k_3\bar{p}(t), \quad (5)$$

where D_{i-1} is the magnitude of diastolic pressure at the end of the previous cardiac cycle, T_{i-1} is the duration of the previous cardiac cycle, $\bar{p}(t)$ is mean AP, and $S(t)$ is the cardiac contractility [3, 4] expressed as follows:

$$S(t) = S'(t) + (S_a - S'(t))\frac{S'(t)^{n_1}}{S_a^{n_1} + S'(t)^{n_1}}, \qquad (6)$$

where $S'(t) = S_0 + k_4 c(t) + k_5 T_{i-1}$ depends on the concentration of sympathetic agent noradrenalin c (4) in the myocardium [4].

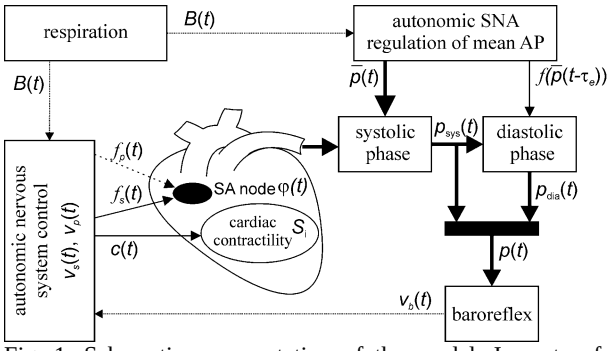

Fig. 1. Schematic representation of the model. Impacts of vagus, sympathetic nervous activity (SNA) and AP are shown by dashed, solid, and bold lines, respectively. Other impacts are shown by dots. The activities of sinoatrial (SA) node and the system of mean AP regulation are modeled too.

In accordance with [3], $p_s(t)$ increases rapidly to a maximum value $p_s^{\max}$, which is reached after a fixed time $T_s = 0.125$ s from the moment of the current heart beat i used as a subscript of variables in the formulas. Blood pressure in the diastolic phase $p_d(t)$ relaxes from the maximal value achieved in systole phase $p_{d0}(t_i + T_s) = p_s^{\max}$ until the next heartbeat. This relaxation is described by the Windkessel effect caused by inertial properties of blood vessels (2). In Eq. (2), C is a constant that determines the elasticity of the aorta and $R(t)$ is the peripheral vascular resistance, which depends on the mechanical properties of blood vessels R_0 and the arterial vasomotor tone as follows:

$$R(t) = R_0(1 + k_6 f(\bar{p}(t - \theta_e)), \qquad (7)$$

where $R_0 C = 1.5$ s, $\theta_e = 3.24$ s is the time lag of the signal propagation in the efferent nerves in the loop of baroreflex regulation of vasomotor tone of arteries, $\bar{p}(t)$ is the mean AP, and f is the nonlinear transfer function of sympathetic nucleus of central nervous system.

The AP $p(t)$ is the joining of the solutions of Eqs. (2) and (5) in the interval of current i-th cardiac cycle:

$$\begin{cases} p(t) = p_s(t), t_i \le t < t_i + T_s, & (8) \\ p(t) = p_d(t), t_i + T_s \le t < t_{i+1}. & (9) \end{cases}$$

To simulate the system of mean AP baroreflex regulation we have rejected the linear conception developed in [3, 4] and in accordance with [5] used Eq. (3), where $\theta = \theta_a + \theta_e = 3.6$ s is the total time of the afferent ($\theta_a = 0.36$ s) and efferent (θ_e) delays in the loop of baroreflex regulation of arterial vessels tone, $\varepsilon = 2.0$ s is the time constant of peripheral vessels, and $B(t)$ is the respiratory signal introduced in the equation according to [6].

The nonlinear function f approximates the experimental transfer function of the nuclei of the central nervous system, governing the regulation circuit of the vasomotor tone. This function has the form:

$$f(x(t-\theta)) = G\left(\frac{r}{1+e^{-\beta(x(t-\theta)-a)}} - \frac{r}{1+e^{\beta(x(t-\theta)-a)}} + b\right) \qquad (10)$$

Taking into account the nonlinear properties of the system, the system in Eq. (3) is described as a nonlinear oscillator with time-delayed feedback, showing stable self-sustained oscillations with the frequency of about 0.1 Hz. Blood pressure is perceived by baroreceptors, and their response $v_b(t)$ is determined by AP value and its derivative according to the experimental results obtained in [7]:

$$v_b(t) = k_7(p(t) - p_0) + k_8 \frac{dp(t)}{dt} + \xi_1(t). \qquad (11)$$

The nuclei of autonomic nervous system process the signals at the output of baroreceptors, providing activation of the sympathetic:

$$v_s(t) = \max\left(0, v_{s0} - k_9 v_b(t) + k_{10}\left|B(t)\right|\right), \qquad (12)$$

and parasympathetic divisions of the autonomic nervous system [3, 4]:

$$v_p(t) = \max\left(0, v_{p0} + k_{11} v_b(t) + k_{12}\left|B(t)\right| + \xi_2(t)\right). \qquad (13)$$

The activity of autonomic nervous system is modulated by respiration $B(t)$ and is influenced by the normally distributed pink noise $\xi_2(t)$, which, as shown in [8], has the central origin. The standard deviation of $\xi_2(t)$ is 0.1.

The effects of sympathetic and parasympathetic loops of baroreflex regulation on HR are expressed by the introduction of the sympathetic influence factor:

$$f_s(t) = 1 + k_{13}\left(c(t) + (c_a - c(t))\frac{c^{n_2}}{c_a^{n_2} + c^{n_2}}\right) \qquad (14)$$

and the factor of parasympathetic influence [3, 4]:

$$f_p(t) = 1 + k_{14}\left(\begin{array}{l} v_p(t-\theta_p) + \\ (v_{pa} - v_p(t-\theta_p))\dfrac{v_p^{n_3}(t-\theta_p)}{v_{pa}^{n_3} + v_p{}^2(t-\theta_p)} \end{array}\right) F(\varphi(t)). \qquad (15)$$

The sympathetic nervous system affects HR through a change in the concentration of noradrenalin (4). Its production is a relatively slow process (the characteristic relaxation time is $\varepsilon_c = 2.0$ s) and is taken into account in Eq. (4) by the delay time $\theta_c = 1.65$ s. The change in concentration of the parasympathetic system agent (acetylcholine) is much faster. This process is directly taken into account in calculating $f_p(t)$ by the delay $\theta_c = 0.5$ s. The so-called curve of phase efficiency:

$$F(\varphi) = \varphi^{1.3}(\varphi - 0.45)\frac{(1-\varphi)^3}{0.008 + (1-\varphi)^3} \qquad (16)$$

allows one to consider the impact of cardiac cycle phase on the operation of parasympathetic part of autonomic nervous system [3].

3. Results

3.1. Modeling of healthy subjects

Many studies [9-11] note that the spectral and statistical analysis of HRV helps to effectively evaluate the functional state of CVS regulatory systems. The calculation of indices characterizing the average oscillation power in different frequency bands, as well as the statistical characteristics of HRV are widely used in physiological research and medical diagnostics.

A typical Fourier power spectrum of HRV signal for a healthy subject estimated by Welch method for a 10-minute experimental realization is presented in Fig. 2 by a bold line. It was compared with the power spectra of HRV signals generated by Kottani's model [4] (hereafter, for short, we will denote it as "Model K") and our model (denoted as "Model M").

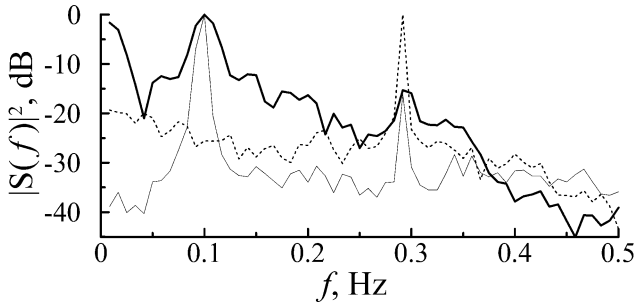

Fig. 2. Power spectra of the experimental HRV of a healthy subject (bold line) and HRV simulated by the Model M (thin solid line) and Model K (dotted line).

Since the self-sustained oscillations in the loop of arterial vessel tone regulation have been taken into account in Model M, we have been able to tune the power of spectral components and to align them accurately with the experimental results. Compared to Model M, the component at a frequency of about 0.1 Hz, which reflects the activity of the sympathetic part of autonomic regulation of the CVS, is not expressed in the HRV spectrum of Model K with the original parameters corresponding to healthy subjects at rest.

3.3. Diagnostics of phase synchronization

Previously, we have experimentally shown that the regulatory systems with the basic frequency of about 0.1 Hz exhibit complex regimes of collective dynamics and can demonstrate the phase and frequency synchronization between themselves [12, 13].

Also it was shown that the systems of regulation are synchronized by the signal of respiration with linear chirp signal. Such behavior is typical for self-sustained oscillators of any origin. We examine how the models behave under the influence of respiration with linear chirp signal.

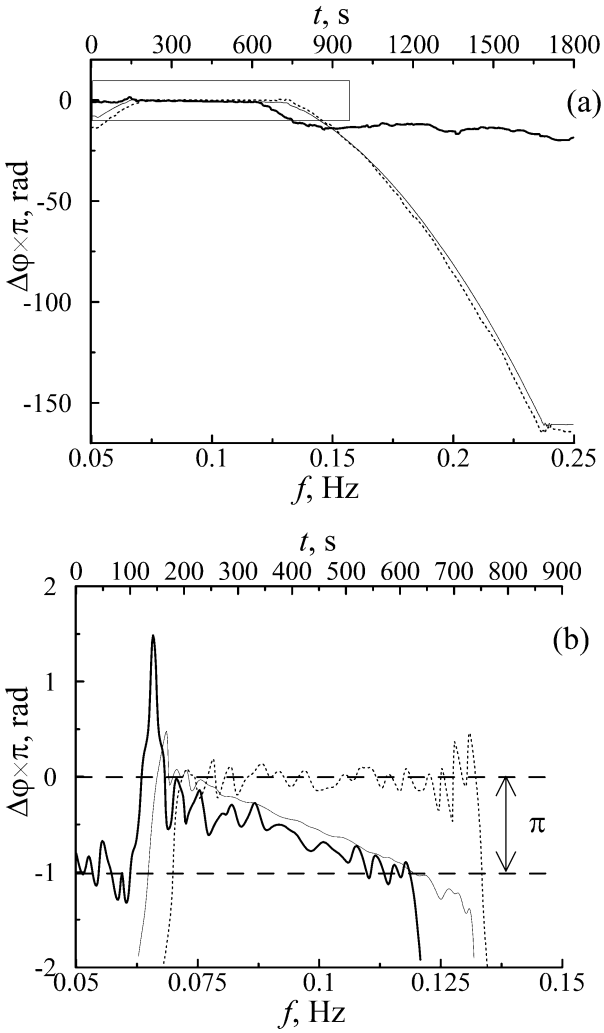

Fig. 3. (a) Differences of instantaneous phases of 0.1 Hz oscillations in the system of mean AP regulation and the driving signal $B(t)$ with the linearly increasing frequency f_r. Grey line – Model M, dot line – Model K, black line – experimental data [13], (b) Enlarged fragment of figure (a).

As it can be seen from Fig. 3, the linear section of the phase difference is varied by π value indicating the presence of phase locking for the experimental signals and Model M signals. Moreover, the intervals of phase locking for Model M and experimental signals are similar.

The phase difference for Model K does not show a linear variation by π value, and as a result, the phase synchronization is not observed in this model. Only the effect of mixing is observed in Model K.

4. Conclusion

The development of mathematical models of biological systems is an important step in studying the living systems. Such models can provide fundamentally important information on the system structure and interaction between its elements, they can describe biological systems both quantitatively and qualitatively. They allow one to investigate the system behavior in time and under parameter variation and predict the effect of physiological tests and medical drugs on the system.

Modeling complex multicomponent biological systems generally requires the use of cumbersome high-dimensional equations. Therefore, model reduction is often resorted to in order to simplify the task. In particular, it is limited to linear representations of the structure of some functional system elements. However, taking into account the nonlinear properties of the simulated systems in accordance with the relevant physiological representation enables us to qualitatively change the model behavior and quantitatively describe the effects observed in the experiments. Moreover, a number of these effects cannot be modeled within linear approximations.

Here we have examined the mathematical Model K proposed in [4], because currently this model can give the most detailed description of the CVS activity regulation. However, the linear description of the mean AP regulation loop used in this model limits its capabilities.

We have proposed a mathematical model with the structure close to that of Model K. However, the qualitative distinction of our model from Model K is in employing nonlinear self-sustained time-delay system for simulation of mean AP baroreflex regulation similarly to the model proposed in [5] on the basis of *in vitro* experiments on animals. The introduction of the autonomous self-sustained element in the proposed model has greatly improved simulation of the spectral properties of the experimental data and statistical indices characterizing HRV properties. Moreover, the proposed model qualitatively and quantitatively simulates the effect of phase synchronization of the dynamics of the loop of mean AP baroreflex regulation by the signal of respiration with linearly changing frequency. This was impossible to achieve with the help of Model K, since its elements are linear.

We believe that our results support the hypothesis of a high autonomy of baroreflex regulation loop of mean AP. The obtained results demonstrate the importance of considering the nonlinear properties of the regulatory systems in their mathematical modelling and point to the fundamental significance of nonlinearity in the operation of physiological systems.

Acknowledgments

This work was supported by the Russian Science Foundation, Grant No. 14-12-00291.

References

[1] J. T. Ottesen, “Modelling the dynamical baroreflex-feedback control,” *Mathematical and Computer Modelling*, vol.31, pp.167-173, 2000.

[2] A. Silvani, E. Magosso, S. Bastianini, P. Lenzi & M. Ursino, “Mathematical modeling of cardiovascular coupling: Central autonomic commands and baroreflex control,” *Auton. Neurosci*., vol. 162, pp. 66-71, 2011.

[3] H. Seidel, H. Herzel, “Bifurcations in a nonlinear model of the baroreceptor-cardiac reflex,” *Physica D*, vol.115, pp.145-160, 1998.

[4] K. Kotani, Z. R. Struzik, K. Takamasu, H. E. Stanley, Y. Yamamoto, “Model for complex heart rate dynamics in health and disease,” *Phys. Rev. E*, vol.72, 041904, 2005.

[5] J. V. Ringwood, S. C. Malpas, “Slow oscillations in blood pressure via a nonlinear feedback model,” *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, vol.280, pp. R1105-R1115, 2001.

[6] D. E. Burgess, J. C. Hundley, D. R. Brown, S.-G. Li & D. C. Randal, “First-order differential-delay equation for the baroreflex predicts the 0.4-Hz blood pressure rhythm in rats,” *American Journal of Physiology*, vol.273, pp. R1878–R1884, 1997.

[7] H. R. Warner, “The frequency-dependent nature of blood pressure regulation by the carotid sinus studied with an electric analog,” *Circulation*, vol.6, pp.35-40, 1958.

[8] A. Bunde, S. Havlin, J. W. Kantelhardt, T. Penzel, J. H. Peter, K. Voigt, “Correlated and uncorrelated regions in heart-rate fluctuations during sleep,” *Phys. Rev. Let.*, vol.85, pp.3736-3739, 2000.

[9] “Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology”, *Circulation*, vol.93, pp.1043-1065, 1996.

[10] G. G. Berntson, J. T. Bigger, D. L. Eckberg, P. Grossman, P. G. Kaufmann, M. Malik, H. M. Nagaraja, S. W. Porges, J. P. Saul, P. H. Stone, M. W. Van der Molen “Heart rate variability: origins, methods, and interpretive caveats,” *Psychophysiology*, vol.34, pp.623-648, 1997.

[11] M. L. Appel, R. D. Berger, J. P. Saul, J. P. Smith, R. J. Cohen, “Beat to beat variability in cardiovascular variables: noise or music?” *J. Am. Coll. Cardiol*, vol.14, pp.1139-1148, 1989.

[12] A. S. Karavaev, M. D. Prokhorov, V. I. Ponomarenko, A. R. Kiselev, V. I. Gridnev, E. I. Ruban & B. P. Bezruchko, “Synchronization of low-frequency oscillations in the human cardiovascular system,” *Chaos*, vol.19, 033112, 2009.

[13] A. E. Hramov, A. A. Koronovsky, V. I. Ponomarenko, M. D. Prokhorov, “Detecting synchronization of self-sustained oscillators by external driving with varying frequency,” *Phys. Rev. E*, vol.73, 026208, 2006.