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Simulating the differences in directional cardiorespiratory coupling in the awake state and different stages of sleep using a comprehensive mathematical model

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Abstract We propose a mathematical model of the human cardiovascular and respiratory systems. The cardiovascular segment of the model simulates the main heart rate, oscillating blood pressure, peripheral vascular resistance, and nonlinear dynamics of the autonomic control of circulation, namely α- and β-sympathetic and parasympathetic control. The respiratory part includes central pattern generator, lungs, and a control loop sensitive to the concentration of CO_2 and O_2 in the arterial blood. Both parts of the model are linked in a physiological manner. The adequacy of the model is demonstrated by comparing the simulated time series to the experimental records of healthy subjects from the SIESTA database using spectral analysis, statistical analysis, and nonlinear measures of directional coupling. The proposed model can become a useful tool for investigation of the cardiovascular dynamics during sleep.

1 Introduction

Investigation of the cardiovascular system in different stages of sleep attracts a lot of attention [1–3]. It was shown that scaling properties of the cardiac dynamics are different during sleep and awake periods [4]. Characteristics of the rapid eye movement (REM) sleep correlate with exacerbation of ischemic heart disease, sometimes even leading to myocardial infarction [5]. These events are most common in patients with coronary artery disease [6]. In experimental studies [6, 7], it was shown that in patients with aortic stenosis, sympathetic activation can lead to decreased myocardial perfusion. The development of respiratory pathologies such as apnea is associated with dysfunction of the autonomic control of the cardiovascular system [8–10]. The influence of the respiratory system on the cardiovascular system is equally important. It was shown that obstructive apnea can cause lasting damage to the cardiovascular system, one of the detrimental factors being constant stress due to tiredness and lower quality of life.

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Despite numerous studies, the individual dynamics of the cardiovascular system (CVS) and respiratory system and their interaction during sleep are not fully understood. This is due to the complexity of these systems, which include numerous interacting nonlinear elements. Other problems are related to the technical difficulties and ethical problems limiting the experimental studies. Therefore, the development of comprehensive mathematical models, which are based on physical and physiological laws, is important [11]. Such models can simulate complex CVS dynamics and generate stationary time series of any length; it is also possible to simulate various pathologies [12, 13], effects of drugs [14], and physiological tests [15]. The model can also be used to perform studies, which are impossible on volunteers, such as selective blockade of one or many components of the system [16]. The models are also commonly used to test different data processing algorithms [17].

The development of mathematical models also promises a solution to the problems of the personalized medicine, since some parameters of the model can be estimated directly from the experimental data of a particular patient to create a mathematical double. Application of personalized mathematical models expands the possibilities of medical diagnostics and therapy, making it possible to predict the course of diseases and simulate the patient's response to medications.

A number of mathematical models of CVS take into account the dynamics of the autonomic control of blood circulation [12–22], but only a few simulate the dynamics of the autonomic control loops and respiratory system during sleep [20–23], the most well-known being PNEUMA [22]. However, PNEUMA lacks several important details, such as production and decay of the noradrenaline. In our opinion, detailed description of the autonomic control is necessary to adequately simulate the individual and coupled dynamics of the CVS and respiratory system in different stages of sleep. Our opinion is based on several experimental results listed below.

In experimental studies, it was shown that non-REM sleep (especially stage 4) is characterized by a decreased tone of sympathetic activity, a decrease in heart rate and average level of blood pressure, and a decrease of blood pressure variability [24]. Other studies reported pronounced respiratory sinus arrhythmia caused by the parasympathetic activity [25].

The REM sleep is more complex, with alternating epochs of sharp increases and decreases in the sympathetic activity [24]. As shown by direct measurements from the sympathetic nerves, on average, there is an increase in sympathetic activity, leading to an increase in blood pressure variability, but the heart rate is similar to a waking person at rest. These results were confirmed in active experiments with blocking of the sympathetic or parasympathetic autonomic control, which compensated for the corresponding changes in the dynamics of CVS [25].

It is known that the transition to sleep is also associated with the influence of the higher nervous system on the autonomic control. In model studies [23, 26], potential ways for the influence of higher nerve centers on autonomic control during sleep are presented.

In the present paper, we propose a comprehensive model of the CVS and respiratory system, capable of simulating the dynamics of the biological systems in different stages of sleep and in the awake state. The model includes detailed description of the nonlinear properties of the autonomic control of circulation and respiration. The model simulates with good accuracy the statistical and spectral properties of the real-world arterial blood pressure (AP) recordings and RR intervals (RRI) time series. As well as our earlier models, it can simulate arterial hypertension [27], reaction to the passive orthostatic test [15], and reaction to the autonomic blockade due to administration of Arfonad [27]. Moreover, the model simulates the chaotic dynamics of heart rate [16] and phase synchronization between the autonomic control loops [28], which is observed in humans [29] and is important for diagnostics and understanding of several circulatory diseases.

The model is used to simulate the individual and coupled dynamics of the CVS and respiratory system in the awake state, during REM sleep, and during non-REM stage 4 deep sleep. The adequacy of the model is demonstrated by comparing the simulated time series with experimental records of healthy subjects from the SIESTA database [30] using spectral analysis, statistical analysis, and nonlinear measures of directional coupling. The results of numerical modeling were compared to the recent experimental data [31].

1.1 Ethics

The model was tested against the experimental data from the SIESTA database, see Sect. 1.3. The studies involving human participants were reviewed and approved by the Ethics Committee of Klinikum der Philipps-Universität Marburg in 35037 Marburg, Germany. The study participants, all above the age of 18 years, provided written informed consent to participate in the study.

1.2 The experimental data

We verified the model by comparing it to the experimental electrocardiogram (ECG) signals from the SIESTA database [30]. The database includes recording from 20 healthy subjects that fulfilled the following criteria: no regular shift work, usual bedtime before midnight, and no acute depressive or anxious symptoms. Each subject was

monitored by wrist-worn actigraphs (Actiwatch, Cambridge Neurotechnology, England) 1 week prior and 1 week after the recording session. Quality control ensured there are no outliers in the final data set, and all signals were recorded with no protocol violations.

For each subject a set of 3 20 min ECG signals was recorded, one record made in the awake state, one during REM sleep, and one during stage 4 of non-REM sleep. Each signal was recorded at sample rate of 200 Hz. The high-pass cutoff frequency was set between 1.6 and 16 Hz.

1.3 Mathematical model

Structure of the model is shown in Fig. 1. Full description of the model, including listing of equations and parameters, is available in the open-access article [21]. Here, we will give a brief qualitative description of the whole model, except for the modification related to the simulation of the CVS dynamics in the different stages of sleep. The modified expressions will be listed and thoroughly explained.

The proposed model consists of 13 nonautonomous differential equations, with over 100 parameters. The proposed model consists of two main parts: CVS and respiratory system. The CVS model is built upon the earlier model by Seidel and Herzel [32], and its further modifications [12], including our own modifications [16]. The heart rate is set by the "Integrate and fire" generator, with β-sympathetic and parasympathetic parts of the autonomic control modulating the frequency of the generator. The autonomic control also regulates the heart contractility, i.e., how much blood it pumps during one cardiac cycle. The pulsatile arterial pressure in the aorta is modeled using two equations. The first equation describes the rapid rise during the first 0.125 s of the cardiac cycle, caused by the blood pumped into the aorta. The second equation describes the slow decrease, caused by the outflow into the peripheral arterial vessels.

The model of the autonomic control of circulation simulates β-sympathetic control of heart rate, α-sympathetic control of arterial pressure, through the regulation of the peripheral resistance, and parasympathetic control of the heart rate. Both loops of the sympathetic control are activated, when the blood pressure drops below normal values, which causes secretion of noradrenaline, leading to the rise in the heart rate, heart contractility, and peripheral resistance. Activation of the parasympathetic control has an opposite effect and is caused by the rise of the arterial pressure. The arterial pressure is measured by the baroreceptors, located in the aorta. The transfer functions of the baroreceptors closely reproduce the experimental data.

The model of respiratory system was adopted from [33]. It includes the central pattern generator, which sets the frequency and amplitude of respiration; gas exchange between the alveoli and arterial blood; autonomic control of respiration. The control of circulation functions similarly to the autonomic control of circulation, but the central carotid baroreceptor measures two values: blood concentration of CO_2 and O_2. The increase in CO_2 and decrease in O_2 cause the ventilation to rise, and in the opposite case the ventilation is lowered. We modified the model of respiration by introducing more detailed transfer functions [34] to the chemoreceptors.

We implemented a bidirectional cardiorespiratory coupling, as it was modeled by Magosso and Ursino [20]: activation of the central chemoreceptors excites both the sympathetic and parasympathetic control of circulation.

Finally, transition between the awake state and different stages of sleep is induced by the influence of the central nervous system on to the parts of the autonomic control. Below we listed the three equations, which were modified by the addition of terms related to the autonomic control.

The first two equations simulate the activation of the α- and β-sympathetic autonomic control (Eq. 33 and 34 in [21]):

$$v_{\alpha s}(t) = \left(v^0_{\alpha s} + C_{\alpha s}\right) - k^b_{\alpha s} v_b(t) + k^c_{\alpha s} v_c(t) - k^r_{\alpha s} V_A(t), \tag{1}$$

$$v_{\beta s}(t) = \left(v^0_{\beta s} + C_{\beta s}\right) - k^b_{\beta s} v_b(t) + k^c_{\beta s} v_c(t) + k^r_{\beta s} V_A(t), \tag{2}$$

where $v^0_{\alpha s}$ and $v^0_{\beta s}$ describe the activity of the sympathetic control under resting conditions; $k^b_{\alpha s}$, $k^c_{\alpha s}$, $k^r_{\alpha s}$, $k^b_{\beta s}$, $k^c_{\beta s}$, and $k^r_{\beta s}$ are the coefficients that reflect the influence of baro- and chemoreceptors activity; $v_b(t)$ is the activity of the arterial baroreceptors, $v_c(t)$ is the activity of the carotid chemoreceptors, $V_A(t)$ is the lung volume; $C_{\alpha s}$ and $C_{\beta s}$ are introduced to reflect the influence of the central nervous system, and in the awake state both coefficients equal to zero, see Table 1.

In a similar manner, we modified the equation for the parasympathetic autonomic control (Eq. 35 in [21]):

$$v'_p(t) = \left(v^0_p + C_p\right) + k^b_p v_b(t) + k^c_p v_c(t) - k^r_p V_A(t) + k^\xi_p \xi(t), \tag{3}$$

where v^0_p is the parasympathetic activity under resting conditions, k^b_p, k^c_p, and k^r_p are the coefficients that reflect the influence of baro- and chemoreceptors activity, and ξ is the red noise of "central" origin [12]; C_p was introduced to reflect the influence of the central nervous system, and in the awake state both coefficients equal to zero, see

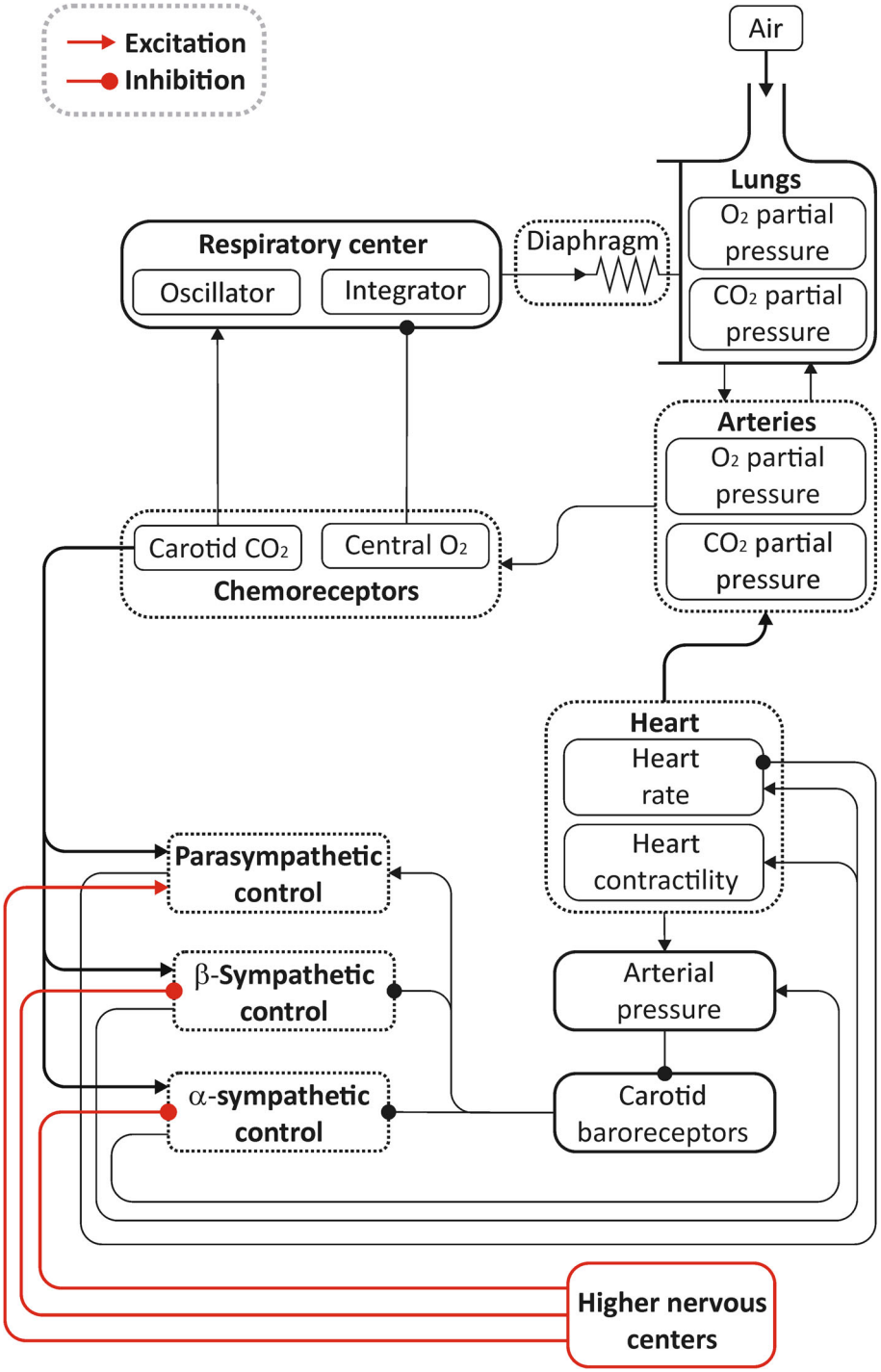

Fig. 1 Structure of the proposed model

Table 1 Values for the coefficients that reflect the influence of the central nervous system in the awake state, REM, and non-REM sleep

Index	Awake	REM sleep	Non-REM sleep
$C_{\alpha s}$	0	− 0.10	− 0.12
$C_{\beta s}$	0	− 0.10	− 0.12
C_p	0	0.10	0.12

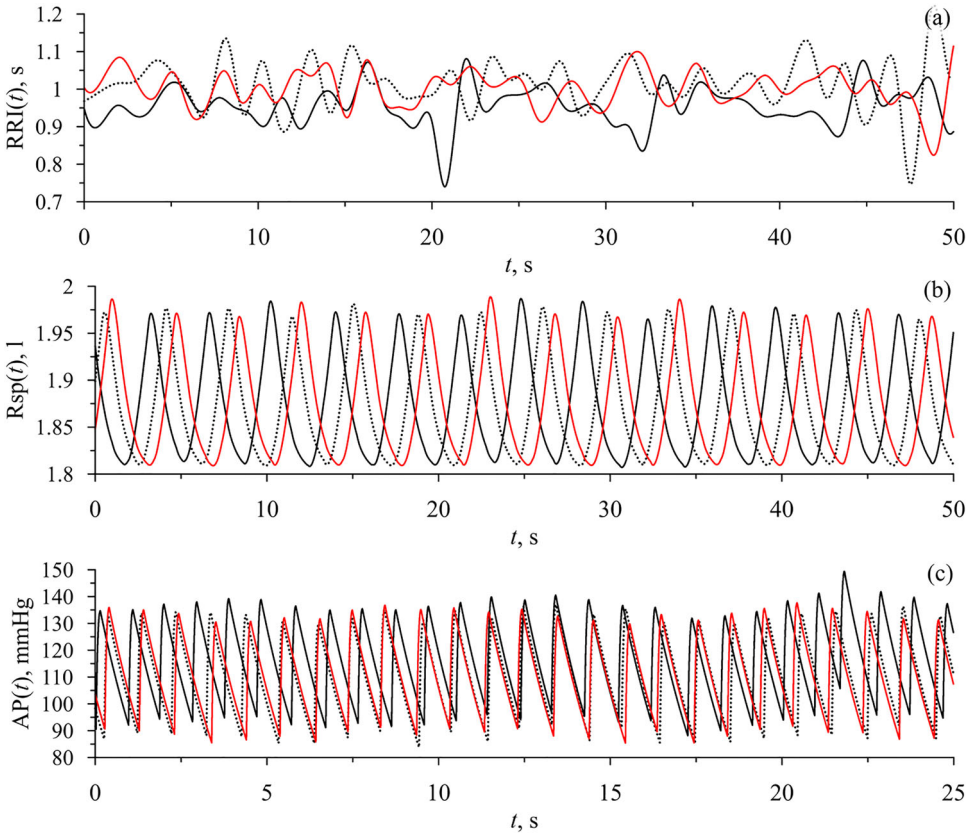

Fig. 2 RRI (**a**), Rsp (**b**) and AP (**c**) time series, solid black lines—awake state, red lines—REM sleep, dashed black lines—non-REM stage 4 deep sleep

Table 1. The values of $C_{\alpha s}$, $C_{\beta s}$ and C_p in different stages of sleep are also listed in Table 1. Simulation of the CVS dynamics in different stages of sleep was achieved only by switching the values of the $C_{\alpha s}$, $C_{\beta s}$ and C_p parameters. All other parameters of the model stayed the same in all simulations.

The model can simulate the following biosimilar signals: RRI, arterial pressure, activity of carotid baroreceptors, activity of α- and β-sympathetic control of circulation (as integrated spiking activity of related nerves), activity of the parasympathetic control of circulation, peripheral vascular resistance, noradrenaline concentration in cardiac tissues and peripheral arteries, output of the rVRG complex, pleural pressure, gas pressure in the alveoli, partial pressure of CO_2 and O_2 in the alveoli, activity of the central CO_2 receptors in the medulla, andactivity of the carotid O_2 receptors.

The model does not take into account the humoral control mechanisms and only simulates the processes with time scales of 0.04–0.4 Hz. Other limitations of the model will be listed and discussed in Sect. 3. The main advantage of the proposed model over other similar models is the more detailed representation of the autonomic control of circulation and respiration, which we think is necessary to faithfully recreate the complexity of the cardiorespiratory interactions.

The model RRI (RRI(t)), arterial pressure, and lung volume (Rsp(t)) time series in the awake state, REM sleep, and non-REM stage 4 sleep are shown in Fig. 2.

1.4 Indices of directional coupling

When analyzing the experimental and model data, we closely followed the protocol established in [31]. From the model and experimental ECG signals, we extracted the RR intervals (RRI), i.e., time intervals between successive R peaks [35], the resulting time series were interpolated using cubic β-splines and resampled with a frequency of 20 Hz.

We compared the experimental respiratory signal (registered using oronasal thermistor flow sensor) to the model signal of lung volume.

We filtered both RRI and respiratory signals (Rsp) using a rectangular digital filter with the bandpass of 0.15–0.50 Hz. In the following formulas, the filtered signals of Rsp and RRI will be referred to as $x_{\mathrm{Resp}}(t)$ and $x_{\mathrm{RRI}}(t)$.

A detailed description of the method we used to estimate the strengths of the directional coupling is available in [31]. First, we extracted the phases $\varphi_{\mathrm{Rsp}}(t)$ and $\varphi_{\mathrm{RRI}}(t)$ from the $x_{\mathrm{Rsp}}(t)$ and $x_{\mathrm{RRI}}(t)$ using the Hilbert transform. Then we constructed a stochastic differential equations modeling the phase dynamics:

$$\mathrm{d}\varphi_{\mathrm{Rsp,\,RRI}}(t)/\mathrm{d}t = \omega_{\mathrm{Rsp,\,RRI}} + G_{\mathrm{Rsp,\,RRI}}(\varphi_{\mathrm{Rsp,\,RRI}}(t),\, \varphi_{\mathrm{Rsp,\,RRI}}(t-\Delta)) + \xi_{\mathrm{Rsp,\,RRI}}(t), \tag{4}$$

where $\omega_{\mathrm{Rsp,RRI}}$ are the angular frequencies of the $x_{\mathrm{Rsp}}(t)$ and $x_{\mathrm{RRI}}(t)$ oscillations, $G_{\mathrm{Rsp,RRI}}(t)$ are 2π periodic functions, Δ is the time delay between the $\varphi_{\mathrm{Rsp}}(t)$ and $\varphi_{\mathrm{RRI}}(t)$ time series, and $\xi_{\mathrm{Rsp,RRI}}(t)$ is a zero-mean Gaussian noise. The strengths of the directional coupling in the direction respiratory signal → RRI were estimated as:

$$c^2_{\mathrm{RRI}\to\mathrm{Rsp}}(\Delta) = \int_0^{2\pi}\int_0^{2\pi} (\mathrm{d}F_{\mathrm{Rsp,\,RRI}}(\varphi_{\mathrm{Rsp,\,RRI}}(t),\, \varphi_{\mathrm{Rsp,\,RRI}}(t-\Delta),\, \mathbf{a}_{\mathrm{Rsp,\,RRI}})/\mathrm{d}\varphi_{\mathrm{RRI,\,Rsp}})^2 \mathrm{d}\varphi_{\mathrm{Rsp}}\mathrm{d}\varphi_{\mathrm{RRI}}, \tag{5}$$

we then normalized the $c^2_{\mathrm{RRI}\to\mathrm{Rsp}}(\Delta)$ and $c^2_{\mathrm{Rsp}\to\mathrm{RRI}}(\Delta)$ indices by the variances σ^2_{RRI} and σ^2_{Rsp}, for example:

$$\rho_{\mathrm{RRI}\to\mathrm{Rsp}}(\Delta) = \frac{c^2_{\mathrm{RRI}\to\mathrm{Rsp}}(\Delta)}{\sigma^2_{\mathrm{RRI}}}. \tag{6}$$

When calculating the indices, Δ varied within the [− 10 s; 10 s] range, and only the maximum value of the $\rho_{\mathrm{RRI}\to\mathrm{Rsp}}(\Delta)$ (or $\rho_{\mathrm{Rsp}\to\mathrm{RRI}}(\Delta)$) index was recorded. The resulted maximum values were averaged across all 20 volunteers to obtain the final estimations.

2 Results

Table 2 shows the spectral and statistical indices estimated from the model and experimental RRI, Rs,p and AP time series. SAP is systolic AP (mmHg); DAP is diastolic AP (mmHg); HR is heart rate (bpm); Rsp is rate (Hz); LF is the spectral power density in the 0.04–0.15 Hz band of the RRI, mainly related to the activity of the sympathetic control of the heart rate (ms^2); HF is the spectral power density in the 0.15–0.40 Hz band of the RRI, related to the activity of the parasympathetic control of the heart rate (ms^2); LF and HF indices are shown as mean value ± standard deviation, and the other indices have no variations due to the stationary nature of the model. In addition, several indices could not be derived from the SIESTA database.

Table 2 shows that the model qualitatively and to a degree quantitatively simulates the data available in the SIESTA database, in the exception of the HF index. However, in this case the SIESTA data contradicts the data from the literature [24, 25]. The arterial pressure, minute ventilation, and heart rate decrease. The LF index decreases, which is also typical and is likely related to the inhibition of the sympathetic control of the heart rate; inversely, the HF index decreases due to the excitation of the parasympathetic control of the heart rate.

Figure 3 shows the model and experimental estimations of the directional coupling indices in the awake state, REM sleep, and stage 4 non-REM sleep. The indices are shown in the normalized units, since their absolute values have no physiological significance [35]. Figure 3 shows good correspondence between the model and experimental

Table 2 The spectral and statistical indices estimated from the model RRI, Rsp, and AP time series

Index	Awake		REM sleep		Deep sleep	
	Model	Exp	Model	Exp	Model	Exp
SAP, mmHg	138	–	134	–	133	–
DAP, mmHg	94	–	89	–	88	–
HR, bpm	57	78 ± 6	60	74 ± 4	61	74 ± 2
Rsp rate, Hz	0.166	–	0.165	–	0.165	–
LF, ms^2	992 ± 256	841 ± 52	500 ± 172	451 ± 56	406 ± 141	187 ± 24
HF, ms^2	775 ± 137	459 ± 47	836 ± 163	392 ± 46	838 ± 155	227 ± 33

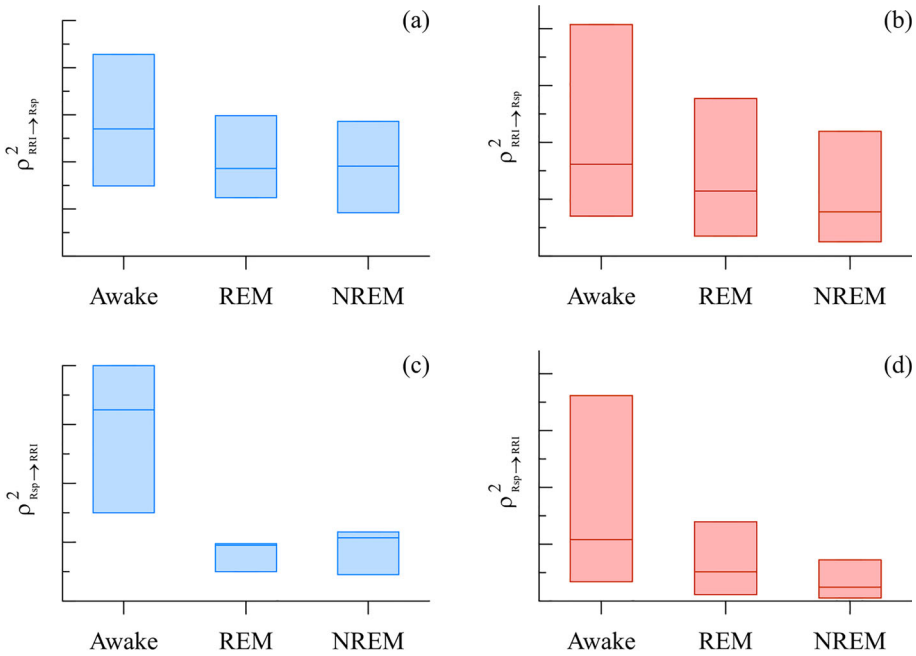

Fig. 3 The experimental (blue bars) and model (red bars) estimations of the directional coupling indices in the awake state, REM sleep and non-REM stage 4 deep sleep

data from [31], and the coupling in both directions becomes weaker in the REM sleep and non-REM stage 4 deep sleep.

3 Discussion

The obtained results show that the model behaves qualitatively and to a degree quantitatively similar to the real cardiovascular system. However, the model also has limitations. The model focuses on the nonlinear properties of the autonomic control of circulation, but it does not account for slower humoral factors, and therefore cannot simulate their effects on the dynamics of the cardiovascular system in different stages of sleep.

Another important limitation is the inability to simulate deep and fast breathing, which requires modeling of additional sections of the respiratory center and additional respiratory muscles. Simulation of the cardiorespiratory coupling, or the dynamics of the cardiovascular system under stressful conditions, such as sleep apnea, will require additional modifications.

Fitting of the model to the experimental data is another important topic, because the choice of parameters has great impact on the behavior of the model, and a badly fitted model could be inadequate even when the structure of the model represents the real-world object well.

The proposed model has more than 100 parameters. In deep machine learning, it is common to train much larger models using stochastic gradient descent, but it requires analytical calculation of the partial derivations, and an analytical approach cannot be applied to the model with stochastic terms and complex differential equations. Numerical implementation of the gradient descent is also possible, but will require too much computational power. Another problem is that the current medical equipment cannot capture all the data needed to reliably fit the model, as was discussed in [22].

To tackle this problem, we made a comprehensible mathematical model. Significant portion of its parameters have physiological meaning and can be estimated from the experimental data. We also tested the adequacy of the model in different experiments using similar sets of parameters. We previously used the isolated model of the cardiovascular system to simulate the passive orthostatic test [15], arterial hypertension [27], blockade of autonomic control [27], and cardiorespiratory synchronization [27].

In the current study, the parameters, related to the influence of the higher nervous centers onto the autonomic control ($C_{\alpha s}$, $C_{\beta s}$, C_p), were fitted to adequately simulate the statistical properties of the cardiovascular system in the awake state and different stages of sleep. We estimated the coupling indices only after the fitting was complete, and the model generalized well, which gives us some grounds to suggest that the model and parameters

are adequate, and the results obtained when investigating the simulated dynamics can be generalized on the real system.

4 Results

We proposed a mathematical model of the human cardiovascular and respiratory systems, capable of simulating the dynamics of the system in the awake state, REM sleep, and non-REM stage 4 deep sleep.

The cardiovascular segment simulates the autonomic control of the heart rate, heart contractility, and the pulsatile arterial pressure, by regulating the peripheral vascular resistance. The respiratory segment includes the central pattern generator, lungs and a control loop, based on the concentration of CO_2 and O_2 in the arterial blood.

The main feature of the model is the detailed description of the α- and β-sympathetic, and parasympathetic control of circulation, and autonomic control of respiration, including simulation of the nonlinear effects, such as self-oscillation and synchronization. This level of detalization made it possible to simulate the difference in the strengths of the bidirectional cardiorespiratory coupling between the awake state, REM sleep and non-REM stage 4 deep sleep.

Comparison of the model results to the experimental data from the SIESTA database has shown that the model shows good qualitative and to a degree quantitative correspondence to the spectral and statistical characteristics of real data in the awake state, and both stages of sleep. The obtained results suggest that the structure of the model and its parameters are adequate, and the results obtained when investigating the simulated dynamics could be generalized to the real system. The proposed model therefore might be useful to predict and explain the results of sleep studies.

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Data availability statement Data will be made available on reasonable request.

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