Technical Physics, 2023, Vol. 68, No. 10

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Determining the directionality of coupling between time series extracted from biological data of rats by modeling the phase dynamics of periodic processes

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Received June 6, 2023
Revised July 14, 2023
Accepted August 14, 2023

The method of identifying the direction of the coupling between oscillators based on the simulation of phase dynamics of weakly coupled and weakly noisy periodic processes is used to determine the direction of the coupling between time series extracted from biological signals. Neuronal activity, arterial pressure and respiratory rate of anesthetized rats were used as initial data. Various options for the direction of the coupling between the analyzed time series were revealed.

Keywords: directionality of coupling, respiratory rate, blood pressure, neuronal activity, index of directionality.

DOI: 10.61011/TP.2023.10.57459.144-23

Introduction

The interaction between loosely coupled dynamical systems is of considerable interest for the analysis of various natural phenomena. Various approaches related to the analysis of frequency and phase synchronization of signals can be used for studying such interaction. For example, the analytical signal method, including the Hilbert transform [1,2] and the wavelet transform method [3] are used to detect synchronization between the rhythms of the cardiovascular and respiratory systems [4–8], between rhythmic stimulation and brain responses [9,10].

An important characteristic of such interaction is the directionality of connections between different physiological systems [11,12]. The interaction between fluctuations in blood pressure and the variability of neuronal activity of the brain at the respiratory rate is considered in this paper, because the interaction of the cardiovascular and respiratory systems involves the nervous control of both systems [13,14]. Pathological conditions can alter these interactions [14–16]. For example, pain effects on anesthetized rats simulating pain in patients with irritable bowel syndrome [17], accompanied by reactions of neurons of the visceral nuclei of the brain stem, changes in heart rate and blood pressure [18]. Such changes suggest the elucidation of the interaction between fluctuations in blood pressure and variability in the activity of brain neurons at the respiratory rate.

It was shown in [4,14,19,20] that breathing fluctuations are dominant in relation to heart rate fluctuations although the degree of directionality may vary over time. The exception should be made for newborns, in whom the binding of the cardiac and respiratory rhythms is symmetrical from the moment of birth to six months, and after six months the influence of the respiratory rhythm on the cardiovascular rhythm becomes dominant, as in adults [21]. It was found in [22] based on the calculation of the directionality index using phase dynamics, that breathing controls the phase synchronization between blood pressure and heart rate fluctuations. However, the relationship between the variability of respiration, blood pressure and neuronal activity intervals has not been analyzed.

The directionality of the links can be evaluated based on various methods of nonlinear dynamics related to the determination of the causal relationship according to Granger [23], with the calculation of the directionality index using phase dynamics [4,19,24,25] or with finding joint recurrences [20,26,27].

Currently, the reciprocity of the connections of the cardiovascular and respiratory, as well as the respiratory and nervous systems is considered not entirely clear [28], therefore, obtaining additional information about the direction of the connections in the systems under consideration is a prerequisite for identifying the role of each connection in homeostasis and pathophysiology.

The aim of this work is to determine the direction of the relationship between the variability of blood pressure and respiration, as well as between the variability of neuronal activity intervals and blood pressure of anesthetized rats by modeling the phase dynamics of weakly coupled and weakly noisy periodic processes.

We used a model of two unidirectionally coupled Van der Pol oscillators to verify the estimates of the statistical significance of the relationship directionality. This method was then applied to experimental data.

1. Method for estimating the directionality of the relationship between time series

The method of detecting directional relationship between interacting systems 1 and 2, considered in works [19,29–34], is based on modeling phase dynamics for weakly coupled and weakly noisy periodic processes $x_1(t)$ and $x_2(t)$. This method involves the construction of an experimental model of the phase dynamics of the analyzed systems based on discrete signal recordings (time series). To do this, for the signals represented by the time series $x_1(t) = \{x_1(t_i)\}_{i=1}^{N}$ and $x_2(t) = \{x_2(t_i)\}_{i=1}^{N}$, where N — the length of the series, $t_i = i\Delta t$, Δt — sampling interval, time series of oscillation phases $\varphi_1(t) = \{\varphi_1(t_i)\}_{i=1}^{N}$ and $\varphi_2(t) = \{\varphi_2(t_i)\}_{i=1}^{N}$ are calculated.

In this paper, the instantaneous phases $\varphi_1(t)$ and $\varphi_2(t)$ were estimated using the Hilbert transform. Then, using the calculated phases, a model of phase dynamics was constructed of the form

$$\Delta\varphi_1(t) = F_1\big(\varphi_1(t), \varphi_2(t), a_1\big) + \varepsilon_1(t),$$

$$\Delta\varphi_2(t) = F_2\big(\varphi_2(t), \varphi_1(t), a_2\big) + \varepsilon_2(t), \qquad (1)$$

where $\Delta\varphi_1(t)=\varphi_1(t+\tau)-\varphi_1(t)$ and $\Delta\varphi_2(t)=\varphi_2(t+\tau)-\varphi_2(t)$ — phase increments over the time interval τ, $\varepsilon_1(t)$ and $\varepsilon_2(t)$ — Gaussian noise with zero mean.

The functions $F_1\big(\varphi_1(t), \varphi_2(t), a_1\big)$ and $F_2\big(\varphi_2(t), \varphi_1(t), a_2\big)$ are described by polynomials of the form [19,29]:

$$F_j(\varphi_1, \varphi_2, a_j) = \sum_{m,n} a_{j,m,n} \exp\big(i(m\varphi_1 + n\varphi_2)\big), \quad j = 1, 2. \qquad (2)$$

The values of τ equal to the smaller of the characteristic oscillation periods for the two analyzed signals and values $m \le 3$, $n \le 3$ were used in this work following [19,29].

The least squares method was used to estimate the values of the coefficients $a_{j,m,n}$, i.e., finding the minimum of the objective function of the form

$$S_j^2 = \sum_{i=1}^{N-\tau} \Big(\Delta\varphi_j(t_i) - F_j\big(\varphi_1(t_i), \varphi_2(t_i), a_j\big)\Big)^2, \quad j = 1, 2, \qquad (3)$$

where $a_j = \{a_{j,m,n}\}$ — vector of coefficients.

After substituting the found coefficient estimates a_j into formulas (2) function estimates were calculated $F_j\big(\varphi_1(t), \varphi_2(t), a_j\big)$, $j = 1, 2$.

Then these functions were used to calculate the coefficients c_1 and c_2, which determine the mutual dependencies of the phase dynamics of the two systems. The impact (impact force) of the second system on the first (the square of the coefficient c_1) is defined as the steepness of the dependence of the function F_1 on φ_2, and the impact force of the first system on the second (the square of the coefficient c_2) is defined as the steepness of the dependence of the function F_2 on φ_1 [19]:

$$c_1^2 = \frac{1}{2\pi^2} \int_0^{2\pi}\int_0^{2\pi} \left(\frac{\partial F_1\big(\varphi_1(t), \varphi_2(t), a_1\big)}{\partial\varphi_2}\right)^2 d\varphi_1 d\varphi_2,$$

$$c_2^2 = \frac{1}{2\pi^2} \int_0^{2\pi}\int_0^{2\pi} \left(\frac{\partial F_2\big(\varphi_2(t), \varphi_1(t), a_2\big)}{\partial\varphi_1}\right)^2 d\varphi_1 d\varphi_2. \qquad (4)$$

After substituting the functions $F_1\big(\varphi_1(t), \varphi_2(t), a_j\big)$ and $F_2\big(\varphi_1(t), \varphi_2(t), a_j\big)$ into expressions (4) according to work [29] there were estimates of the coefficients c_1^2 and c_2^2 expressed in terms of the coefficients of the polynomials (2) in form

$$\gamma_1 = \bar{c}_1^2 = \sum_{m,n} n^2 a_{1,m,n}^2, \quad \gamma_2 = \bar{c}_2^2 = \sum_{m,n} m^2 a_{2,m,n}^2. \qquad (5)$$

The condition $\gamma_j - 1.6\sigma_j < 0$ was taken as a criterion of statistical significance, where the estimates of variances σ_j of values γ_j, $j = 1, 2$ are calculated for the same analyzed series according to the formulas proposed in work [30]:

$$\sigma_1^2 = \sum_{j=1}^{3} n_j^4 \sigma_{1,j}^4, \quad \sigma_2^2 = \sum_{j=1}^{3} m_j^4 \sigma_{2,j}^4, \qquad (6)$$

where

$$\sigma_{k,j}^2 = \frac{2\sigma_{\varepsilon k}^2}{N}\Bigg[1+2\sum_{i=1}^{\tau/\Delta t-1}(1-i\Delta t/\tau)\cos\big((m_i a_{k,1,1,}+n_i a_{k,2,1}) \times i\Delta t/\tau\big)\exp\big(-(m_j^2\sigma_{\varepsilon1}^2 + n_j^2\sigma_{\varepsilon2}^2)i\Delta t/2\tau\big)\Bigg], \; k = 1, 2; \qquad (7)$$

the noise variance estimates $\sigma_{\varepsilon1}^2$ and $\sigma_{\varepsilon2}^2$ are calculated by formulas

$$\sigma_{\varepsilon1}^2 = \frac{1}{N-1}\sum_{i=1}^{N}\Bigg[\big(\varphi_1(t_i+\tau) - \varphi_1(t_i)\big) - \frac{1}{N}\sum_{i=1}^{N}\big(\varphi_1(t_i+\tau) - \varphi_1(t_i)\big)\Bigg]^2,$$

$$\sigma_{\varepsilon2}^2 = \frac{1}{N-1}\sum_{i=1}^{N}\Bigg[\big(\varphi_2(t_i+\tau) - \varphi_2(t_i)\big) - \frac{1}{N}\sum_{i=1}^{N}\big(\varphi_2(t_i+\tau) - \varphi_2(t_i)\big)\Bigg]^2. \qquad (8)$$

Such a criterion corresponds to a confidence interval of 95%, when the condition $\gamma_1 - 1.6\sigma_1 > 0$ is met, it is concluded that there is an impact of the second system

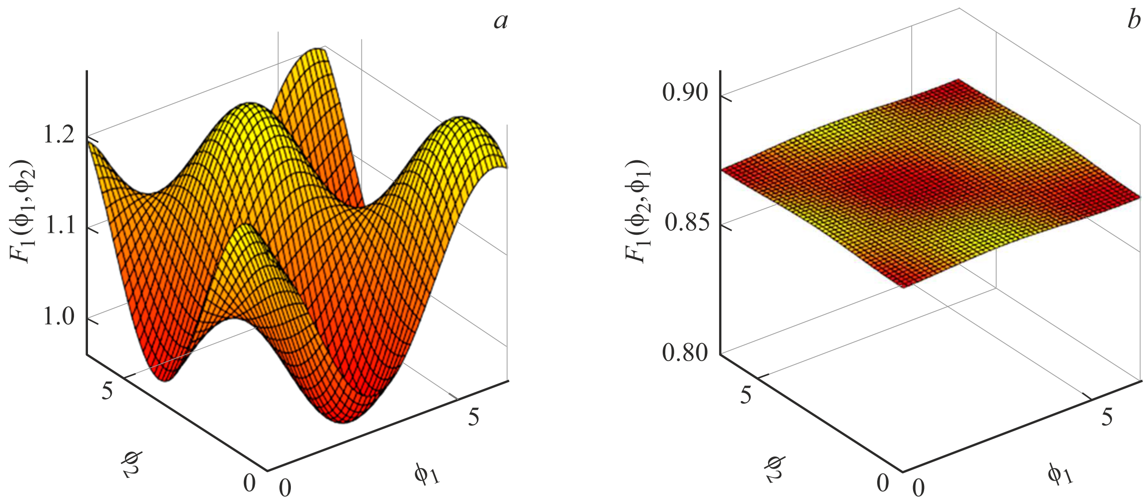

Figure 1. *a* — relationship asymmetry for a model of two unidirectionally coupled Van der Pol oscillators; *b* — relationship functions $F_1(\varphi_1, \varphi_2)$ and $F_2(\varphi_2, \varphi_1)$.

on the first one with an error probability not more than 0.05, and when the condition $\gamma_2 - 1.6\sigma_2 > 0$ is met, the predominant influence of the first system on the second one with the same error probability is taken into account. If both conditions are met simultaneously, it is concluded that there is a bidirectional or mutual influence of the two systems on each other [35].

The relationship directionality index is calculated according to the formula proposed in [19]:

$$d^{(1,2)} = \frac{\sqrt{\gamma_2} - \sqrt{\gamma_1}}{\sqrt{\gamma_2} + \sqrt{\gamma_1}}. \tag{9}$$

The directionality index $d^{(1,2)}$ ranges from -1 to $+1$. The value $d^{(1,2)}$, close to $+1$, corresponds to unidirectional relationship, in which system 1 controls system 2. The value $d^{(1,2)}$, close to -1, corresponds to unidirectional relationship in the opposite direction, in which system 2 controls system 1. The value $d^{(1,2)}$, close to zero, corresponds to a symmetric bidirectional relationship.

It is shown in [29] that the method of estimating the relationship directionality between interacting systems based on modeling the phase dynamics of the analyzed systems can be applied to data for which the value of the phase synchronization index ρ does not exceed the value 0.6. In this regard, we have previously calculated the phase synchronization index using the following formula [4]:

$$\rho = \left| \frac{1}{N} \sum_{i=1}^{N} \exp\big(j\left(\varphi_2(t_i) - \varphi_1(t_i)\right)\big) \right|. \tag{10}$$

2. Model of two coupled Van der Pol oscillator

As a model, consider two unidirectionally coupled systems of Van der Pol oscillators with frequencies ω_1 and ω_2 and relationship parameter μ [36]. This model is described by the equations

$$\frac{d^2x_1}{dt^2} - 0.5(1 - x_1^2)\frac{dx_1}{dt} + \omega_1^2 x_1 = \mu\left(\frac{dx_2}{dt} - \frac{dx_1}{dt}\right),$$

$$\frac{d^2x_2}{dt^2} - 0.5(1 - x_2^2)\frac{dx_2}{dt} + \omega_2^2 x_2 = 0. \tag{11}$$

The equations (11) were solved numerically using the fourth-order Runge–Kutta with a step of 0.03 s, the integration time duration was 600 s, which corresponded to 20 000 data values.

Figure 1 illustrates the asymmetry of the relationship for the model parameters $\omega_1 = 1.11$, $\omega_2 = 0.89$ and $\mu = 0.1$. As can be seen from Fig. 1, the graph of the relationship function $F_2(\varphi_2, \varphi_1)$ has a flat form (Fig. 1, *b*), in contrast to the graph of the sinusoidal relationship function $F_1(\varphi_1, \varphi_2)$ (Fig. 1, *a*). This indicates a weak influence of the first system on the second and a significant influence of the second system on the first. The value of the phase synchronization index is $\rho = 0.12$, i.e. less than the threshold value 0.6 [29]. The value of $\gamma_1 = 0.036$, the variance estimate $\sigma_1 = 0.005$, $\gamma_1 - 1.6\sigma_1 > 0$, i.e. the assessment of the influence of the second system on the first one can be considered statistically significant with a probability of error not more than 0.05.

The value of the relationship directionality index $d^{(1,2)} = -0.98$, which corresponds to unidirectional relationship, in which the second Van der Pol oscillator is the master, and first is the slave.

3. Analysis of experimental data

As experimental data, simultaneously recorded fluctuations in blood pressure, respiration and neuronal activity of rats were considered, provided by the Laboratory of

Cortico-Visceral Physiology of the Pavlov Institute of Physiology of the Russian Academy of Sciences, and registered in accordance with the Directive of the Council of the European Community (86/609/EEC), as well as the requirements of the Commission for the Control of the Keeping and Using of Laboratory Animals at the Pavlov Institute of Physiology of RAS (conclusion №02/24 of February 24, 2020). These data were obtained for 10 rats intraperitoneally anesthetized with urethane (1.5mg/kg, ICN Biomedical Inc., USA). A series of recordings for each rat was repeated 6 times.

Blood pressure was recorded using a semiconductor pressure sensor located in a catheter installed in the femoral artery (MLT0670, ADInstruments Ltd., UK). Respiratory fluctuations were defined as concentration fluctuations CO_2, measured on inhalation and exhalation using a sensor located in the endotracheal tube (CapnoScan End-Tidal CO_2 Monitoring Modular System, USA).

Extracellular neuronal activity was recorded with a tungsten electrode (WPI, USA) with a tip with a diameter of $1\,\mu$m and a resistance of about $1-2\,\mathrm{M\Omega}$ immersed in the brain tissue in the area corresponding to the caudal ventrolateral reticular formation of the medulla oblongata. This is due to the fact that it is in this area of the medulla oblongata that groups of neurons have been found that respond to painful colorectal stretching [37,38].

The duration of recording of one series of records was 65 s, sampling rate — 10 000 Hz.

From the provided data of neuronal activity and fluctuations in blood pressure, we identified the curves of variability of neuronal activity intervals (NAV) and variability of systolic blood pressure intervals (BPV). These curves contained sequences of time intervals between local maxima of the initial data of neuronal activity and blood pressure.

Due to the irregularity of these intervals, the resulting sequences were not equidistant in time. In order to convert non-equidistant sequences into equidistant ones, we used interpolation of the obtained sequences by cubic splines with oversampling to frequency 1000 Hz.

Then, in the case of non-linear trends and low- and high-frequency oscillations in the obtained equidistant NAV and BPV sequences, these sequences were confirmed by trend removal and bandpass filtering in the range from 1 to 3 Hz for further analysis of the components of these curves with fundamental frequencies close to the respiratory rhythm frequency (RES).

Previously, these data were used by us in the study [31], in which, using the method of synchro-compressed wavelet transform, we showed the presence of phase synchronization between the time series NAV and BPV at the respiratory rate or between BPV and RES with painful colorectal stretching.

We analyzed in this paper the directionality of the relationship between the NAV, BPV and RES time series before the pain and the phase synchronization caused by this effect, since the method of determining the directionality of the relationship between time series based on phase dynamics modeling is not applicable for the phase synchronization mode, since in this case the phases of two interacting systems are not independent variables for the construction of phase models [19].

Fig. 2 shows examples of short fragments with 2 s experimental recordings of neuronal activity (Fig. 2, *a*) and rat blood pressure fluctuations (Fig. 2, *b*), fragments with a duration of 25 s of respiratory oscillations (Fig. 2, *c*), and also fragments of calculated curves of time series of the neuronal activity interval variability (NAV) (Fig. 2, *d*) and the blood pressure interval variability (fig. 2, *e*).

The narrow-band Fourier spectra of these NAV and BPV time series with fundamental frequencies close to the respiratory rhythm frequency, shown in Fig. 2, *f*, *g*, demonstrate the possibility of finding instantaneous phases based on modeling the phase dynamics of loosely coupled periodic processes.

Figure 3 shows a variant of the relationship between the time series of the neuronal activity interval variability and the blood pressure interval variability. These plots indicate the asymmetry of relationship and the significant influence of the variability of blood pressure intervals on the variability of neuronal activity intervals, since the relationship function $F_{\mathrm{BPV}}(\varphi_{\mathrm{NAV}}, \varphi_{\mathrm{BPV}})$ has a smaller range of fluctuations around the circular frequency $\omega \sim 2\pi f_{\mathrm{BPV}} \sim 11.2$ (Fig. 3, *c*) compared to the function $F_{\mathrm{NAV}}(\varphi_{\mathrm{NAV}}, \varphi_{\mathrm{BPV}})$ (Fig. 3, *b*). The value of the phase synchronization index $\rho = 0.11 < 0.6$. Score $\gamma_1 = 0.15$, estimated variance $\sigma_1 = 0.06$, $\gamma_1 - 1.6\sigma_1 > 0$, i.e. for this example, the evaluation of the impact of the second (cardiovascular) system on the first (nervous) is statistically significant with an error probability of more than 0.05. Value the relationship directionality index $d^{(\mathrm{NAV,BPV})} = -0.61$, which corresponds to unidirectional relationship, in which the system generating the BPV time series is a master system, and the system generating the NAV series is a slave system.

Fig. 4 illustrates a variant of the relationship between the time series of variability of blood pressure intervals and the breathing rhythm. The function $F_{\mathrm{BPV}}(\varphi_{\mathrm{BPV,RES}})$ is characterized by a large range of changes in values (Fig. 4, *b*) compared with the function $F_{\mathrm{RES}}(\varphi_{\mathrm{BPV,RES}})$ fluctuating around the cycle frequency $\omega \sim 2\pi f_{\mathrm{BPV}} \sim 11.5$ (Fig. 4, *c*). This allows concluding that the breathing rhythm has a significant effect on the variability of blood pressure intervals in this example. The value of the phase synchronization index $\rho = 0.27 < 0.6$. The estimate $\gamma_1 = 0.34$, the variance estimate $\sigma_1 = 0.09$, $\gamma_1 - 1.6\sigma > 0$, i.e. the estimation of the impact of the second (respiratory) system on the first (cardiovascular) is statistically significant with a probability of error not greater than 0.05. The value of the relationship directionality index is $d^{(\mathrm{BPV,RES})} = -0.73$, this corresponds to unidirectional relationship, in which the system generating the respiratory rhythm RES turns out to be a master system, and the system generating the BPV series is a slave system.

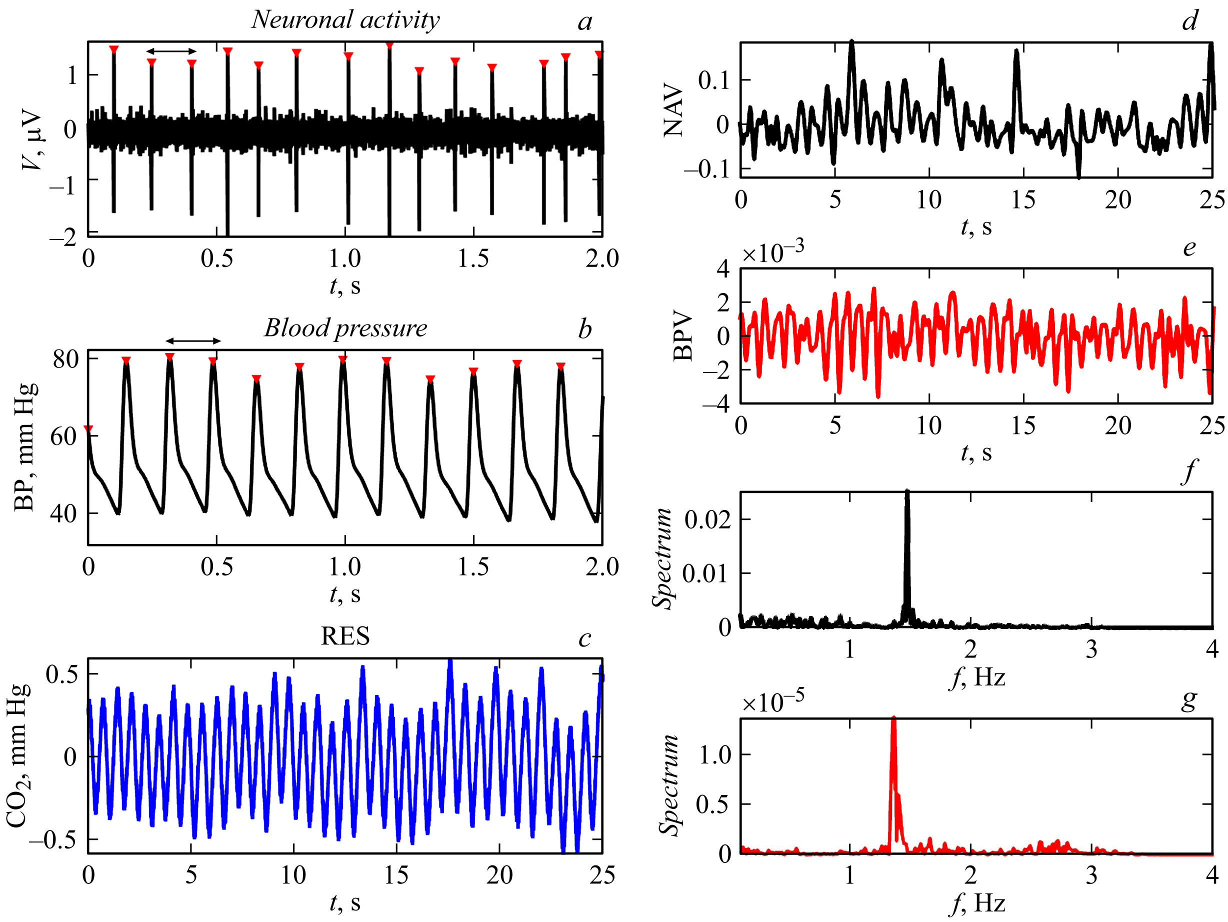

Figure 2. Fragments of neuronal activity (*a*), blood pressure (*b*) and respiratory fluctuations (*c*). The intervals between local maxima are indicated by arrows. Curves of variability of the neuronal activity intervals (NAV) (*d*) and variability of blood pressure intervals (BPV) (*e*); *f, g* — Fourier spectra for NAV and BPV.

Values of phase synchronization $\rho^{\text{NAV–BPV}}$, $\rho^{\text{BPV–RES}}$ and relationship directionality indices $d^{(\text{NAV, BPV})}$, $d^{(\text{BPV, RES})}$, and also estimates $\gamma_{\text{NAV}} - 1.6\sigma_{\gamma\text{NAV}}$ and $\gamma_{\text{BPV}} - 1.6\sigma_{\gamma\text{BPV}}$

№	$\rho^{\text{NAV–BPV}}$	$d^{(\text{NAV, BPV})}$	$\gamma_{\text{NAV}} - 1.6\sigma_{\gamma\text{NAV}}$	$\rho^{\text{BPV–RES}}$	$d^{(\text{BPV, RES})}$	$\gamma_{\text{BPV}} - 1.6\sigma_{\gamma\text{BPV}}$
1	0.12	−0.71	0.018	0.25	−0.81	0.045
2	0.27	−0.73	0.008	0.17	−0.87	0.036
3	0.17	−0.75	0.004	0.28	−0.85	0.015
4	0.13	−0.80	0.006	0.23	−0.82	0.026
5	0.25	−0.62	0.039	0.16	−0.77	0.019
6	0.23	−0.77	0.007	0.34	0.07	0.067
7	0.17	0.05	0.045	0.37	0.05	0.055
8	0.27	0.09	0.037	0.15	0.09	0.048

The relationships between time series of NAV and BPV and between BPV and RES were found based on the results of the estimation of the relationship orientation. The data are listed in the following table. The value of the phase synchronization index is less than the threshold $\rho < 0.6$ for all data, which indicates the absence of phase synchronization between the analyzed time series NAV and BPV and between BPV and RES.

None of the conditions $\gamma_{\text{NAV}} - 1.6\sigma_{\text{NAV}} > 0$, $\gamma_{\text{BPV}} - 1.6\sigma_{\text{BPV}} > 0$, or $\gamma_{\text{RE}} - 1.6\sigma_{\text{RES}} > 0$ were met in two

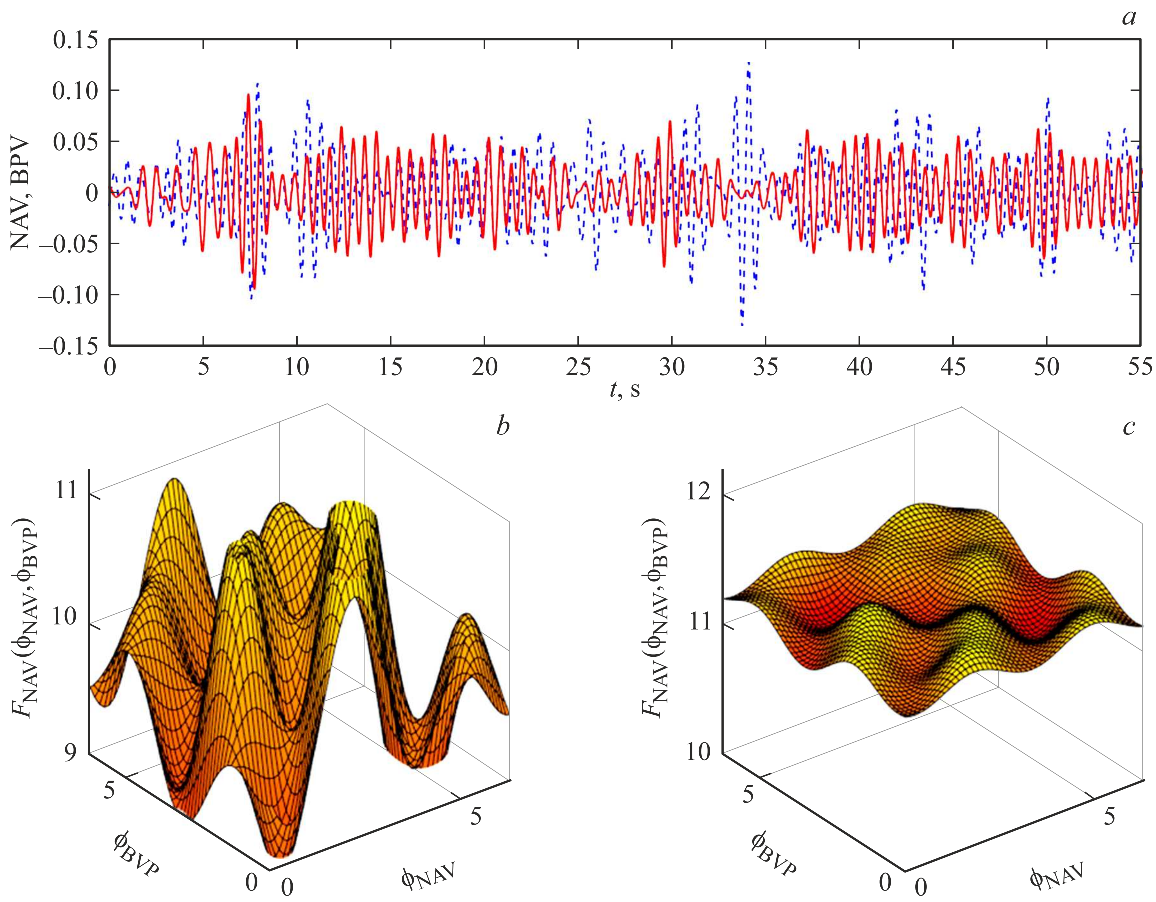

Figure 3. The relationship between the neuronal activity interval variability and the rat blood pressure interval variability; *a* — fragments of NAV (dashed curve) and BPV (solid curve); *b, c* — $F_{\mathrm{NAV}}(\varphi_{\mathrm{NAV}}, \varphi_{\mathrm{BPV}})$ and $F_{\mathrm{BPV}}(\varphi_{\mathrm{NAV}}, \varphi_{\mathrm{BPV}})$ relationship functions.

out of ten rats, so it was not possible to determine the relationship direction for them. For this reason the table contains data for eight rats.

The table data show that unidirectionality of the relationship (BPV→NAV) between NAV and BPV time series is found in 6 out of 8 rats. This is evidenced by the fulfillment of the condition $\gamma_{\mathrm{NAV}} - 1.6\sigma_{\mathrm{NAV}} > 0$ and the negative value of the directionality index $d^{(\mathrm{NAV,BPV})}$ close to -1. The average value of the directionality index for these series is $d^{(\mathrm{NAV,\ BPV})} = -0.71 \pm 0.06$. This negative value indicates that the cardiovascular system is a master system for these data, and the nervous system is a slave system. The relationship between the NAV and BPV time series is defined as bidirectional for the remaining 2 out of 8 rats. In this case, both conditions $\gamma_{\mathrm{NAV}} - 1.6\sigma_{\mathrm{NAV}} > 0$ and $\gamma_{\mathrm{BPV}} - 1.6\sigma_{\mathrm{BPV}} > 0$ and the directionality index value close to zero (the average value of the directionality index $d^{(\mathrm{NAV,BPV})} = 0.07 \pm 0.02$) are met. The nervous and cardiovascular systems turn out to be interdependent in these cases.

When analyzing the relationship between BPV and RES time series, statistically significant unidirectionality was determined for 5 out of 8 rats. In this case, the condition $\gamma_{\mathrm{BPV}} - 1.6\sigma_{\mathrm{BPV}} > 0$ is met, and the value of the directionality index $d^{(\mathrm{BPV,RES})}$ is close to -1. The average value of the directionality index $d^{(\mathrm{BPV,RES})} = -0.82 \pm 0.04$. The respiratory system in these series of recordings is a master system, and the cardiovascular system is a slave system.

In the remaining data (for 3 out of 8 rats), the relationship between the BPV and RES time series was determined to be bidirectional because the directionality index value $d^{(\mathrm{BPV,RES})}$ is close to zero and both conditions $\gamma_{\mathrm{BPV}} - 1.6\sigma_{\mathrm{BPV}} > 0$ and $\gamma_{\mathrm{RES}} - 1.6\sigma_{\mathrm{RES}} > 0$ are met. The average value of the directionality index $d^{(\mathrm{BPV,RES})} = 0.07 \pm 0.02$.

Thus, the unidirectionality of relationship between interacting systems is characteristic for most of the analyzed experimental data. At the same time, the breathing rhythm controls fluctuations of blood pressure, and fluctuations of blood pressure control the dynamics of the intervals of neuronal activity of neurons of the reticular formation of the medulla oblongata of anesthetized rats.

The controlling role of the respiratory system was determined in [4,21,22] based on the calculation of the directionality index using phase dynamics. In these studies, it was shown that the human breathing rhythm can control the rhythm of the cardiovascular system, namely, the

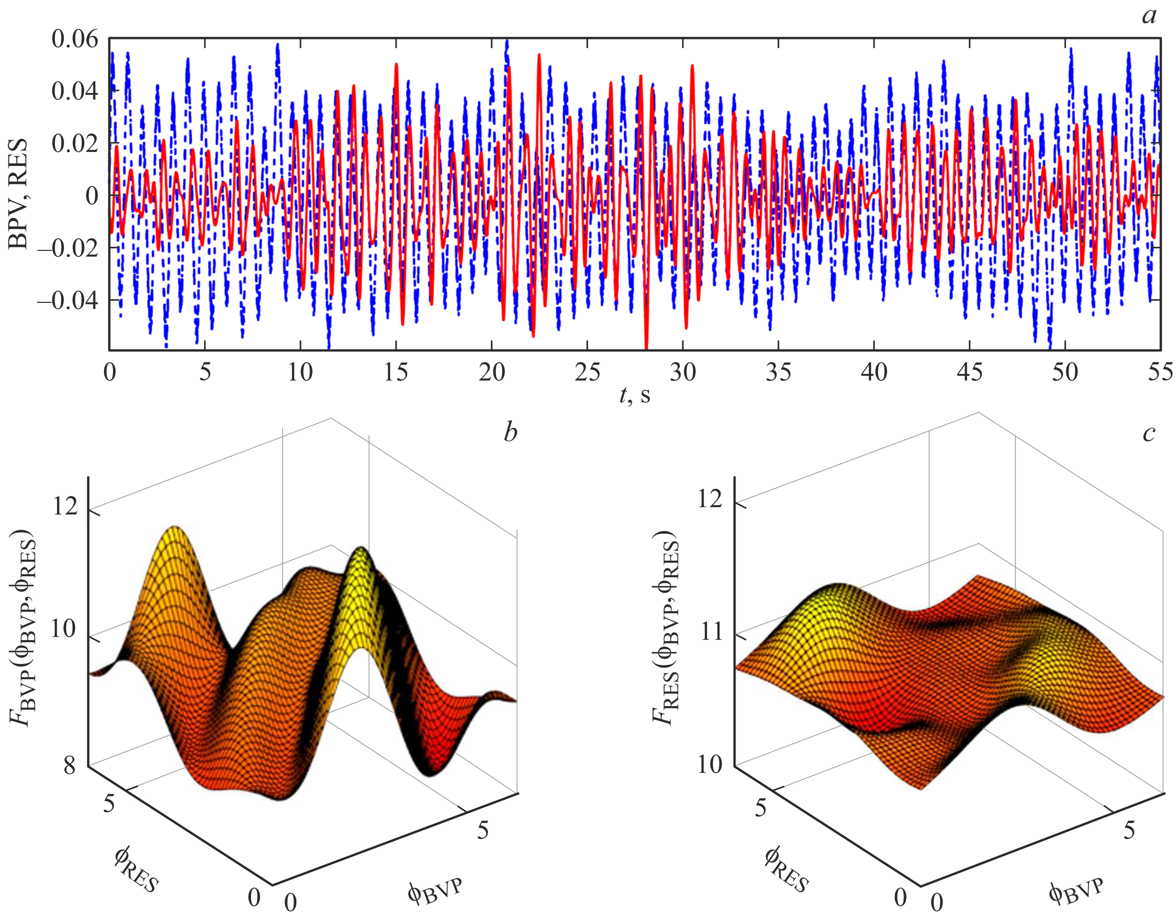

Figure 4. Relationship between variability of blood pressure intervals and rat breathing rhythm; *a* — fragments of RES (dashed curve) and BPV (solid curve); *b, c* — relationship functions $F_{\text{BPV}}(\varphi_{\text{BPV}}, \varphi_{\text{RES}})$ and $F_{\text{RES}}(\varphi_{\text{BPV}}, \varphi_{\text{RES}})$.

variability of the allocated RR intervals. Both unidirectional and bidirectional nature of the relationship between the variability of RR intervals and blood pressure in pregnant women was found using the method of finding joint recurrences in [39], however, there was no clear direction of the relationship between blood pressure and respiration.

The statistically significant nature of the relationship between the analyzed signals of the respiratory, cardiovascular and nervous systems in a small group of anesthetized animals was identified based on modeling the phase dynamics of loosely coupled and weakly noisy periodic processes. The absence of a pronounced orientation on the part of the rat nervous system may be due to anesthesia, which, as is known, increases the duration of synchronization between the signals of the respiratory and cardiovascular systems and reduces the effect of pain sensitivity on these systems [13,14].

Conclusion

The method of detecting directional relationship between interacting systems based on phase dynamics modeling and the evaluation of the statistical significance of the obtained directional indices for the first time allowed determining the directional relationship options (unidirectional and bidirectional) between the analyzed time series isolated from biological data recorded in the form of neuronal activity, fluctuations in blood pressure and respiratory rhythm of anesthetized rats. A further processing of signals from a larger number of animals in various experiments is required for a reliable physiological interpretation of the directionality of relationships in the subject systems, which can serve as the subject of further studies.

Compliance with ethical standards

All applicable international, national, and/or institutional guidelines for animal care and management were observed.

Acknowledgments

The authors thank O.A Lyubashin, the head of the Lab. of Cortico-Visceral Physiology of Pavlov Institute of Physiology, for providing experimental data.

Conflict of interest

The authors declare that they have no conflict of interest.

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