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Modelling the homeostatic regulation of the sleep-wake cycle: role of diversity

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Abstract—We study a physiologically-motivated multi-neuron model of sleep-wake cycle, taking into account the circadian rhythm and the homeostatic regulating role of orexins. Heterogeneity is introduced in the system by diversifying different parameters and its effect on the wake-sleep cycle is investigated. It is shown that in all the cases considered the model exhibits a strong dependence on diversity, either in the form of a diversity-induced resonance or through more complex types of responses.

1. Introduction

Disorder, naturally present in all biological systems, is not necessarily harmful to the systems' functioning. For example in the *diversity-induced resonance* the disorder constructive role is well illustrated by an assembly of heterogeneous excitable units presenting an optimal response to an external forcing for a suitable degree of heterogeneity [1, 2, 3].

Here we study the effects of diversity (heterogeneity) on the sleep-wake cycle by using a physiologically based model [4]. This model in turn is a multi-neuron version of a previous minimal two-neuron model [5].

These models employ a novel mechanism of the homeostatic regulation of sleep based on the dynamics of a wake-promoting neuropeptide orexin (also called hypocretin), assuming depression of orexinergic synapses during wakefulness and their recovery during sleep, following experimental findings of the role of the orexin system in maintaining wakefulness and its ability to integrate sleep-wake relevant information from many brain areas [6, 7].

In the model studied here a set of orexin neurons and one local glutamate neuron B are reciprocally connected to each other according to the experimentally established physiological connections [8]. Both orexin and glutamate neurons are firing during wakefulness and are silent during sleep. The transitions between firing and silence are governed by the interplay between the circadian input and homeostatic mechanisms as initially proposed by Borbely [9]. Only one type of orexin neurotransmitter is considered and it is assumed that the system can be either in the wake state or in a generic non-Rapid Eye Movement sleep state.

Our investigations are motivated by the mentioned constructive role of disorder and the well-known fact that neurons are highly heterogeneous by their nature, in particular the orexin neurons [6, 10, 11]. In the following we recall the model and its main features and illustrate a most representative example of diversity effects, already considered in Ref. [4], related to the diversification of the glutamate threshold potentials. Then we proceed to diversify other model parameters, related to the leakage currents and the activation thresholds of the ion channels present in a neuron. In all the cases considered a clear diversity-induced resonance is found.

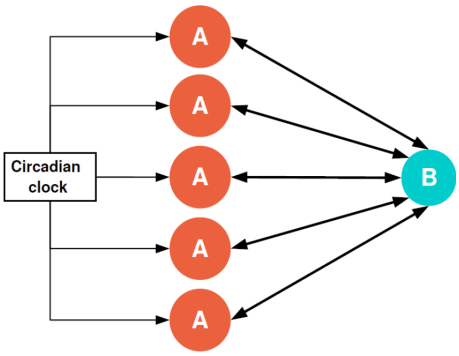

Figure 1: Example of model system with five orexin neurons A and one glutamate neuron B. See text for details.

2. Model

We set up the model schematically depicted in Fig. 1, composed of N_A orexin neurons A and one local glutamate neuron B. Neurons A are acted upon by a stimulus in pace with the circadian rhythm and interact with each other through an all-to-all coupling (not shown). The double arrows in Fig. 1 represent the mutual interaction, i.e. the A $\rightarrow$ B and B $\rightarrow$ A glutamate projections as well as the A $\rightarrow$ B orexin projection. The dynamics is described by

$$C_A dV_A^{(i)}/dt = I_{ext} - I_{A,L}^{(i)} - I_{A,Na}^{(i)} - I_{A,K}^{(i)} - I_{A,gl}^{(i)} - \sum_j I_{ij}, \quad (1)$$

$$C_B dV_B^{(1)}/dt = -I_{B,L}^{(1)} - I_{B,Na}^{(1)} - I_{B,K}^{(1)} - I_{B,gl}^{(1)} - I_{B,ox}. \quad (2)$$

Table 1: Parameters of the model

α	g_α (μS/cm^2)	E_α (mV)	S_α (mV^{-1})	W_α (mV)	τ (ms)
L	0.1	-60			
Na	3	50	0.25	-25	$\tau_{\rm Na} \approx 0$
K	4	-90	0.25	-25	$\tau_{\rm K} = 2$
gl	0.15	50	1	-20	$\tau_{\rm gl} = 30$
ox	0.135 0.2	50	1	-20	$\tau_{\rm ox} = 300$ $\tau^+_{\rm ox} = 7500$ $\tau^-_{\rm ox} = 920$
ext					$\tau = 24000$ $\tau_0 = 500$

Here and in the following, $p = {\rm A}, {\rm B}$ labels the neuron type while i labels neurons, i.e. $i = 1, \ldots, N_{\rm A}$ for $p = {\rm A}$ and $i \equiv 1$ for $p = {\rm B}$. The equations for the membrane potentials and the form of the current terms are of a Hodgkin-Huxley-type: $C_p = 1\mu{\rm F/cm}^2$ are the membrane capacitances per unit area; $I_{\rm ext}$ represents the circadian stimulus as a square pulse of height $I_0 > 0$ and length τ_0 at the beginning of each daily period τ, see also figures below; $I^{(i)}_{p,{\rm L}} = g_{\rm L}(V^{(i)}_p - E_{\rm L})$ are the leakage currents, where $g_{\rm L}$ is the maximum conductance and $E_{\rm L}$ the equilibrium potential; $I^{(i)}_{p,\alpha} = g_\alpha(V^{(i)}_p - E_\alpha)a^{(i)}_{p,\alpha}$ ($\alpha = {\rm Na}, {\rm K}, {\rm gl}, {\rm ox}$), where g_α, E_α have similar meaning and $a_{p,\alpha}$ are the activation variables, are the the ionic currents of Sodium, Potassium, and those induced by glutamate and orexin (the latter only for neuron B), respectively; $I_{ij} = k_{\rm int}(V^{(i)}_{\rm A} - V^{(j)}_{\rm A})$ is the interaction current between two orexin neurons ${\rm A}_i$, ${\rm A}_j$.

The Na-currents are assumed to be activated instantaneously: $a^{(i)}_{p,{\rm Na}} \equiv \Phi(S_{\rm Na}(V^{(i)}_p - W_{\rm Na}))$, $\Phi(x) = 1/[1+\exp(-x)]$ is a sigmoid function, $S_{\rm Na}$ the slope parameter and $W_{\rm Na}$ the activation threshold. Instead, the K-currents equation is: $da^{(i)}_{p,{\rm K}}/dt = [a^{(i)}_{p,{\rm K}} - \Phi(S_{\rm K}(V^{(i)}_p - W_{\rm K}))]/\tau_{\rm K}$, with analogous parameters but a finite relaxation time $\tau_{\rm K} > 0$.

Unlike the Na and K currents, the coupling currents $I^{(i)}_{\rm p,gl}$ and $I_{\rm B,ox}$ depend on the activity of both presynaptic and postsynaptic neurons. Since both glutamate and orexin are excitatory neurotransmitters, they are assumed to open depolarizing ion channels. For glutamate in neurons A:

$$da^{(i)}_{\rm A,gl}/dt = [a^{(i)}_{\rm A,gl} - \Phi(S_{\rm gl}(V^{(1)}_{\rm B} - W^{(i)}_{\rm B,gl}))]/\tau_{\rm gl}. \qquad (3)$$

Notice that (a) this is an interaction term, since it depends on $V^{(1)}_{\rm B}$; and that (b) here we introduce diversity through the diversified thresholds $W^{(i)}_{\rm B,gl}$. In neuron B the glutamate-current is assumed to be given by the averages of the contributions of all neurons A,

$$da^{(1)}_{\rm B,gl}/dt = \tau^{-1}_{\rm gl}\left[a^{(1)}_{\rm B,gl} - \frac{1}{N_{\rm A}}\sum_{i=1}^{N_{\rm A}} \Phi(S_{\rm gl}(V^{(i)}_{\rm A} - W^{(i)}_{\rm A,gl}))\right]. \qquad (4)$$

As for the orexin dynamics, besides the orexin activation variable $a_{\rm B,ox}$, there are $N_{\rm A}$ additional variables $M^{(i)}(t)$ representing the availability of orexin produced by neuron ${\rm A}^{(i)}$; also in this case, the global effect of neurons A on neuron B is expressed as an average,

$$dM^{(i)}/dt = (M^{(i)} - 1)/\tau^+_{\rm ox} - M^{(i)}\Phi(S_{\rm ox}(V^{(i)}_{\rm A} - W_{\rm ox}))/\tau^-_{\rm ox}, \qquad (5)$$

$$da_{\rm B,ox}/dt = \tau^{-1}_{\rm ox}\left[a_{\rm B,ox} - \frac{1}{N_{\rm A}}\sum_{i=1}^{N_{\rm A}} M^{(i)}\Phi(S_{\rm ox}(V^{(i)}_{\rm A} - W_{\rm ox}))\right]. \qquad (6)$$

These equations describe the production of orexin in neurons A and its consumption following the spiking activity. See Ref. [4] for further details about the model and Table 1 for the parameter values.

The Orexin sector of the dynamics is expected to direct the homeostatic sleep process by (i) initiating wakefulness from a sufficiently strong stimulus associated to the circadian rhythm — this in turn activates neuron B; (ii) maintaining wakefulness once the pulse is finished — i.e. the system remains in the wake state with both neurons A and B firing due to reciprocal excitation between the neurons; (iii) initiating sleep — this is the transition from wake to sleep — by stopping the firing activity in both neurons due to decreased availability of orexin according to the dynamics of the M-variables.

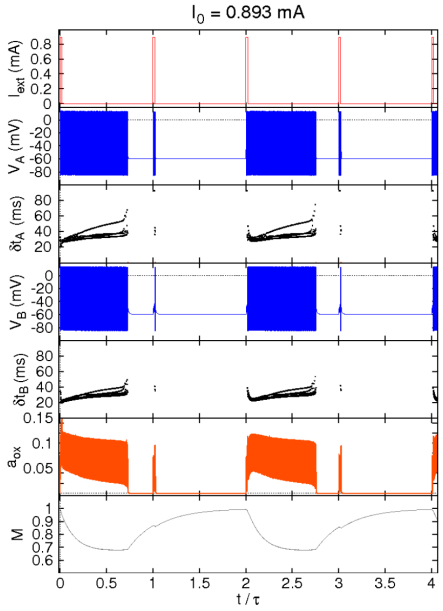

Figure 2: Sample of four periods of some relevant variables *versus* time for neuron ${\rm A}_1$ and B for a height of the external current pulse $I_0 = 0.893$ mA and length $\tau_0 = 0.5$ s (the daily period is $\tau = 24$ s). For these parameter values and the others in Table 1 the response of the system presents a 2τ periodicity.

3. Results: effect of diversity

We quantify the quality of a sleep wake cycle through the coefficient r, given by

$$r(\langle\Delta t^{(1)}\rangle, \langle\Delta t^{(2)}\rangle) = \langle\Delta t^{(1)}\rangle/\tau_1 - \langle\Delta t^{(2)}\rangle/\tau_2\,. \qquad (7)$$

Here $\langle\Delta t^{(k)}\rangle = \sum_{n=1}^{N_{\rm sp}} \Delta t^{(k)}_n/N_{\rm sp}$, $k = 1, 2$, is the average of

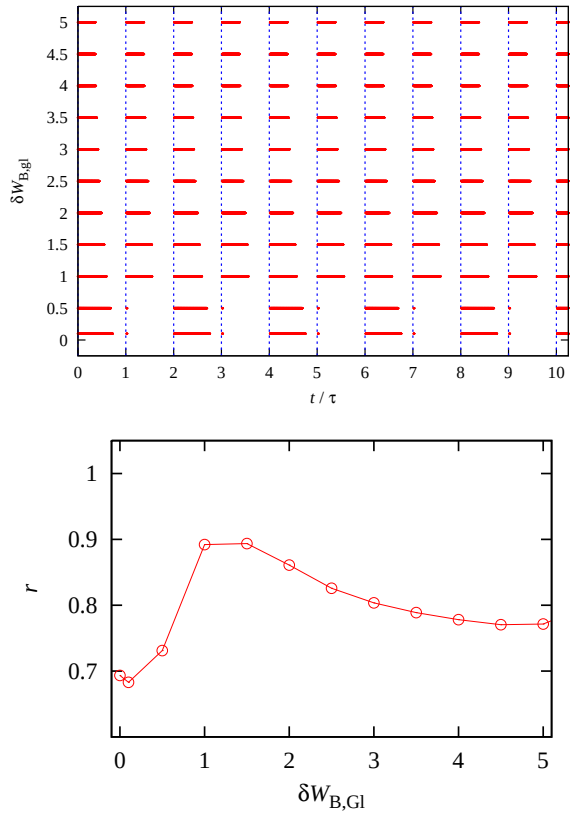

Figure 3: Effect of diversity in the B→A$_i$ synapses for different heterogeneity levels $\delta W_{\rm B,gl}$. Above: ten periods of raster plots of neuron B. Below: coefficient r, Eq. (7). See text for details.

the wakefulness time intervals in the day ($k = 1$) and night ($k = 2$), $N_{\rm sp}$ being the total number of periods of the simulation, while τ_k are the length of day and night, respectively, assumed to be $\tau_1 = 2\tau/3$ and $\tau_2 = \tau/3$ (τ is the daily period). The coefficient r can vary in the interval (-1,1), the maximum (minimum) value $r = 1$ ($r = -1$) corresponding to an optimal (to the worst possible) cycle. Deviation from the optimal state $r = 1$, obtained for $\Delta t^{(1)} = \tau_1$ (wakefulness during the entire day) and $\Delta t^{(2)} = 0$ (sleep during the entire night), imply a $\Delta t^{(1)} < \tau_1$ or $\Delta t^{(2)} > 0$.

In the examples considered the initial configuration in the absence of diversity is a sub-threshold state illustrated in Fig. 2, characterized by a response that has period 2τ — therefore undesirable from the point of view of a good sleep-wake cycle — obtained for a value of the current pulse height $I_0 = 0.893$ mA (the other parameters are in Table 1). Such an under-threshold non-optimal configuration is a most convenient starting state since it is very sensitive to the effects of added heterogeneity.

Since similar results are obtained when diversifying the thresholds at neurons A or at neuron B, we limit ourselves to a discussion of the former case, i.e. when the thresholds $W^{(i)}_{\rm B,gl}$ of the B→A$_i$ synapses at the neurons A are diversified. Therefore each neuron A$_i$ responds in a different way to the stimulation from the neuron B. We studied a system with $N_{\rm A} = 20$ neurons A$_i$ with diversified threshold parameters $W^{(i)}_{\rm B,gl}$, $i = 1, \ldots, N_{\rm A}$ extracted from bell-shaped distributions of width $\delta W_{\rm B,gl}$, but always with the same average value $\overline{W}_{\rm B,gl} = W_{\rm B,gl}$ for all values of the diversity $\delta W_{\rm B,gl}$. The resulting raster plots of the activity of neuron B are shown in Fig. 3-Above and the time dependencies of some variables of neuron A_1 and B for the particular cases of diversities $\delta W_{\rm B,gl} = 1$ mV and $\delta W_{\rm B,gl} = 5$ mV are shown in Fig. 4. The existence of an optimal degree of diversity between $\delta W_{\rm B,gl} = 1$ and 1.5 mV can be seen also in Fig. 3-Below from the coefficient r *versus* $\delta W_{\rm B,gl}$. The underlying mechanism leading the system from the double- to the single-periodic response as diversity is increased can be interpreted following the prototype mechanical model of diversity-induced resonance introduced in Ref. [1], see Ref. [4] for a detailed discussion of this point.

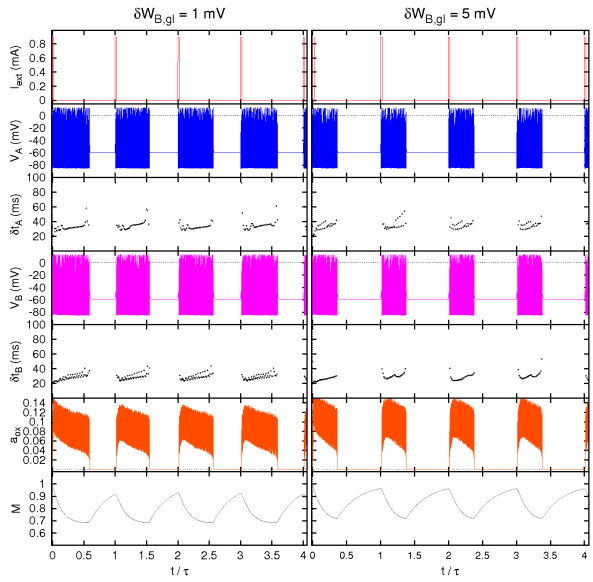

Figure 4: Sample of four periods of some relevant variables and inter-spike times $\delta t_{\rm p}$ ($p = {\rm A, B}$) *versus* time for neuron A$_1$ and neuron B for different levels of the threshold diversity $\delta W_{\rm B,gl} = 1$ mV (left) and $\delta W_{\rm B,gl} = 5$ mV (right). Compare Fig. 3 and see text for further details.

In addition to the variation of the glutamate thresholds, already reported in Ref. [4], here we diversify some other system parameters.

In Fig. 5 we show the raster plots of neuron B (for the same values of the other parameters) when the equilibrium potentials $E_{\rm L}$ of the leakage currents of neurons A are diversified in a way similar to that described above for the glutamate threshold. The diversity levels $\delta E_{\rm L}$ are shown on the right axis of Fig. 5. In this case one does not really observe a diversity-induce resonance, yet there is clear qualitative improvement of the system response, when going from a homogeneous system ($\delta E_{\rm L} = 0$) to one with heterogeneity $\delta E_{\rm L} > 0$, that evolves from the one with period 2τ into a robust periodic response of period τ (despite

the wakefulness daily time remains quite short respect to the ideal value $2\tau/3$).

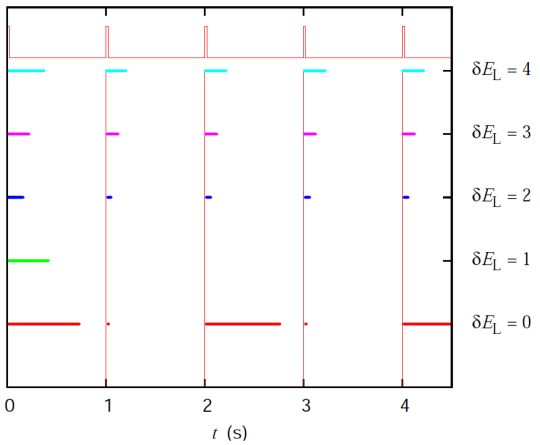

Figure 5: Raster plot of neuron B for different levels of diversity of the leakage equilibrium potential E_L.

As a last, different way to look at diversity in this model, we report about the variation of the slope parameters S_{gl}, appearing in the dynamics of the glutamate activation variables, Eqs. (3) and (4). This parameter and the similar ones are known to provide a macroscopic measure of the level of heterogeneity of the activation thresholds of the ion-channels located in a neuron. That is, increasing the value of S_{gl} is equivalent to decreasing the heterogeneity level in the ion-channel thresholds of the corresponding neuron. As one can see in Fig. 6, the response of the system has a complex but very strong dependence on S_{gl}. There are various types of response, shortly described on the left side of Fig. 6, including, besides the starting homogeneous configuration with period 2τ, other responses with period τ. Optimal responses are obtained for two different values of S_{gl}; this could be described in terms of a double diversity-induced resonance.

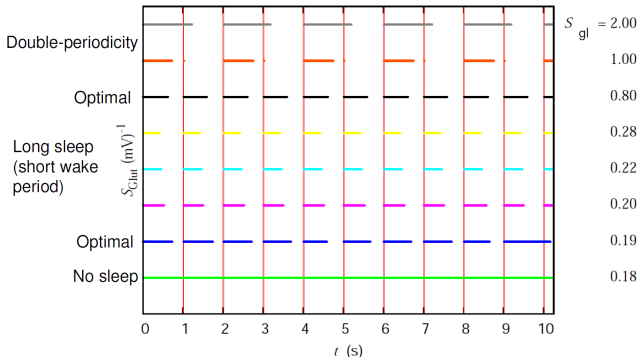

Figure 6: The raster plot of neuron B presents a complex dependence on the diversity S_{gl} of the ion-channel thresholds.

In conclusion, the results presented suggest that diversity can improve various features in the response of neuronal systems, such as encoding efficiency and periodicity. This holds for different types of diversity, that can be present at various levels ranging from ion-channel dynamics to the homeostatic mechanism regulating the sleep-wake cycle on a daily time scale.

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