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A Model of Human Cardiovascular System Containing a Loop for the Autonomic Control of Mean Blood Pressure

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Abstract—We propose a model for the human cardiovascular system that describes the cardiac cycle, the autonomic regulation of heart and vessels, the baroreflex, and the formation of blood pressure. The model also allows for the influence of respiration on these processes. It has been found that an allowance for nonlinearity and insertion of a loop for the autonomic control of mean blood pressure (having the form of self-oscillating time-delay system) enables obtaining model signals with statistical and spectral characteristics that are qualitatively and quantitatively similar to those for experimental signals. The model reproduces the phenomenon of synchronization of the loop for mean blood pressure regulation with a basic frequency of approximately 10 s by the signal of respiration.

Keywords: cardiovascular system, baroreflex, mathematical model, blood pressure
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The studies of complex multicomponent systems of the real world are usually accompanied by a consistent improvement of the model representations used for the consideration of the object. Models start from less complex block diagrams, which describe the behavior of the real system only on a qualitative level, with the acquiring of knowledge the models develop, become more complex, formalized in the form of systems of equations, claiming not only a qualitative but also quantitative description of the observed phenomena. Quantitative estimations obtained using such models often force to reconsider initial quality presentations and schemes. The modeling in physiology, biology, and medicine, where possibilities of invasive experimental research and the range of permissible effects on the object of research are fundamentally limited, is of particular interest. One of the important tasks is stimulation of the human cardiovascular system (CVS).

Systems of biological nature are complex and nonsteady. They are characterized by a network structure, including a number of interacting elements. Therefore, at this time, only a few mathematical models of the CVS are known that take into account the operation of the loop for autonomic control [1–4]. However, the need for a simulation of a large number of interacting functional elements in these studies lead to a simplification and linearization of the model representations of such elements. In particular, the system of baroreflex of blood pressure in all these studies was modeled by a first order differential-delay equation. Such models of the blood pressure (BP) cannot demonstrate stable self-oscillation. Only forced-self-oscillation regimes under action of noises and due to the effect of other elements of the system affecting them are possible in such models [5].

However, based on the results of real experiments, a number of researches pointed out the autonomous and self-oscillating nature of baroreflex BP control systems [6–9]. In our experimental studies, with the synchronization of rhythms of regulation systems by forced breathing, similar conclusions were drawn [10–14]. Moreover, Ringwood and Malpas [15] proposed a linear feedback model of baroreflex comprising a delay term based on the results of in vitro animal studies. In this study, it was shown that this system in human can operate independently and demonstrates stable self-oscillations with a characteristic period of about 10 s.

In this study, we propose a model for the CVS that takes into account nonlinear properties of the barore-

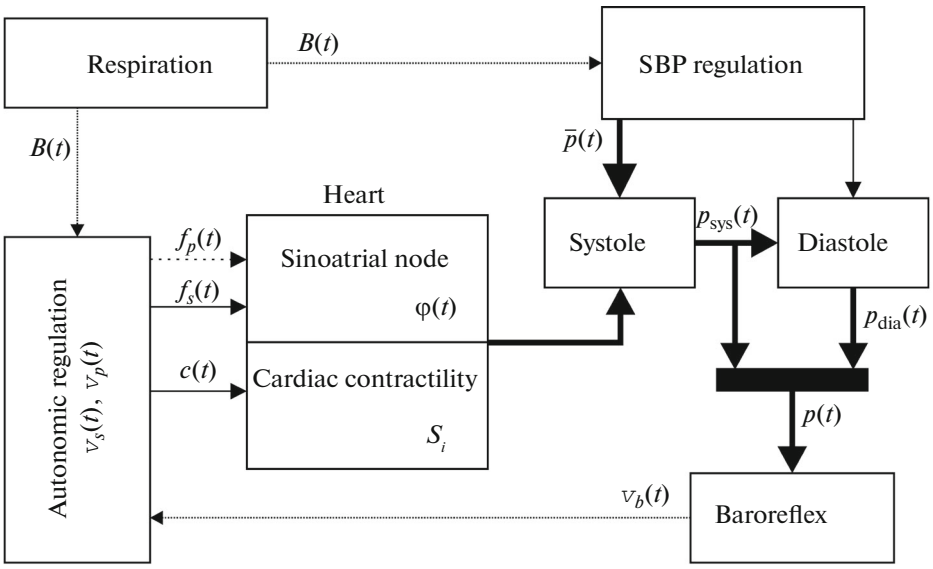

Fig. 1. Block diagram of the proposed model. The effect of vagus is shown by dashed line, sympathetic activity is shown by solid line, BP is shown by bold line, and other effects are shown by dotted line.

flex system. The functionality of the model was studied by comparison of the results of the statistical and spectral analysis of heart rate variability (HRV) with the experimental data, as well as by the implementations of known model proposed by Kotani et al. [4], which is characterized by the most detailed records of features of dynamics of the regulation of CVS. The phase synchronization of 0.1 Hz signals of baroreflex system by the breathing at a linearly varying frequency was investigated by experiments and based on signals of compared models.

MODEL OF THE AUTONOMIC CONTROL OF CARDIOVASCULAR SYSTEM

The proposed mathematical model describes the following processes: the heart rate, the effect of divisions of the autonomic nervous system on heart rate (HR) and their strength, baroreflex, the formation of blood pressure during systole and diastole phase, taking into account the effect of the respiration on these processes. The structure of the model is shown in Fig. 1.

The proposed dynamic model includes four first-order differential equations, some of which have delays:

$$\begin{cases} \dfrac{d\varphi(t)}{dt} = \dfrac{1}{T_0} f_s(t) f_p(t), & (1) \\ \dfrac{dp_{\text{dia}}(t)}{dt} = -\dfrac{p_{\text{dia}}(t)}{R(t)C}, & (2) \\ \varepsilon \dfrac{d\bar{p}(t)}{dt} = -\bar{p}(t) + f(\bar{p}(t-\tau)) + k_m^r B(t), & (3) \\ \dfrac{dc(t)}{dt} = -\dfrac{c(t)}{\tau_c} + k_c^s v_s(t-\theta_c). & (4) \end{cases}$$

The operation of the sinoatrial node is described by Eq. (1) of the "*integrate and fire*" type [16]. In Eq. (1): $\varphi(t)$ is the cardiac contraction phase, $T_0 = 0.55$ s is the contraction period of denervated heart, $f_s(t)$ and $f_p(t)$ are the effecst of the sympathetic and parasympathetic divisions, respectively. In the absence of regulatory effects (at denervation of the heart) $f_s = f_p = 1$ and the sinoatrial node generates periodic impulses with the period of T_0. In the presence of the impact of the autonomic nervous system, the frequency of heart rate is modulated and variability occurs. $p_{\text{dia}}(t)$ is the pressure during diastole phase of cardiac contraction, $R(t)$ is the peripheral vascular resistance, C is the aortic elasticity, $\bar{p}(t)$ is the mean AP, $c(t)$ is the myocardial noradrenaline concentration, $v_s(t)$ is the activity of sympathetic regulation, θ_c is the time delay caused by the time of cardiac response to changes in the myocardial noradrenaline concentration.

The dynamics of BP during the systole phase (designated as $p_{\text{sys}}(t)$):

$$p_{\text{sys}}(t) = D_{i-1} + S(t)\frac{(t - T_{i-1})}{T_{\text{sys}}} \times \exp\left(1 - \frac{(t - T_{i-1})}{T_{\text{sys}}}\right) + k_p^M \bar{p}(t) \quad (5)$$

affected by D_{i-1}, diastolic pressure at the end of the previous cardiac cycle; T_{i-1}, the length of the previous cardiac cycle; $T_{\text{sys}} = 0.125$ s, the fixed duration of systole; $\bar{p}(t)$, mean blood pressure; and cardiac contractility, $S(t)$ [3, 4]. $S(t)$ is expressed as follows:

$$S(t) = S'(t) + (\hat{S} - S'(t))\frac{S'(t)^{n_c}}{\hat{S}^{n_c} + S'(t)^{n_c}}, \quad (6)$$

where $S'(t) = S_0 + k_S^c c(t) + k_S^t T_{i-1}$ depends on the concentration of sympathetic agent noradrenaline in the myocardium, $c(t)$ (Eq. (4)); n_c determines the concentration of noradrenaline, the exceedance of which does not lead to a further increase in the intensity of cardiac contractions [4].

According to the study [3], $p_{\text{sys}}(t)$ fast increases up to the maximum $p_{\text{sys}}^{\max}$, which is achieved a fixed time $T_{\text{sys}} = 0.125$ s, after the current cardiac contraction i (in the equation, a subscript index).

Blood pressure in the diastole phase $p_{\text{dia}}(t)$ relaxes from the maximum reached in the systole phase $p_{\text{dia}}^0(t_i + T_{\text{sys}}) = p_{\text{sys}}^{\max}$, to the time of the next cardiac contraction. This relaxation is described by Windkessel's effect, caused by inertial properties of arterial vessels (Eq. (2)). In Eq. (2), C is a constant that determines the elasticity of the aorta, $R(t)$ is the peripheral resistance depending on the mechanical properties of blood vessels (R_0) and vasomotor tone as follows:

$$R(t) = R_0(1 + k_v^M f(\overline{p}(t - \tau_e)), \quad (7)$$

where R_0 is the vascular resistance at rest, C is the aortic elasticity, and $R_0C = 1.5$ s, $\tau_e = 3.24$ s is the time delay in the propagation of the signal via the efferent nerves in the loop of baroreflex control of vasomotor tone, $\overline{p}(t)$ is the mean blood pressure (MAP), f is the nonlinear transfer characteristic of sympathetic nuclei of the central nervous system.

BP, denoted by $p(t)$, sewing together the solution of the Eqs. (2) and (5) for the interval of the current ith cardiac cycle:

$$\begin{cases} p(t) = p_{\text{sys}}(t),\ t_i \le t < t_i + T_{\text{sys}}, \\ p(t) = p_{\text{dia}}(t),\ t_i + T_{\text{sys}} \le t < t_{i+1}. \end{cases} \quad (8)$$

For the simulation of the baroreflex system, we abandoned the linear representations, developed by Seidel et al. [3], Kotani et al. [4], and according to Ringwood and Malpas [15] used the equation of the form (3). Here, $\tau = \tau_a + \tau_e = 3.6$ s is the total time of afferent ($\tau_a = 0.36$ s) and efferent (τ_e) delays in the loop for the baroreflex control of arterial vascular tone, $\varepsilon = 2.0$ s is the inertia of the peripheral vessels, $B(t)$ is the respiration signal introduced in the equation according to Burgess et al. [5]. In experiments with a fixed respiration $B(t)$ was chosen in the form of harmonic signal:

$$B(t) = \sin(2\pi f_r t), \quad (9)$$

where $f_r = 0.29$ Hz is the respiration rate. In experiments with linearly increasing frequency, the harmonic signal is linearly modulated in frequency was used as $B(t)$.

The nonlinear function f approximates the experimental transfer function of the nuclei of the central nervous system, controlling the operation of the loop for the baroreflex control of vascular tone.

The function is as follows:

$$f(x(t - \tau) = G\left(\frac{r^*}{1 + e^{-\beta(x(t-\tau)-x^*)}} - \frac{r^*}{1 + e^{\beta(x(t-\tau)-x^*)}} + y^*\right). \quad (10)$$

The principal provision for the nonlinear properties of the system leads to the fact that the Eq. (3) is an oscillator with delayed feedback, showing stable self-oscillations with a frequency of about 0.1 Hz, even in autonomous mode.

Blood pressure is perceived by baroreceptors. Their response $v_b(t)$ is determined by the blood pressure and its derivative, in accordance with the experimental results, obtained by Warner [17]:

$$v_b(t) = k_1(p(t) - p_0) + k_2\frac{dp(t)}{dt}, \quad (11)$$

where p_0 is the the minimal BP to which baroreceptors react. Nuclei of autonomic nervous system process signals at the output of baroreceptors, providing the activation of the sympathetic and parasympathetic divisions of the autonomic nervous system [3, 4] (Eqs. (12) and (13), respectively).

$$v_s(t) = \max\left(0, v_S^{(0)} - k_S^b v_b(t) + k_S^r |B(t)|\right) \quad (12)$$

$$v_p(t) = \max\left(0, v_p^{(0)} + v_b(t) + k_p^r |B(t)| + \xi(t)\right) \quad (13)$$

$v_s^{(0)}$ and $v_p^{(0)}$ are the activities of the sympathetic and parasympathetic systems at rest. The activity of autonomic nervous system is modulated by respiration $B(t)$ and affected by the dynamic of normally distributed pink noise $\xi(t)$, which, as shown by Bunde et al. [18], has a central origin. The standard deviation $\xi(t)$ was 0.1.

The effect of the sympathetic and parasympathetic loops for HR baroreflex control is expressed via insertion of factors of respectively sympathetic and parasympathetic effects [3, 4] (Eqs. (14) and (15), respectively).

$$f_s(t) = 1 + k_\varphi^c\left(c(t) + (\hat{c} - c(t))\frac{c^{n_s}}{\hat{c}^{n_s} + c^{n_s}}\right) \quad (14)$$

$$f_p(t) = 1 + k_\varphi^p\left(v_p(t - \theta_p) + (\hat{v}_p - v_p(t - \theta_p) \times \frac{v_p^{n_p}(t - \theta_p)}{\hat{v}_p^{n_p} + v_p^2(t - \theta_p)}\right)F(\varphi(t)). \quad (15)$$

Table 1. Parameters of the proposed model used in the study

T_0	0.55 s	ε	2.0	k_1	0.02 1/mmHg	k_φ^c	1.6
$\hat{S}$	35 mmHg	τ	3.6 s	k	0.00125 s/mmHg	$\hat{c}$	2.0
n_c	3	k_m^r	2.5	p_0	50 mmHg	n_c	2.0
k_S^c	40 mmHg	f_r	0.29 1/s	$\nu_s^{(0)}$	0.8	k_φ^p	5.8
k_S^t	10 1/mmHg	G	1.65	k_s^b	0.7	θ_p	0.5 s
T_{sys}	0.125 s	r^*	2	k_s^r	0.025	$\hat{\nu}_p$	2.5
k_p^M	3 mmHg	α	1	$\nu_p^{(0)}$	0.0	n_s, n_p	2.0
R_0C	1.5 s	β	2	k_p^b	0.3	τ_c	2.0 s
k_ν^M	0.015	x^*	0.5	k_p^r	0.025	k_c^s	1.2
τ_e	3.24 s	y^*	0	std $\xi(t)$	0.1	θ_c	1.65 s

T_0 is the contraction period of denervated heart; n_c determines the concentration of noradrenaline, the exceedance of which does not lead to a further increase in the intensity of cardiac contractions; T_{sys} is the fixed duration of systole; R_0 is the peripheral vascular resistance; C is the aortic elasticity; τ_e is the efferent delay in the loop for the baroreflex control of arterial vascular tone; ε is the the inertia of the peripheral vessels; τ is the the total delay in the loop of control of peripheral vascular tone; f_r is the respiration rate; G is the gain of the central nervous system; p_0 is the minimal pressure to which baroreceptors react; $\nu_s^{(0)}$ is the activity of the sympathetic system at rest; $\nu_p^{(0)}$ is the activity of the parasympathetic system at rest; std $\xi(t)$ is the standard deviation of $1/f$ of noise $\xi(t)$; θ_p is the time delay caused by the finiteness of the rate of change of acetylcholine concentration; n_s, n_p determine the concentration of noradrenaline and acetylcholine the exceedance of which does not lead to a further intensification of sympathetic and parasympathetic factors; τ_c is the characteristic relaxation time of noradrenaline concentration; θ_c is the time delay, caused by the time of cardiac response to changes in the myocardial noradrenaline concentration.

n_s, n_p determine the concentration of norepinephrine and acetylcholine, the excess of which does not lead to further enhancement of the sympathetic and parasympathetic factors.

The sympathetic nervous system affects HR via the change in the concentration of noradrenaline, $c(t)$ (Eq. (4)). The production of noradrenaline is a relatively slow process (characteristic relaxation time $\tau_c = 2.0$ s) and taken into account in Eq. (4) by time delay $\theta_c = 1.65$ s. The change in the concentration of the agent of the parasympathetic nervous system acetylcholine is much faster. This process is accounted for calculation of $f_p(t)$ in the form of the delay $\theta_p = 0.5$ s.

The so-called phase-efficiency curve

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

allows accounting for the effect of the phase of the cardiac cycle on the operation of parasympathetic division of the autonomic nervous system [3].

The model parameters used for the numerical simulations are shown in Table 1.

RESULTS OF THE ANALYSIS OF MODEL FUNCTIONALITY

The spectral and statistical analysis. In several studies [19–21], the informative value of the spectral and statistical analysis of HRV for assessment of the functional state of the control of CVS was noted. The calculation of the indices, characterizing the average power of the oscillations in the frequency intervals, as well as the statistical characteristics of HRV are commonly used in physiological studies and medical diagnostics.

Therefore, in the study of possibilities and applicability limits of CVS models we compared the power spectra of signals of HRV models and experimental data. The typical Fourier power spectrum of HRV signal of the healthy man estimated by Welch's method for 10 min of the experiment is shown in Fig. 2 (solid line). It was compared with the power spectral densities of Kottani's model with original settings (for brevity sake, we will call it model *K*), and the parameters modified by us (model *KM*) and with the model, proposed by us (model *M*). It can be seen that in the spectrum of model *K* the component at a frequency of about 0.1 Hz was not expressed.

We modified model *K* for approximation to the power spectral density to a form that is characteristic of the experimental data (Fig. 3). Parameters of the

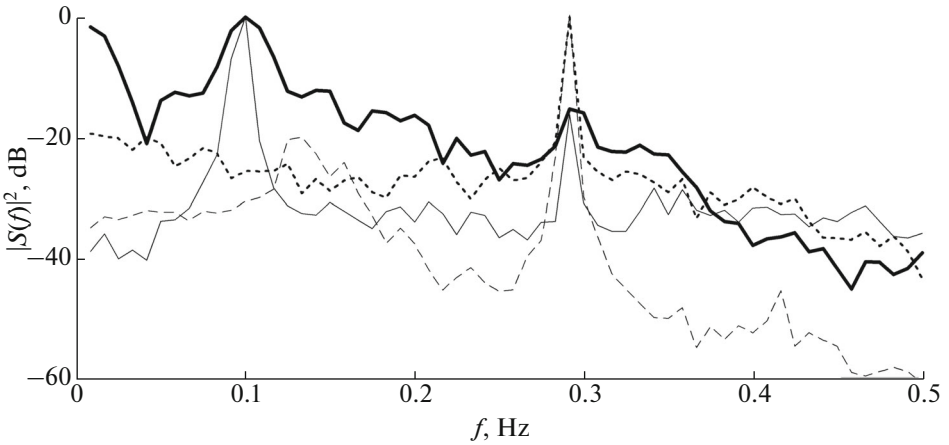

Fig. 2. The spectral power densities of the experimental realization of HRV of healthy person (bold line) in the model proposed by us (thin line), model *K* proposed in the study [4] (points), and the modification of the model *K* (strokes).

modified model *KM*, changed with respect to the original model *K*, are shown in Table 2.

The consideration of self-oscillating nature of the loop for the control of vascular tone in model *M* allowed adjusting the power of the spectral components, bringing them in good agreement with the experimental results. In contrast to the model *M*, in HRV spectrum of model *K* with original parameters, corresponding to healthy men at rest, component on a frequency of about 0.1 Hz, reflecting the activity of the sympathetic division of autonomic regulation of CVS activity was not expressed.

HRV signals from experimental realization and HRV and BP time series of both models are shown in Fig. 3.

For different models ratios of systolic and diastolic BP was 200 and 110 mmHg for model *K*, 150 and 60 mmHg for the model *KM* and 145 and 70 mmHg for model *M*. Thus, AP values a characteristic for healthy people allow reproducing models *KM* and *M*.

A HRV of 10 healthy men from 20 to 25 years of age at rest was studied. Signals of electrocardiograms (ECG) were recorded in II standard lead determined by Einthoven, in prone position, 2 h after a meal. The duration of each record was 10 min. All experimental signals obtained in the study were recorded using standard device with a sampling frequency of 250 Hz, quantization bit rate of 14 bits, the bandpass was 0.05–100 Hz. A notch filter was used for suppression of power line noise. HRV signal was selected from ECG for the analysis.

Indices widely used in medical practice and physiological studies were calculated: LF, the average power spectral density calculated in the band of 0.04-0.15 Hz; HF, the average power spectral density calculated in the band of 0.15–0.4 Hz; LF/HF, the ratio of these indices; LF_{norm} and HF_{norm} the ratios of LF and HF indices, respectively, to the power averaged in the band of 0.04–0.4 Hz; and statistical characteristics of HRV, including the average heart rate (*HR*), *RMSSD*, and pNN50. The indices were calculated in accordance with guidelines presented in the study [22].

HRV indices calculated from the experimental signals were compared with the results of the statistical analysis of HRV signals of models. Ensembles of 10 runs were obtained from each model, the duration of each was the equivalent of 10 min of the experimental recording.

The calculated indices are shown in Table 3. Comparison shows that indices calculated by HRV signals of model *M* were much closer to the experimental indices, than indices for models *K* and *KM*.

Diagnosis of phase synchronization. The indices calculated in the course of spectral analysis of HRV showed their informative value and importance in medical diagnostics. However, the linear spectral estimates do not provide information about the features of complex nonlinear collective dynamics of regulatory systems and peculiarities of their interaction. This can be attributed to the complexity of studied signal systems, analysis of which requires the development of specialized nonlinear methods. In previous experimental studies, we demonstrated that regulatory systems with characteristic frequency of about 0.1 Hz

Table 2. Parameters of the model of Kotani et al. [4] changed in comparison with the original study

T_0	1.1 s	$k^s_{c_{cNa}}$	3
p_0	20 mmHg	$k^s_{c_{vNa}}$	3
k^r_s	0.006	k_p	0.22
k^r_p	0.09		

T_0 is the contraction period of denervated heart; p_0 is the minimal BP to which baroreceptors react.

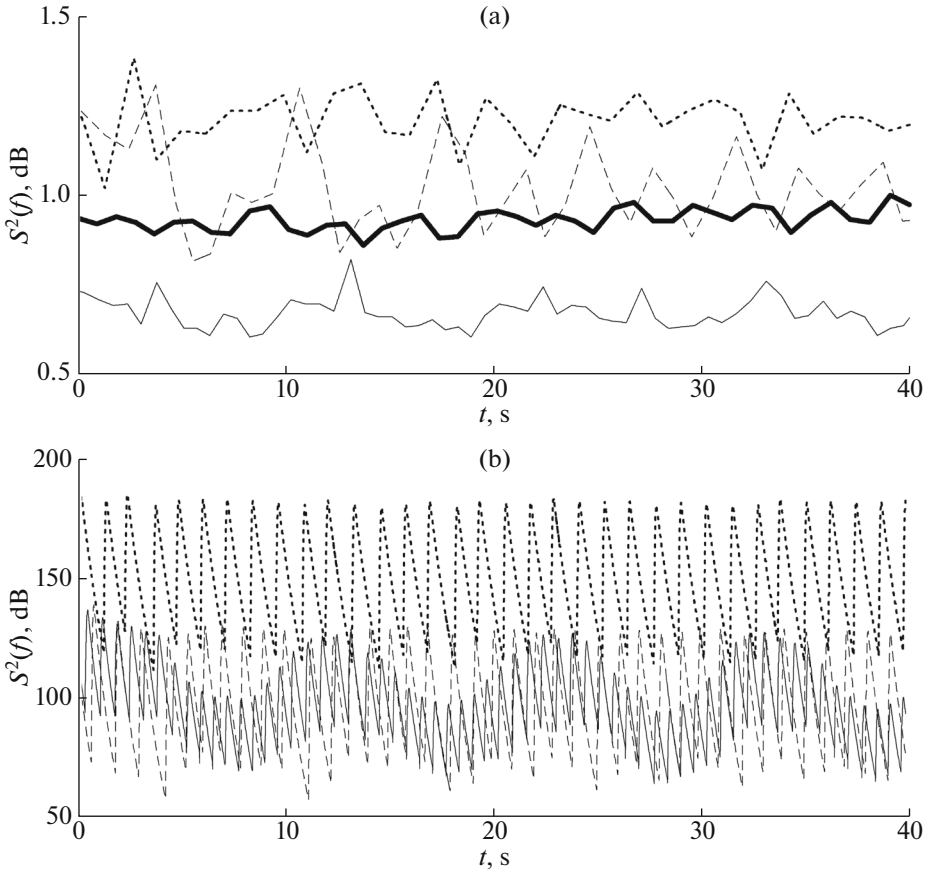

Fig. 3. Segments of model runs: (a) HRV (thick line shows experimental signal); (b) BP. Thin line, model *M*; dot line, model *K*; dashed line, model *KM*.

exhibit complex modes of collective dynamics, synchronizing by phase and frequency [10, 11]. In our studies, we demonstrated the importance of these results for medical diagnosis [12, 13]. We have also shown that these regulation systems synchronized by the respiration signal at linearly varying frequency, demonstrating the behavior characteristic, e.g., for radio physical oscillators [14]. This study examined the operation of models in the course of experiments with respiration.

In the study of synchronization of complex signals, such as temporal series of biological nature, the use of specialized methods of the analysis allowing the diagnosis of the oscillation phases locking in the presence of instrumental and dynamic noises is required.

An important issue is also the distinction between the non-linear effect, namely, the phase locking, from the so-called leakage, i.e., linear admixing of the external signal to the dynamics of the studied system. The approach that we proposed earlier [23, 24] was used for the solution of this problem. The method is based on the allocation of instant oscillation phase using a continuous wavelet transform. It was shown that in experiments with synchronization of oscillators by the signal at linearly varying frequency, phase difference within the frequency locking area was linearly changed by π. Alternatively, external signal leakage, or a combined effect of the leakage and phase synchronization was diagnosed.

In our experimental studies, subjects without cardiovascular pathologies performed inspirations of a linearly increasing frequency. The frequency of signal varied from 0.05 to 0.25 Hz for 30 min. In the experiment respiration signal (registered by oronasal sensor) and ECG were recorded simultaneously. HRV signal was isolated from ECG for the analysis. During the experiment, the subject was in a sitting position with closed eyes in a quiet darkened room.

In the simulation, implementation length and properties of the signal were equivalent.

A typical phase difference of one of the experiments and signals of models affected by breathing at a linearly increasing rate is shown in Fig. 4.

Figure 4 shows that the linear part of the phase difference changes by π, showing phase locking band only for the experimental phase difference and the phase difference of model *M*. Moreover, intervals of phase locking for model *M* and experimental signal are

Table 3. Ensemble average indexes with the average error estimate

Index	Model *M*	Model *K*	Model *KM*	Experiment
HR	89.7 + 0.02	46.6 + 0.00	59.7 + 0.02	74.6 + 2.86
X mean	671 + 0.22	1211 + 0.00	1010 + 0.175	824 + 32.0
D	2082 + 21.8	4157 + 77.2	8610 + 242	3546 + 424
SDNN	45.6 + 0.24	64.5 + 0.59	92.7 + 1.33	57.8 + 3.66
CV	6.79 + 0.04	5.32 + 0.05	9.17 + 0.13	6.95 + 0.25
RMSSD	52.4 + 1.19	122 + 1.56	140 + 1.09	46.8 + 5.85
*PNN*50	29.7 + 0.80	71.0 + 0.91	80.8 + 0.83	26.9 + 5.64
Mo	0.68 + 0.00	1.22 + 0.01	0.94 + 0.01	0.82 + 0.035
Amo	465 + 5.50	3285 + 3.63	2385 + 5.3	414 + 22.4
Xmax	0.82 + 0.01	1.38 + 0.01	1.28 + 0.01	0.99 + 0.04
Xmin	0.58 + 0.00	1.05 + 0.00	0.82 + 0.005	0.67 + 0.02
*CC*1	0.22 + 0.02	–0.17 + 0.04	0.04 + 0.06	0.39 + 0.05
*CC*0	2375 + 250	937 + 46.9	1062 + 46.9	1800 + 199
HF	249 + 11.2	1719 + 44.1	3594 + 73	543 + 110
LF	607 + 14.5	228 + 12.1	752 + 67	549 + 69.2
LF/HF	2.47 + 0.17	0.13 + 0.01	0.21 + 0.02	1.92 + 0.37
HF*pc*	29.2 + 2.16	66.8 + 0.80	84.7 + 1.85	30.4 + 4.08
LF*pc*	69.4 + 2.46	11.4 + 0.88	15.2 + 1.48	40.1 + 4.53

HR—heart rate; *Xmean* is the average value in milliseconds; *D* is the variance of the heart rate variability signal; *SDNN* is the total index of variability of *RR* intervals; *CV* is the coefficient of variation; *RMSSD* is the activity index of parasympathetic part of autonomic regulation; *NN*50 is the amount of *RR* intervals, separated by time higher than 50 milliseconds; *PNN50* is the percentage of *NN50* among the total number of *RR* intervals; *Mo* is the most frequent *RR* interval; *Amo* is the number of *RR* intervals with the length of *Mo*; *Xmax* is the longest *RR* interval; *Xmin* is the shortest *RR* interval; *CC*1 is the autocorrelation coefficient with a shift of 1 *RR* interval; *CC*0 is the number of shifts, after which *CC1* value of is negative; HF is the absolute total power of the signal in the range of 0.15-0.4 Hz; LF is the absolute total power of the signal in the range of 0.04-0.15 Hz; LF/HF is the ratio of LF to HF; HF*pc* is the ratio of HF to the total signal power in the range 0.015–0.4 Hz; LF*pc* is the ratio of LF to the total signal power in the range of 0.015–0.4 Hz.

well matched. The phase difference of models *K* and *KM* does not show a linear change by π. In other words, phase synchronization was not observed in this model, there is only leakage effect.

DISCUSSION

The development of mathematical models of biological systems intended for their qualitative and quantitative description is an important step in the study of living systems. Such models can provide important fundamental information about the structure of the studied systems and characteristics of the interaction of their elements; allow investigating the behavior of systems in time and changing of control parameters, predicting the impact of physiological tests and medicines on the system.

Simulation of complex multicomponent systems of biological nature requires, as a rule, the use of bulky high-dimensional equations. Therefore, the reduction is often used for the simplification of the problem. In particular, linear representations of the structure of some of the functional elements of studied systems are used. At the same time, consideration of nonlinear properties of the simulated object in accordance with the relevant physiological representations can qualitatively change the behavior of the model, allowing reproduction and quantitative description of effects observed in the experiments. The number of such effects cannot be reproduced within the framework of linear approximations.

In our study, we examined the mathematical model *K* proposed by Kotani et al. [4]. Today, this model is the most detailed description of the control of CVS operation. However, the linear representation of loops of sympathetic regulation, proposed in this model, limits its capabilities.

In particular, the baroreflex regulation of vascular tone system described in the model *K* by the equation, which is a linear relaxer with the delay. Therefore, the reproduction of characteristic peak at a frequency of about 0.1 Hz, reflecting the activity of sympathetic regulation systems in the experimental data, in the power spectra of HRV signal of this model is possible only in the case of the excitation by dynamic noise and external signals. The appearance of peak at a frequency of about 0.1 Hz in the power spectrum of model *MK* may be only due to the resonance proper-

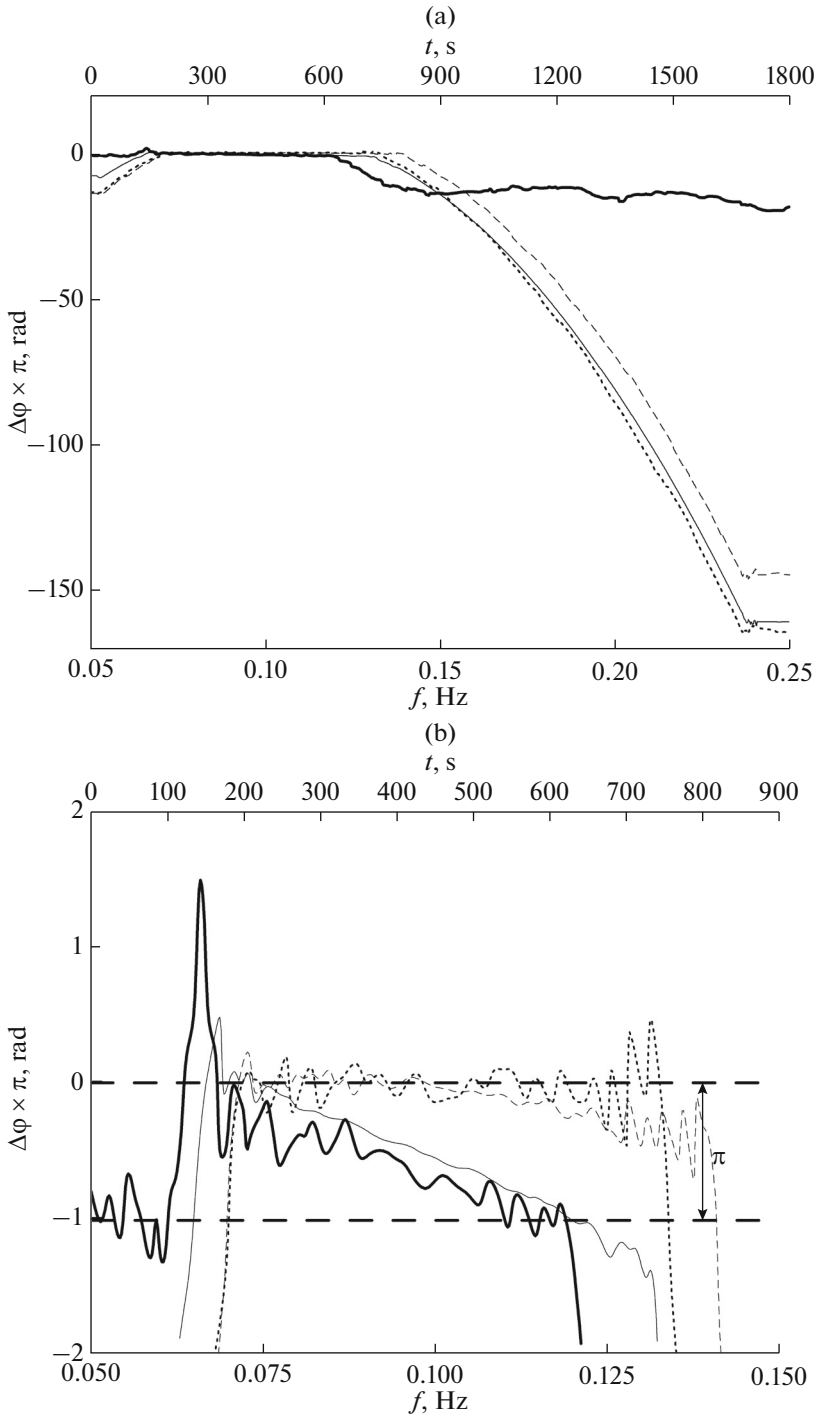

Fig. 4. (a) Instantaneous phase differences of oscillations of the external signal of impact $B(t)$ with linearly increasing frequency *fr*; (b) the enlarged fragment of the phase differences in the phase synchronization region by the external signal of the experimental realization.

ties of the system and the amplitude-frequency characteristics of the relaxation oscillators.

We proposed a mathematical model with a structure close to the structure of model *K*. A qualitative difference includes simulation of baroreflex system in the form of non-linear oscillating system with delayed feedback, similar to the model proposed by Ringwood and Malpas [15] based on in vitro animal experiments.

The introduction of this self-oscillatory autonomous element allowed significant improvement of the reproduction of the spectral properties of the experimental data and statistical indexes, characterizing the

properties of HRV by the proposed model. In addition, the proposed model qualitatively and quantitatively reproduces phase synchronization effect of the dynamics of baroreflex loop by external signal of forced breathing at a linearly increasing rate, which was impossible in models *K* and *KM* due to the linearity of their elements.

We believe that our results support the hypothesis of a high degree of autonomy of baroreflex system. The results emphasize the importance of accounting for non-linear properties of the regulatory systems in their mathematical simulation and indicate the crucial importance of nonlinearity in the functioning of the studied systems of biological nature.

CONCLUSIONS

In this study, a model for the human cardiovascular system was proposed. Its capabilities and applicability were compared with the results of the analysis of experimental signals and time realizations of the model proposed earlier by Kotani et al. [4]. Two sets of parameters were used for the model of Kotani et al. The first set was proposed in the original study [4]. We proposed the second set for a better correspondence of the model to the experimental data. In the course of the comparison, a statistical and spectral analysis of HRV signals was performed, and locking of instantaneous oscillation frequencies at 0.1 Hz of the rhythm of cardiointervalogram in experiments with linearly varying frequency of forced breathing was diagnosed.

The study shows that the insertion of a loop for the baroreflex control of mean blood pressure in the form of oscillator with the delay (which corresponds to the modern physiological concepts) allowed better reproduction of power spectra, statistical indices of HRV and the ratio of systolic and diastolic BP, typical for healthy subjects at rest, that in the original and the modified models from the study [4]. The proposed model also demonstrated the ability to reproduce the phenomenon of phase synchronization at 0.1 Hz of the rhythm of the baroreflex control system by breathing with a linearly varying frequency, which was previously shown in our experimental studies.

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