Eur. Phys. J. Spec. Top. (2024) 233:579–588
https://doi.org/10.1140/epjs/s11734-024-01142-1

THE EUROPEAN PHYSICAL JOURNAL SPECIAL TOPICS

Regular Article

Cortisol dynamics and sleep–wake switching: a modeling study

Elena Litvinenko[a], Ksenia Merkulova[b], and Dmitry Postnov[c]

Institute of Physics, Saratov State University, 83 Astrakhanskaya Street, Saratov 410012, Russia

Received 30 November 2023 / Accepted 2 March 2024 / Published online 8 March 2024

Abstract Normally, the sleep–wake cycle is synchronized with the body's circadian rhythm, which in turn is synchronized with the 24-h period of sunlight. Circadian changes in key hormones, particularly cortisol, also tend to follow the body's circadian rhythm, masking their involvement in controlling the transition between sleep and wakefulness. In our work, we study the behavior of an extended mathematical model that describes the dynamics of both switching between sleep and wakefulness and the process of cortisol production, including their mutual influence. The main goal of our work is to evaluate the behavior of such an extended model in the light of the phenomenon of spontaneous internal desynchronization (SID). Our results indicate that the influence of the cortisol subsystem on the switch between sleep and wakefulness depends significantly on the strength of this feedback. In particular, the increased contribution of cortisol leads to desynchronization between the sleep–wake cycle and the circadian rhythm. With random deviations in the speed of the homeostatic process, the action of cortisol, on the one hand, increases the predictability of the behavior of physiological markers of the sleep–wake cycle, and on the other hand, can lead to the appearance of "excesses of activity"—days with early awakening and late falling asleep.

1 Introduction

Normally, the sleep–wake cycle is synchronized with the body's circadian rhythm, which in turn is synchronized with the 24-h period of sunlight. Circadian changes in major hormones, and in particular cortisol, also tend to follow a circadian rhythm, masking their involvement in controlling the transition between sleep and wakefulness. In addition to changes in illumination, many natural and social factors carry information about the time of day, this is the so-called Zeitgebers ("zeitgeber", German). This is the name given to external signals that can reset (or distract) the circadian clock. Zeitgebers include temperature changes [1], stress [2, 3], physical activity [4], and social interaction [5]. The most studied zeitgebers can be considered light [6] and food [7]. Normally, all the processes mentioned above are synchronized with the 24-h light cycle. However, in a number of situations this synchronization is disrupted.

An example of a transient disruption of rhythm coherence is jetlag [8, 9]. This is a common situation in the age of air travel and therefore is a fairly well-studied phenomenon. In the fight against it, along with drug therapy, therapy associated with the regulation of daylight [10], and mathematical modeling methods [11] are used.

Shift work can lead to persistent desynchronization of rhythms. Areas such as healthcare, manufacturing, shipping and others are function with a 24/7 schedule. Working on a shift schedule with night shifts leads to desynchronization of sleep–wake cycles with the circadian rhythm, thereby causing damage to health [12, 13]. In this regard, the working conditions of shift workers are being studied to normalize the sleep–wake cycle [8, 14].

Finally, the phenomenon of SID—spontaneous internal desynchronization can arise as a pathology, or sleep disorders. Various forms of this phenomenon are observed, for example, Advanced Sleep Phase Disorder, Delayed Sleep Phase Disorder, Free-Running Disorder, and Irregular Sleep–Wake Rhythm [8].

[a] e-mail: ells03@yandex.ru
[b] e-mail: merksenia@gmail.com
[c] e-mail: postnovdmitry@googlemail.com (corresponding author)

Experimental studies of the above effects are in progress, but they are labor-intensive and their capabilities are fundamentally limited from the point of view of the safety of the participating volunteers. For this reason, modeling studies have played an increasingly important role in the field.

One of the main model "frameworks" on which many mathematical models are built that describe the dynamics of sleep–wake cycle is the model by Borbély [15], where the regulation of sleep is determined by the interaction of homeostatic (process S) and circadian (process C) processes. Sleep deficit, described by the homeostatic process S, increases during wakefulness and decreases during sleep. The periodicity of these oscillations is controlled by process C, the circadian pacemaker of day and night. A recent review by Borbély et al [16] summarized their work over the past 30 years.

The two-process model has been very productive, but it is inevitably limited. In particular, it does not take into account brain activity outside the designated sleep and wakefulness centers. This model does not reproduce phenomena such as short episodes of sleep, or, for example, sleepwalking. It can be said that the main limitation of the Borbely model is that this model abstracts from all zeitgeber except the 24-h light rhythm.

A reasonable expansion of two-process model is relevant, so that it can take into account some other events and processes and thus drive the whole model more close to reality. In doing so, one obvious task is to take into account the influence of cortisol, the dynamics of which in turn are closely related to both the circadian clock and the rhythm of nutrition.

Cortisol, produced in the hypothalamic-pituitary-adrenal axis (HPA), is the primary neuroendocrine system responsible for the stress response and regulates many body functions, including energy balance, emotions and the immune system [17]. The HPA axis includes the paraventricular nucleus of the hypothalamus (PVN), the anterior pituitary gland, and the adrenal cortex. The major phase of cortisol production involves the release of corticotropin-releasing hormone (CRH) by the PVN, which activates the release of adrenocorticotropic hormone (ACTH) from the pituitary gland. ACTH, in turn, leads to the release of cortisol from the adrenal cortex. High concentrations of cortisol cause a decrease in the release of CRH and ACTH and thereby regulate the process. Cortisol and ACTH concentrations can be measured in the blood and show clear circadian and ultradian patterns. In our work, we examine the behavior of an extended mathematical model of sleep–wake cycle, which we obtained by combining the two-process model as proposed in the works of [18] and another model that describes the dynamics of cortisol production under the control of the circadian rhythm and the sleep–wake cycle, as proposed in the work [19].

The main goal of our work is to evaluate the behavior of such an extended model from the point of view of the stability of rhythm synchronization. Namely, we examine how the addition of a cortisol generation subsystem changes the dynamics of the two-process model in the parameter range previously substantiated as the most adequate in describing experimental data. To evaluate the model's behavior under more realistic conditions, we account for day-to-day variability in the condition in the form of random variations in the rate of change of the homeostatic variable H, which corresponds to variability in fatigue accumulation during the day and sleep quality at night.

The results we obtained show that the previously proposed and published parts of the mathematical model, when working together, demonstrate dynamics that do not contradict physiological data. Further, the effect of the cortisol subsystem on the sleep–wake switch depends significantly on the strength of this feedback. Areas of parameter values were found where cortisol leads to desynchronization of the sleep–wake cycle and circadian rhythm. The general nature of the displacement of the boundaries of the synchronization region has been established. It was found that with fluctuations in the rate of the homeostatic process, the action of cortisol, on the one hand, increases the predictability of the behavior of physiological markers of the sleep–wake cycle, and on the other hand, can lead to the appearance of "excesses of activity"—days with early waking up and late falling asleep.

2 The model

The parts included in the model and the ways of their interaction are shown schematically in Fig. 1.

2.1 The sleep–wake switch model

The activity of neural nuclei is described by Eqs. (1) and (2), where $Q(V_i)$ is the sigmoid function (7) of the average voltage of the corresponding population V_i, taking into account the maximum possible impulse generation frequency $Q_{max} = 100$ Hz and the average neuron action potential relative to rest $\Theta = 10$ mV with standard deviation $\sigma'\pi/\sqrt{3}$ ($\sigma = 3$ mV) [20]. The rate of change in the states of the nuclei is determined by the time constants τ_v and τ_m, as well as by the parameters of the coupling strength between the nuclei ν_{mv} and ν_{vm}, A_v and A_m take into account the influence of sides of other neuron populations. The influence of homeostatic and circadian processes is scaled by the parameters $\nu_{vH}H$ and $\nu_{vC}C(X, Y)$.

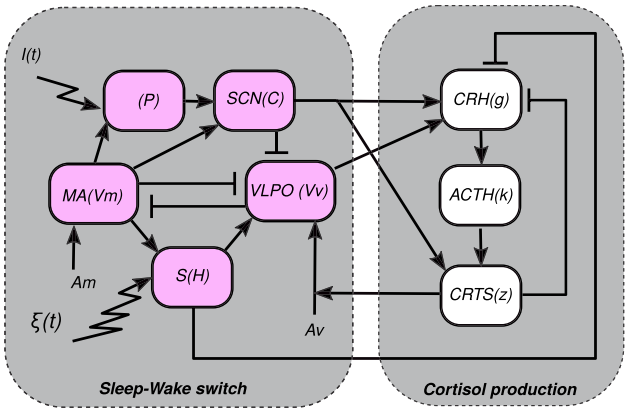

Fig. 1 Model flowchart. The bar-headed and arrow-headed lines indicate inhibitory and excitatory connections, respectively. The abbreviations are: P photoreceptors, SCN suprachiasmatic nucleus of the hypothalamus, S homeostatic process, MA monoaminergic nuclei of the hypothalamus and brainstem, $VLPO$ ventrolateral preoptic nucleus of the hypothalamus, CRH corticotrophin-releasing hormone, $ACTH$ adrenocorticotropic hormone, $CRTZ$ cortisol

The homeostatic process H is described by Eq. (3), where ν_{Hm} is the parameter of the influence on H from monoaminergic nuclei, and τ_{H} is the time constant of the homeostatic process. We have added to this equation a source of fluctuations in the form of Gaussian noise $\xi(t)$, the intensity of which is specified by the parameter D. In this way, we simulate the combined influence of various external and internal factors that slow down or accelerate the processes of accumulation of drowsiness and recovery. The circadian process C is modeled by Eqs. (4) and (5), for the variables X and Y, respectively, where $\tau_{\mathrm{x}} = \tau_{\mathrm{y}}$ are the time constants defining the period circadian oscillator, γ is a parameter that controls the shape of the oscillations, and τ_{c} and δ are introduced to be consistent with experimental data [21].

The effect of light on the circadian oscillator is specified using empirically selected nonlinear functions C_{Xp}, C_{Yp} (expressions (8) and (9)) for each of the oscillator variables. The parameters ν_{YY} and ν_{YX} make the effect dependent on the current phase of the circadian oscillator, and ϵ sets the degree of sensitivity of the light component to circadian variables.

The activity of photoreceptors—ganglion cells in the retina of the eyes that influence light on the circadian center [22, 23]—is modeled through the variable P by Eq. (6), where the function α_{I} shows the rate of activation ready for it parts of photoreceptors $(1 - P)$, which then spontaneously deactivate at a rate of β. Parameters α_0, I_0, I_1 set the dependence of photoreceptor activity on light intensity, τ_{p} is the activation time constant.

The feedback influence of neural nuclei on the circadian process is taken into account by the state function S, indicating whether the system is "sleeping" or "awake" ($U(x)$=1, when x¿0 and $U(x)$ =0 otherwise), as well as ν_{Xn}—the constant influence of factors not related to light. The r parameter modulates the timing of effects depending on the phase of the circadian oscillator.

In turn, the influence of the circadian oscillator on the activity of the sleep center is given in Eq.(1), where the strength of the circadian influence is expressed by the parameter ν_{vC}, and the shape of the nonlinear function, first proposed in Ref. [24] to better fit the experimental data, is regulated by the parameters c_1, c_2 and c_3.

The equations of the model (1)–(6) have the form:

$$\tau_{\mathrm{v}}\frac{\mathrm{d}V_{\mathrm{v}}}{\mathrm{d}t} = \nu_{\mathrm{vm}}Q(V_{\mathrm{m}}) - V_{\mathrm{v}} + \nu_{\mathrm{vH}}H + \nu_{\mathrm{vC}}C(X, Y) + A_{\mathrm{v}}, \tag{1}$$

$$\tau_{\mathrm{m}}\frac{\mathrm{d}V_{\mathrm{m}}}{\mathrm{d}t} = \nu_{\mathrm{mv}}Q(V_{\mathrm{v}}) - V_{\mathrm{m}} + A_{\mathrm{m}}(z), \tag{2}$$

$$\tau_{\mathrm{H}}\frac{\mathrm{d}H}{\mathrm{d}t} = \nu_{\mathrm{Hm}}Q(V_{\mathrm{m}}) - H + D\xi(t), \tag{3}$$

$$\tau_{\mathrm{x}}\frac{\mathrm{d}X}{\mathrm{d}t} = Y + \gamma\left(\frac{1}{3}X + \frac{4}{3}X^3 - \frac{256}{105}X^7\right) + C_{\mathrm{Xn}} + C_{\mathrm{Xp}}, \tag{4}$$

$$\tau_{\mathrm{y}}\frac{\mathrm{d}Y}{\mathrm{d}t} = -\left(\frac{\delta}{\tau_{\mathrm{c}}}\right)^2 X + C_{\mathrm{Yp}}, \tag{5}$$

$$\tau_{\mathrm{P}}\frac{P}{\mathrm{d}t} = \alpha_{\mathrm{I}}(1 - P) - \beta P. \tag{6}$$

The relations (7)–(13) included in the equations above have the form:

$$Q(V_{\mathrm{i}}) = \frac{Q_{\max}}{1 + e^{(\Theta - V_{\mathrm{i}})/\sigma'}}, \quad i = m, v, \tag{7}$$

$$C_{\mathrm{Xp}} = \nu_{\mathrm{Xp}} \alpha_{\mathrm{I}} (1 - P)(1 - \epsilon X)(1 - \epsilon Y), \tag{8}$$

$$C_{\mathrm{Yp}} = \alpha_{\mathrm{I}} (1 - P)(1 - \epsilon X)(1 - \epsilon Y)(\nu_{\mathrm{YY}} Y - \nu_{\mathrm{YX}} X), \tag{9}$$

$$C_{\mathrm{Xn}} = \nu_{\mathrm{Xn}} \left(\frac{1}{3} - (1 - S) \right) (1 - tanh(rX)), \tag{10}$$

$$S = U(V_{\mathrm{m}} - V_{th}), \tag{11}$$

$$C(X, Y) = 0.1 \frac{(X + 1)}{2} + \left(\frac{c_1 X - c_2 Y + c_3}{X + 2} \right)^2, \tag{12}$$

$$\alpha_{\mathrm{I}} = \alpha_0 S \frac{I(t)}{I(t) + I_1} \sqrt{\frac{I(t)}{I_0}}. \tag{13}$$

The daily illumination profile $I(t)$ corresponds to a signal of the "meander" type, where the model control parameters I_{amb} and I_{ext} set the night and day intensity, respectively.

2.2 Model of cortisol production

The model was proposed and justified in the work [19]. Equations (14)–(16) describe the dynamics of three variables: g denotes the concentration of corticotropin-releasing hormone (CRH), k denotes the concentration of adrenocorticotropic hormone (ACTH), ν_{kg} is the parameter determining relation between the CRH and ACTH concentrations, and τ_k is the ACTH degradation time constant. Variable z stands for the concentration of cortisol:

$$\frac{\mathrm{d}g}{\mathrm{d}t} = \frac{a_C S G_1(X)}{G_2(H)(1 + e^{s_{gr}(z - z_{gr})})} - \frac{g}{\tau_g}, \tag{14}$$

$$\frac{\mathrm{d}k}{\mathrm{d}t} = v_{kg} g - \frac{k}{\tau_k}, \tag{15}$$

$$\frac{\mathrm{d}z}{\mathrm{d}t} = v_{zk} k + bC(X, Y) - \frac{z}{\tau_{\mathrm{z}}}. \tag{16}$$

Unlike the original model, where the influence of the circadian rhythm is represented by a shifted harmonic function, in our modification, we use the value $G_1(X)$ which renormalizes the circadian variable X to coordinate the work of the two parts of the model. The quantity $G_2(H)$ performs the same function for the variable H:

$$G_1(X) = 0.5(X + 1.14); \tag{17}$$

$$G_2(H) = 100(1 + (H - 11.64)/(13.28 - 11.64)). \tag{18}$$

The feedback of cortisol on the dynamics of sleep–wake switching is implemented in Eq. (2), where the activity parameter of lateral neuronal populations A_{m} is made dependent on z and has the form $A_{\mathrm{m}}(z) = A_{m0}(1 + r_{\mathrm{z}}(z/z_{gr} - 1))$. This choice was made on the assumption that when r_{z}, the parameter of cortisol contribution to overall activity, was zeroed, the dynamics of the (1)–(6) subsystem would correspond to the publication [24]. Further, it would be logical to ensure that as the contribution of cortisol oscillations increases, the time-average level of A_{m} would be maintained. However, this is difficult to do, since the average value of the variable z is different for different oscillatory modes. Therefore, we use the parameter z_{gr}, which is proposed in the publication [19] and corresponds to approximately half the intensity of CRH production.

It can be noted that some variables have physical dimension, while other variables are dimensionless. This is explained by the fact that some quantities included in the model do not have an unambiguous physical interpretation. Namely, the amplitude of the circadian rhythm and the amplitude of the homeostatic process. In fact, only the time characteristics of these processes, such as phase and period, are important for the operation of the model.

2.3 Numerical methods and values of control parameters

Numerical integration of model equations was carried out by the 4th order Runge–Kutta method, adapted for solving stochastic differential equations. Maps of periods on the plane of two parameters were calculated by means of parallel computing, thus, each combination of parameters from the 400 × 100 matrix was checked.

The set of control parameters was compiled according to the mentioned publications[18, 19]. In these works, the dynamics of both models are validated against experimental data, which correspond to "typical healthy person". We used the set of control parameters from [18, 19], except for those that we changed during the simulation courses, as described in Sect. 3: Q_{max}= 100 Hz; Θ = 10 mV; σ' = 3 mV; $\tau_{\rm v} = \tau_{\rm m}$ = 50/3600 h; $\nu_{\rm vm}$ = −2.1/3600 mV h; $\nu_{\rm mv}$ = −1.8/3600 mV h; $A_{\rm v}$ = −10.3 mV; A_{m0} = 1.3 mV; V_{th} = -2 mV; $\nu_{\rm vH}$ = 1 mV; $\nu_{\rm vC}$ = −0.5 mV; τ_H=59 h; $\nu_{\rm Hm}$ = 4.57/3600 h; $\tau_{\rm x} = \tau_{\rm y}$ = 24/(2π) h; γ = 0.13; τ_c = 24.2 h; δ = 24.2/0.99729 h; c_1= 0.838; c_2 = 0.676; c_3 = 1.136; $\nu_{\rm Xn}$ = 0.032; r = 10 h; ν_{Xp} = 2220; $\nu_{\rm YY}$ = 739.8 h; $\nu_{\rm YX}$ = 1221 h; ϵ = 0.4; β = 0.007/60 Hz; α_0 = 0.1/60 Hz; I_0 = 9500 lx; I_1 = 100 lx; I_{amb} = 0 lx; I_{ext} = 100 lx and 200 lx; $\tau_{\rm p}$= 1/3600 h; a_C = 1.8 nmol/(L·h); s_{gr} = 1 L/nmol; z_{gr} = 150 nmol/L; τ_g = (4/ln 2)/60 h; ν_{kg} = 600 h^{-1}; τ_k = (15/ln 2)/60 h; ν_{zk} = 12000 h^{-1}; b = 30 nmol/(L·h); $\tau_{\rm z}$ = (70/ln 2)/60 h.

3 Results

3.1 Model dynamics under weak cortisol-mediated feedback

As a first step, we checked that the modifications we introduced when combining the model parts did not lead to distortion of the dynamics, namely, that the relationships between the phases of the circadian rhythm, the homeostatic variable and the generation of cortisol were not disrupted. We also checked that the introduced feedback in the form of the dependence $A_{\rm m}(z)$ does not break the stability of the model, at least for small $r_{\rm z}$.

Figure 2 illustrates the results of such testing. It shows the time courses of the three key variables of the model: X indicates the phase of the circadian cycle, H characterizes the homeostatic process, with its minimums and maximums corresponding to the physiological markers, awakening time (AT) and time of falling asleep (sleep onset, SO), respectively. The graph of the variable z reflects the characteristic features of the diurnal cycle of changes in cortisol concentrations. Namely, (i) its daily period is controlled by the circadian rhythm, (ii) a significant surge accompanying waking up, and (iii) the presence of ultradian fluctuations, which are believed to provide rapid adaptation to changes in external conditions, and in the model arise due to feedback from z to g, which controls the production of CRH depending on the level of cortisol.

The blue solid line in the panels of Fig. 2 illustrates the case when $r_{\rm z}$ = 0 and cortisol production does not affect the dynamics of the sleep–wake switching pattern. The red dotted line corresponds to $r_{\rm z}$ = 0.05, when the dynamics of cortisol causes a 5% modulation of the parameter A_{m0}. As you can see, the differences in the time courses of the variables are insignificant. This means that the feedback we introduced does not affect the structural stability of the model dynamics. The panels on the right show an enlarged view of the moments of transition from wakefulness to sleep (A) and back (B). You may notice a slight shift in these moments towards earlier falling asleep

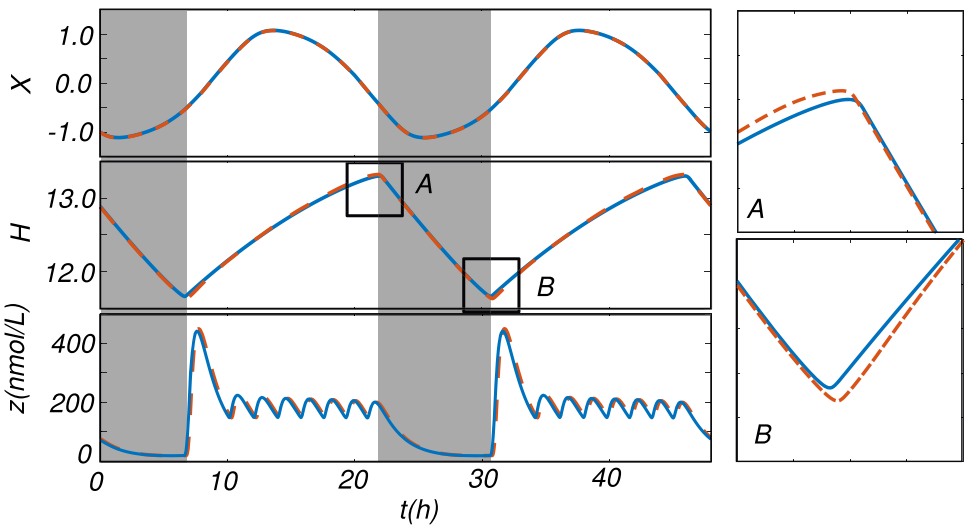

Fig. 2 Representative time courses of model variables. Sleep intervals are shaded in gray. Solid blue lines show the dynamics of the model without the feedback of cortisol, $r_{\rm z}$ = 0. Red dotted lines correspond to $r_{\rm z}$ = 0.05. Graphs for X and H are given in dimensionless units

and waking up later. Our next task was to find out how much the effect of cortisol can influence the period of the homeostatic rhythm in relation to the circadian rhythm.

3.2 Cortisol-induced spontaneous internal desynchronization

Previously, in the work [25], we investigated in which parameter areas the circadian and homeostatic rhythms of the model are synchronized and in which they are not. To study the action of the cortisol subsystem, the most straightforward way is to construct the boundaries of the region of rhythm synchronization as the value of r_z increases. Note that in our simulations, the average period of the circadian rhythm always remained at 24 h. Therefore, in the diagrams below, we display only the period of the homeostatic process T_S, the deviation of which from the value of 24 h means its desynchronization with the circadian one.

In Fig. 3, the value of T_S is given in color coding on the plane of parameters τ_H and ν_{vC}.

The choice of these particular parameters is based on the fact that τ_H controls the (uncoupled) period of the sleep–wake switching process, and ν_{vC} sets the strength of the influence from the circadian oscillator. This choice (coupling strength vs. frequency detuning) is typical for synchronization theory problems, and the expected structure in the diagram is a triangular-shaped synchronization region, with the tip on the line of zero external force $\nu_{vC} = 0$ (white dotted line). The synchronization region itself, where $T_S = T_C$, is highlighted in green, and its boundaries are more accurately shown by a black solid line.

As expected, at $r_z = 0$, the synchronization region reaches zero width at $\nu_{vC} = 0$. Note that above this line, synchronous modes also exist, but in antiphase (daytime sleep), so we do not consider this area. The dotted lines for $r_z = 0.17$ and $r_z = 0.25$ show that in this case the synchronization region continues into the region of positive ν_{vC}, where it has the form of a narrow channel. This means that the cortisol subsystem provides its own communication pathway to influence the circadian rhythm on the homeostatic one. Indeed, Eq. (14) includes $G_1(X)$ and provides a 24-h cycle of morning cortisol surges. Obviously, this is enough to replace the direct effect of the circadian oscillator with a homeostatic one at $\nu_{vC} \approx 0$.

Within the framework of our work, it is of particular interest where the boundary of the synchronization region will shift in relation to the typical mode, which is highlighted in the diagram with a filled circle. As can be seen, above this point the synchronization region expands for $r_z > 0$, and below it shrinks. We studied the influence of cortisol when choosing parameters in the vicinity of this point separately. The results are presented in Fig. 4.

Line L starts from the level $r_z = 0$, when there is no effect of cortisol. Moving upward along this line, one can see that the contribution of cortisol does not disrupt the synchrony of the regime up to $r_z \approx 0.14$. The characteristic appearance of the phase projections in this interval is given on the left for point A. This is a closed orbit with numerous small curls, reflecting ultradian fluctuations in cortisol concentration. Further, as r_z grows, there are two areas where the period $T_S < 24$, they are green and blue in the diagram (Fig. 4). These areas correspond

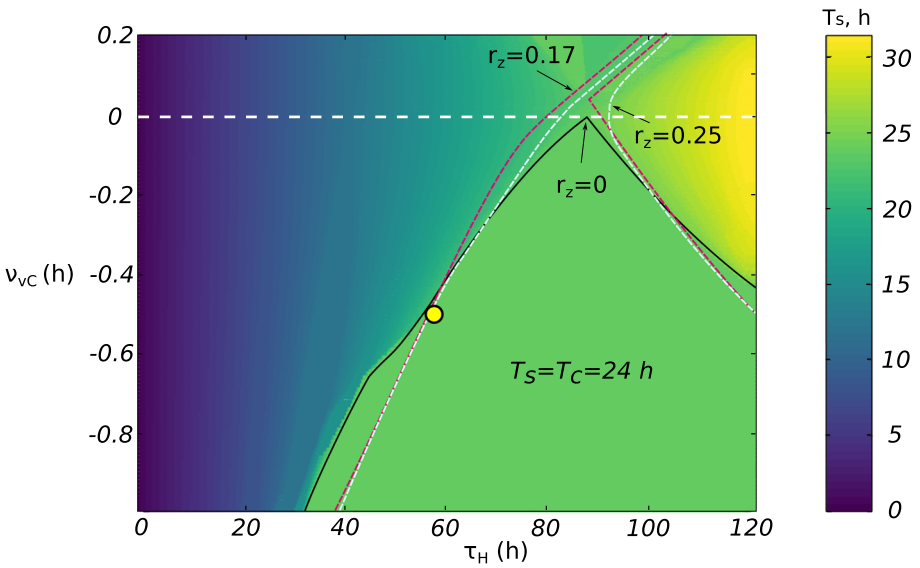

Fig. 3 The area of synchronization of the circadian rhythm with the period $T_C = 24.0$ and the process of sleep–wake switching with a period of T_S. The region of the main resonance, within which $T_S = T_C$, is shown by a solid line. Dashed lines show how the boundaries of the area shift at $r_z = 0.17, 0.25$. The horizontal dotted line highlights the case $\nu_{vC} = 0$, when at $r_z = 0$ the circadian process does not affect the homeostatic one and there is no synchronization. The filled circle denotes the parameter range for which the model was verified using experimental data in [18]. See text for further details

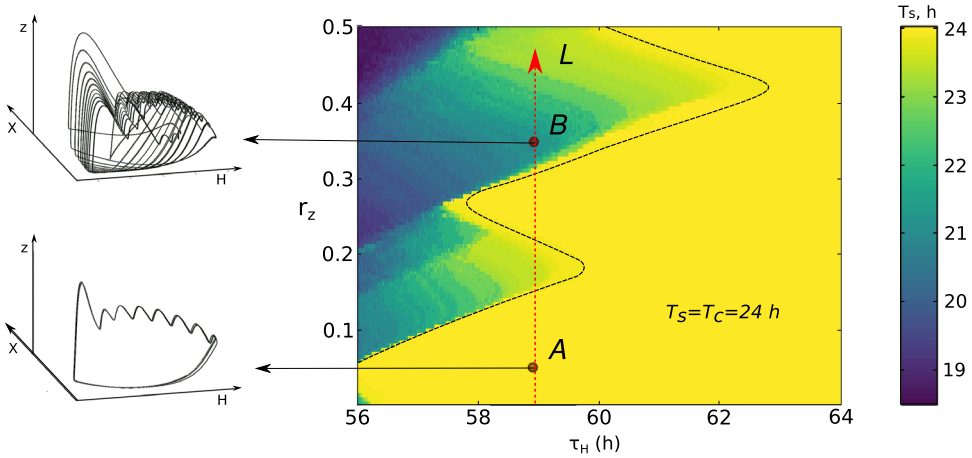

Fig. 4 The average period of the sleep–wake cycle T_S on the plane of parameters τ_H and r_z. At $r_z = 0$, the cortisol generation subsystem (14)–(16) does not affect the sleep–wake switch (1)–(6). The vertical dotted line with an arrow L shows the trajectory on the parametric plane, which is discussed in the text. The characteristic view of phase projections is given in the side panels

to the regime of spontaneous internal desynchronization, when the model system loses the normal relationship between rhythms due to internal dynamics, rather than due to external disturbing factors. The phase portrait for point B, at $r_z = 0.35$, has the characteristic form of non-periodic (quasiperiodic or chaotic) oscillations. A detailed inspection of this parameter region reveals numerous transitions between similar regimes, but an exhaustive study of them is beyond the scope of our work.

Summarizing the results of these computational experiments, there is a significant parameter range within which the contribution of the cortisol subsystem does not disrupt the normal functioning of the sleep–wake switch model. This is in favor of using such a combined model. Further, with a more significant contribution from the dynamics of cortisol, its reciprocal coupling with the homeostatic variable H lead to the fact that their joint dynamics become unlocked from the circadian rhythm. However, areas of synchronous dynamics remain. These areas presumably correspond to a favorable ratio of periods T_C and T_S. There are still many details that deserve to be studied using nonlinear dynamics methods.

3.3 Effect of cortisol subsystem under environmental fluctuations

It was noted that in reality, the processes described by the two-process model of sleep–wake switching are influenced by many factors, a significant part of which does not repeat every day, but is episodic in nature. Thus, in the work of [26] it was proposed to add an external signal, "psycho-sensory drive" as an image of many factors that can interfere with the normal sleep cycle. From a modeling point of view, there are two main approaches. The first is based on constructing an artificial signal to describe a specific situation and then consider their reasonable types. The second approach is based on the assumption that a combination of different events forms a noise-like signal that causes deviations from the norm.

In our work, we follow the second approach. As stated above in the description of the model, we added a random signal to Eq. (3). This option gives a random variation in the rate of the homeostatic process. In our opinion, this is more realistic than introducing a random fluctuation into the equations for V_v or V_m, although this issue is under discussion.

Since the sleep–wake switch model describes a system with two states, the main result of including fluctuations in the model is changes in the ratio between duration of sleep and wakefulness states, both dynamic (switch moments) and averaged (mean duration). For these reasons, in this section, we use discrete time series of values that are known as physiological markers: awakening time AT_i and sleep onset SO_i, where the subscript i denotes the number of day. The pair of values AT_i and SO_i characterizes the i-th day, and their difference $SO_i - AT_i$ gives the duration of the active part of the day.

Figure 5 shows the characteristic appearance of such time-discrete trajectories with coordinates (AT_i, SO_i) on the parameter plane (D, r_z).

For the sake of readability of the figure, we do not show values along the coordinate axes. All values of AT_i and SO_i are scattered around the values 6.7 and 22.3, respectively.

Three insets, which are shown on the x-axis, where $r_z = 0$, show that the effect of noise expectedly causes a scattering of the moments of waking up and falling asleep around their average values. The shape of the scatter spot suggests that for each day these moments are practically independent, each event occurs with its own deviation from the average.

Next, three inserts along the vertical axis for which there is no noise ($D = 0$) correspond to Fig. 4, showing either stable values of AT_i and SO_i (red dots and arrows) or jumping between two branches, which is typical for areas of asynchronous behavior.

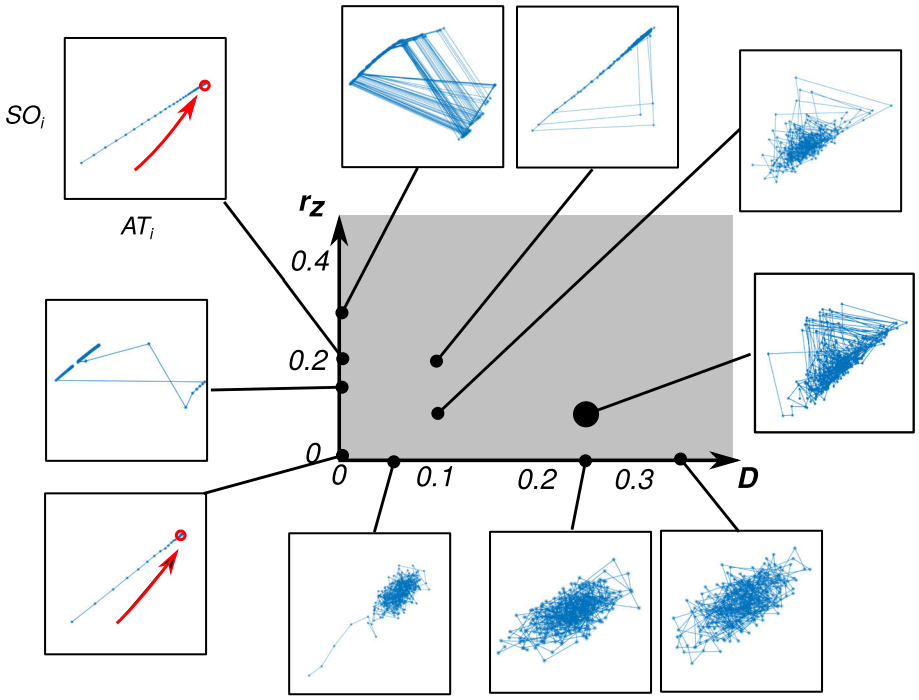

Fig. 5 The effect of cortisol on the dynamics of sleep–wake switching during fluctuations in the rate of the homeostatic process. The insets show the mapping $AT_{\mathrm{i}} \to SO_{\mathrm{i}}$ for the positions on the plane of parameters D and r_{z} indicated by arrows

Finally, when choosing $r_{\mathrm{z}} = 0.1$ and different noise intensities D, an interesting effect can be observed: the mapping $(AT_{\mathrm{i}}, SO_{\mathrm{i}} \to AT_{i+1}, SO_{i+1})$ shows a structure that is not observed if one of the factors (noise or cortisol action) is absent. Let us consider in more detail the case $D = 0.25$, $r_{\mathrm{z}} = 0.1$, highlighted in the figure with a bold circle. Details are given in Fig. 6.

The curves at $r_{\mathrm{z}} = 0$ are shown in gray for reference. You can see that in all three panels the type of dependence is approximately the same. The daily activity time of $(SO - AT)$ has a spread approximately the same as the graphs for AT and SO separately. On the contrary, the black curves for the case $r_{\mathrm{z}} = 0.1$ show that the time of daytime activity exhibits sharp peaks, which correspond to broad elevations in the AT and SO curves. One can find, that the peak time of daytime activity occurs because (i) the bursts of AT and SO are shifted by one time step and (ii) after the upward jump, the graph of both AT and SO does not fall immediately, but gradually decreases over several days. Therefore, there is no significant deviation in sleep time. Interestingly, this behavior fits well the well-known fact that our tends body to compensate for lost sleep time not at once, but in portions, distributing the compensation over several days.

Summarizing the dynamics of the model, we found that the cortisol subsystem transforms the dynamics of fluctuations of the H variable. On the one hand, it introduces a correlation into the random process; the predictability

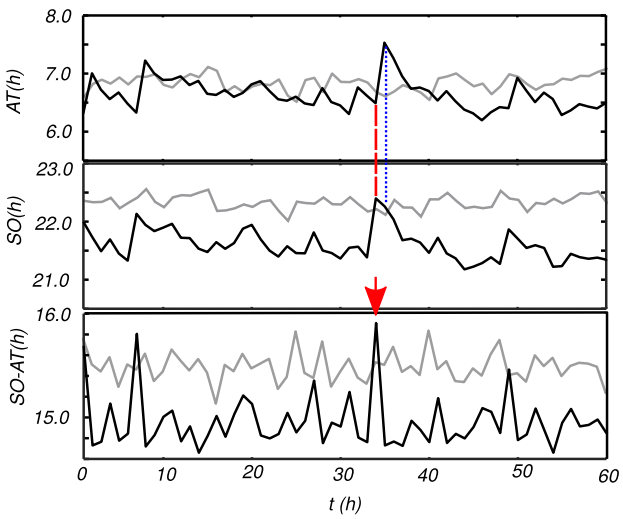

Fig. 6 Fragments of time courses of AT, SO and SO-AT for $D = 0.25$ and $r_{\mathrm{z}} = 0.1$. Dashed and dotted lines explain the appearance of increased activity time (shown by the arrow). See text for further details

of the values of AT and SO over time increases, but the spread of daily activity times increases. Since similar behavior can be found in a simpler form in desynchronization zones, clarifying the details can begin there. In this section, we have shown that the presence of fluctuations in the homeostatic process can serve as a trigger that activates cortisol-mediated dynamics.

4 Conclusion

In this work, we presented some results of a model-theoretical study of the dynamics of sleep–wake switching with the participation of cortisol. Specifically, we aimed to clarify how large diurnal and ultradian oscillations in cortisol levels may affect the relationship of sleep phases in relation to the circadian rhythm. In doing so, we combined into one two models previously proposed in the publications [18] and [19] in order to check how compatible they are and, most importantly, what new can be brought into the process of alternating sleep and wakefulness by such an important factor as pulsation of one of the main hormones.

Since it is difficult to quantify such influences, we acted differently. Namely, we assessed how the dynamics of the model were changing, and based on this we assumed physiologically reasonable parameter values. Thus, we can conclude that cortisol fluctuations can account for up to 15% of the total level of lateral (external to the sleep–wake switch) neural activity without critical deviation from the normal course of processes. At the same time, we found that including fluctuations can significantly change the situation. Overall, the extended model exhibits an expanded set of behaviors and we believe will be useful.

If we talk about the limitations of our modeling study, it is first of all that we have not yet added a single external zeitgeber. The most obvious choice and next task is to take into account the close connection of cortisol with feeding behavior. The task of understanding the impact of various nutritional patterns on sleep has an obvious applied aspect and at the same time is an achievable goal for modeling study.

Acknowledgements This research was supported by the Russian Science Foundation, project #22-15-00143. The authors would like to thank Dr.Svetlana Postnova, University of Sydney, for her interest in the work and valuable suggestions.

Data availability This work has no associated data.

References

1. L. Rensing, P. Ruoff, Temperature effect on entrainment, phase shifting, and amplitude of circadian clocks and its molecular bases. Chronobiol. Int. **19**(5), 807–864 (2002)
2. C. Kinoshita, K. Miyazaki, N. Ishida, Chronic stress affects period2 expression through glycogen synthase kinase-3β phosphorylation in the central clock. NeuroReport **23**(2), 98–102 (2012)
3. Y. Tahara, S. Aoyama, S. Shibata, The mammalian circadian clock and its entrainment by stress and exercise. J. Physiol. Sci. **67**(1), 1–10 (2017)
4. Y. Yamanaka, K.-I. Honma, S. Hashimoto, N. Takasu, T. Miyazaki, S. Honma, Effects of physical exercise on human circadian rhythms. Sleep Biol. Rhythms **4**, 199–206 (2006)
5. J.B. Panksepp, J.C. Wong, B.C. Kennedy, G.P. Lahvis, Differential entrainment of a social rhythm in adolescent mice. Behav. Brain Res. **195**(2), 239–245 (2008)
6. J.A. Perez-Leon, E.J. Warren, C.N. Allen, D.W. Robinson, R. Lane Brown, Synaptic inputs to retinal ganglion cells that set the circadian clock. Eur. J. Neurosci. **24**(4), 1117–1123 (2006)
7. F. Dang, X. Sun, X. Ma, R. Wu, D. Zhang, Y. Chen, Q. Xu, Y. Wu, Y. Liu, Insulin post-transcriptionally modulates bmal1 protein to affect the hepatic circadian clock. Nat. Commun. **7**(1), 12696 (2016)
8. R.L. Sack, D. Auckley, R.R. Auger, M.A. Carskadon, K.P. Wright Jr., M.V. Vitiello, I.V. Zhdanova, Circadian rhythm sleep disorders: part i, basic principles, shift work and jet lag disorders. Sleep **30**(11), 1460–1483 (2007)
9. W.H. Walker, J.C. Walton, A.C. DeVries, R.J. Nelson, Circadian rhythm disruption and mental health. Transl. Psychiatry **10**(1), 28 (2020)
10. R.L. Sack, The pathophysiology of jet lag. Travel Med. Infect. Dis. **7**(2), 102–110 (2009)
11. C.O. Diekman, A. Bose, Reentrainment of the circadian pacemaker during jet lag: East-west asymmetry and the effects of north-south travel. J. Theor. Biol. **437**, 261–285 (2018)
12. S. Davis, D.K. Mirick, R.G. Stevens, Night shift work, light at night, and risk of breast cancer. J. Natl Cancer Inst. **93**(20), 1557–1562 (2001)
13. L. Kervezee, A. Shechter, D.B. Boivin, Impact of shift work on the circadian timing system and health in women. Sleep Med. Clin. **13**(3), 295–306 (2018)
14. O.H. Meléndez-Fernández, J.A. Liu, R.J. Nelson, Circadian rhythms disrupted by light at night and mistimed food intake alter hormonal rhythms and metabolism. Int. J. Mol. Sci. **24**(4), 3392 (2023)

15. A.A. Borbély, A two process model of sleep regulation. Hum. Neurobiol. **1**(3), 195–204 (1982)
16. A.A. Borbély, S. Daan, A. Wirz-Justice, T. Deboer, The two-process model of sleep regulation: a reappraisal. J. Sleep Res. **25**(2), 131–143 (2016)
17. Smith, S.M., Vale, W.W.: The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Dialogues in clinical neuroscience (2006)
18. S. Postnova, S.W. Lockley, P.A. Robinson, Prediction of cognitive performance and subjective sleepiness using a model of arousal dynamics. J. Biol. Rhythms **33**(2), 203–218 (2018)
19. Postnova, S., Fulcher, R., Braun, H., Robinson, P.: A minimal physiologically based model of the hpa axis under influence of the sleep-wake cycles. Pharmacopsychiatry **46**(S 01), 36–43 (2013)
20. A. Phillips, P.A. Robinson, A quantitative model of sleep-wake dynamics based on the physiology of the brainstem ascending arousal system. J. Biol. Rhythms **22**(2), 167–179 (2007)
21. M.A.S. Hilaire, E.B. Klerman, S.B.S. Khalsa, K.P. Wright Jr., C.A. Czeisler, R.E. Kronauer, Addition of a non-photic component to a light-based mathematical model of the human circadian pacemaker. J. Theor. Biol. **247**(4), 583–599 (2007)
22. D.M. Berson, Strange vision: ganglion cells as circadian photoreceptors. Trends Neurosci. **26**(6), 314–320 (2003)
23. K.Y. Wong, F.A. Dunn, D.M. Graham, D.M. Berson, Synaptic influences on rat ganglion-cell photoreceptors. J. Physiol. **582**(1), 279–296 (2007)
24. S. Postnova, S.W. Lockley, P.A. Robinson, Sleep propensity under forced desynchrony in a model of arousal state dynamics. J. Biol. Rhythms **31**(5), 498–508 (2016)
25. D.E. Postnov, K.O. Merkulova, S. Postnova, Desynchrony and synchronisation underpinning sleep-wake cycles. The European Physical Journal Plus **136**(5), 488 (2021)
26. P.T. George, The psycho-sensory wake drive-a power source for power naps and other common sleep-wake phenomena: a hypothesis. Sleep Breath. **22**(1), 41–48 (2018)