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Effect of diversity in a neuronal model for the wake-sleep cycle

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Collaboration

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Svetlana Postnova and Hans Braun

Neurodynamics group - Institute of Physiology, Philipps University, Marburg

Goal: study study the effect of diversity and noise in neuronal systems

Minimal Model: 2-unit A-B model of Postonova, Voigt, and Braun.

Generalized Model: model with many A-units and one B-unit.

Effect of disorder on the response to a periodic signal:

- Heterogeneity of intrinsic parameters (frequencies)

- Heterogeneity of coupling parameters

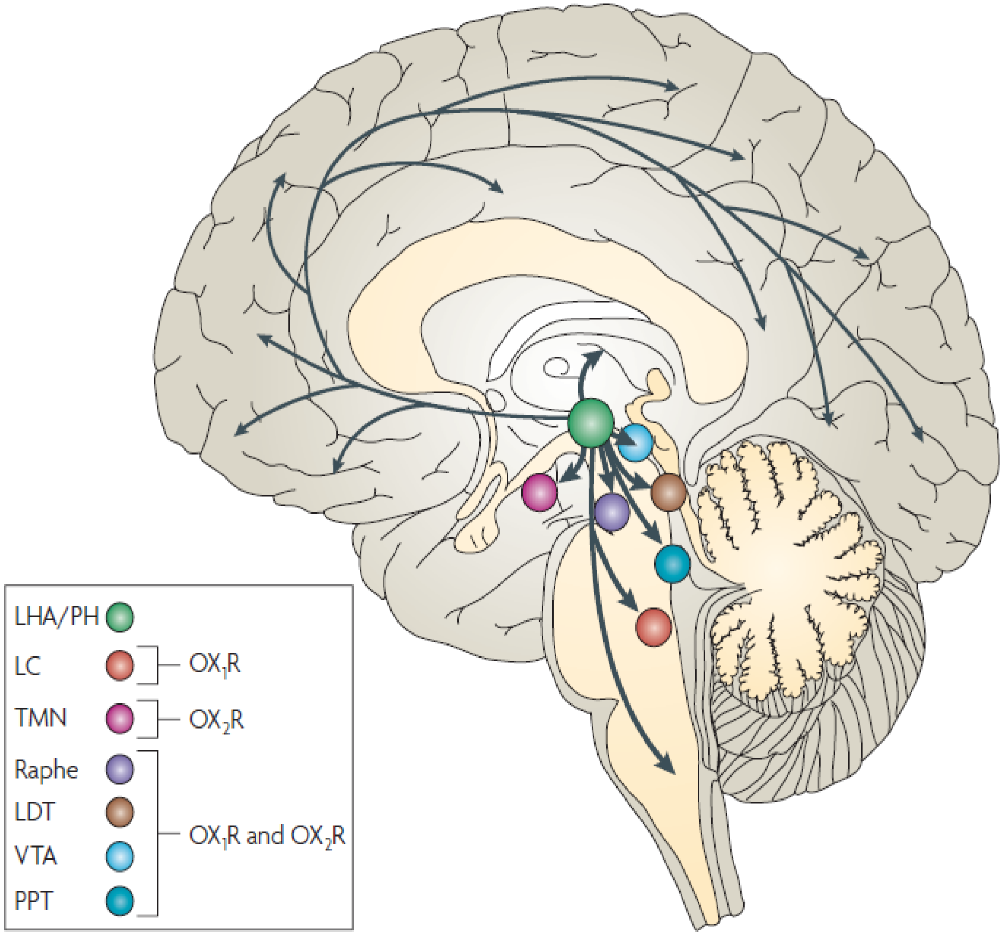
- Different response of one unit (diversity of ion-channels)

orexin in sleep and sleep-disorders

The neuropeptide orexin was initially thought to be responsible only for appetite and metabolism but later it became clear that it controls many more processes and is necessary to maintain awaken state.

orexin-producing neurons send excitatory projections to almost all brain areas.

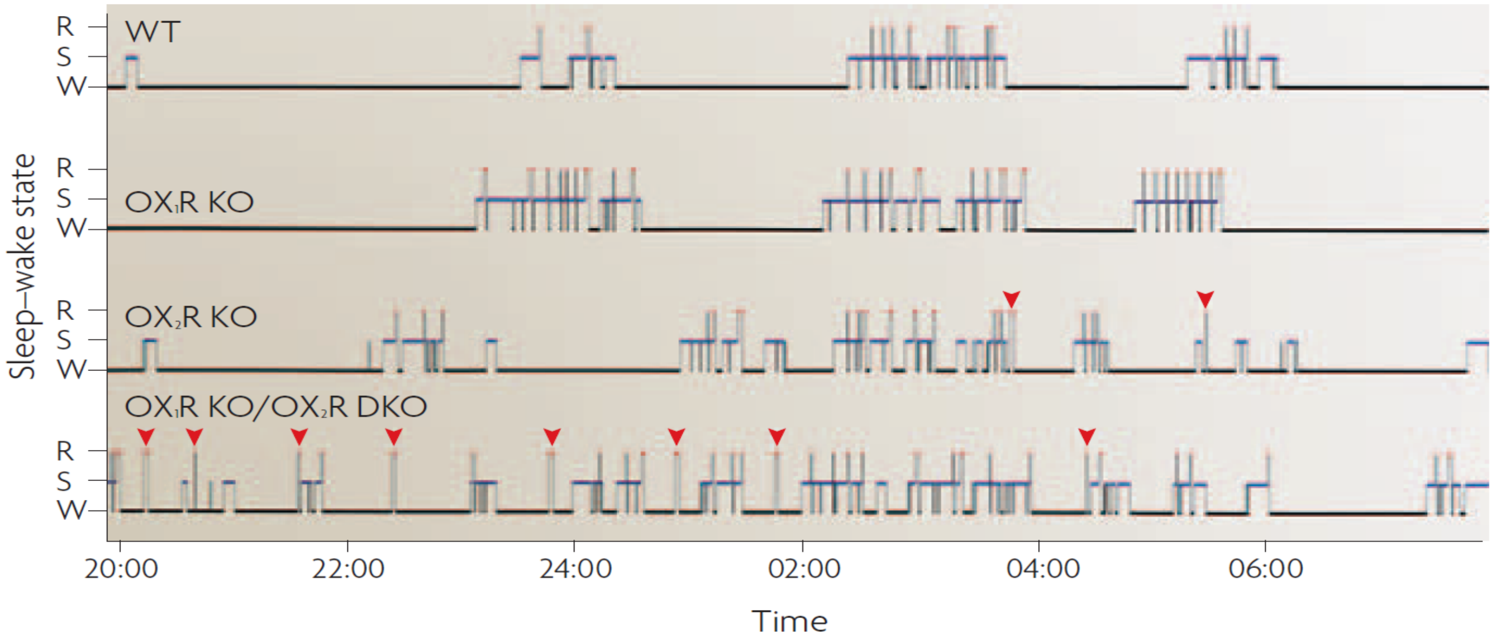
orexin-producing neurons fire tonically in the awaken state and are almost silent during sleep.



Narcolepsy:

appears as a series of sudden transitions from wakefulness to sleep, namely to REM sleep; they last a few seconds instead of ~ 90 min as in normal (human) sleep.

has been shown to be caused by a *lack of orexin*, due to
1) lack of specific orexin-producing neurons or
2) absence/malfunctioning of orexin-receptors



T. Sakurai, Nature Rev. 8 (2007) 171

wake-sleep model of Postnova, Voigt, and Braun [1]

- Only 1 LH (Lateral Hypothalamus) and 1 PFC (Pre-Frontal Cortex) neuron

- The LH neuron is subject to a circadian signal.

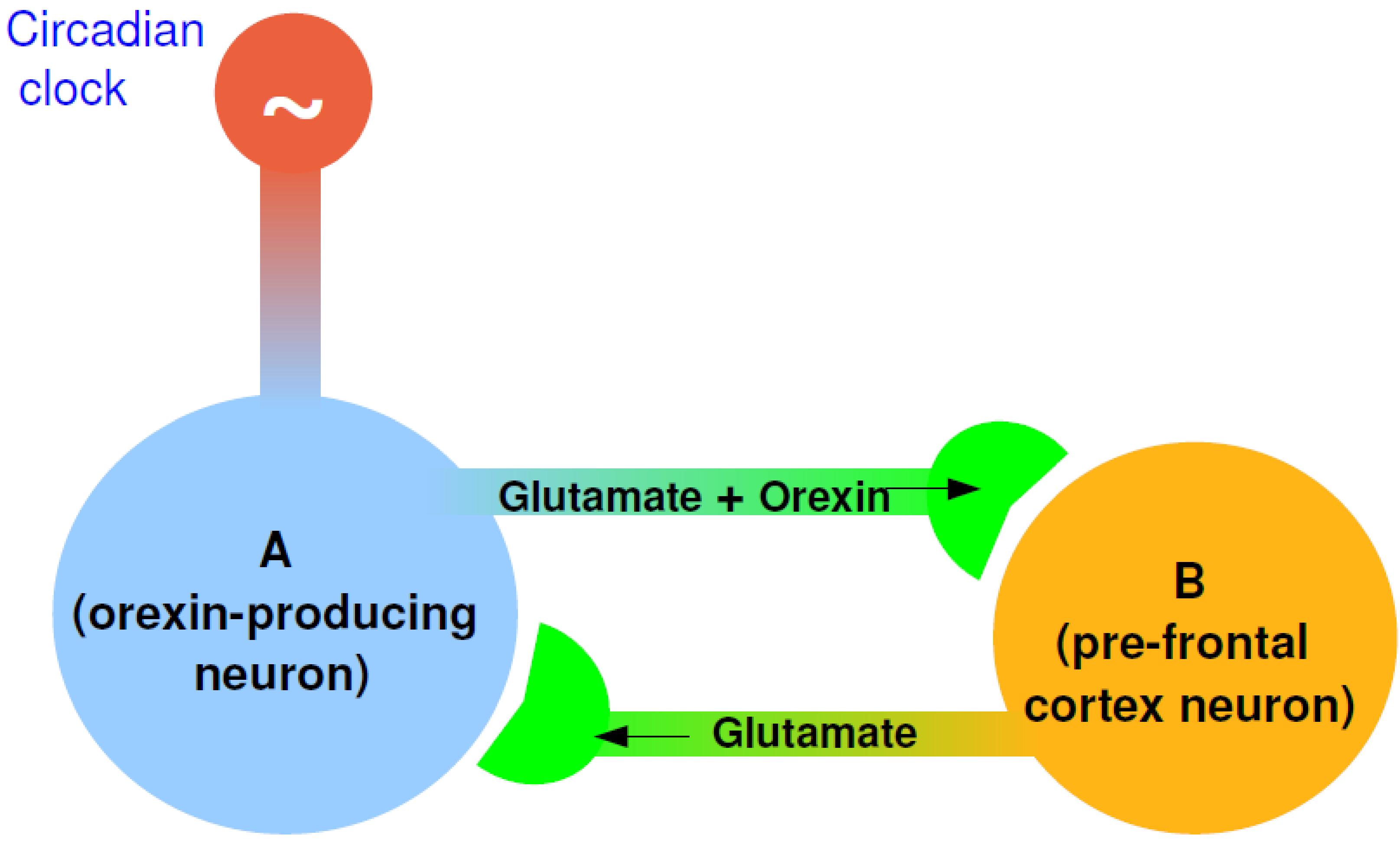
- Orexin is produced only by the LH neuron, transmitted to the PFC neuron through a positive feedback of glutamate, and consumed, with a time scale of the order of 1 day.

- Glutamate is produced and transmitted by both neurons.

- Glutamate interaction, which directly activates ionotropic receptors, has a fast time scale. Instead the Orexin interaction, which proceeds through a long series of intermediate reactions, is modeled with a *much larger time scale* reaction.

[1] S. Postnova, K. Voigt, H.A. Braun, *A mathematical model of homeostatic regulation of sleep-wake cycles by hypocretin/orexin*, BioSim Preprint.

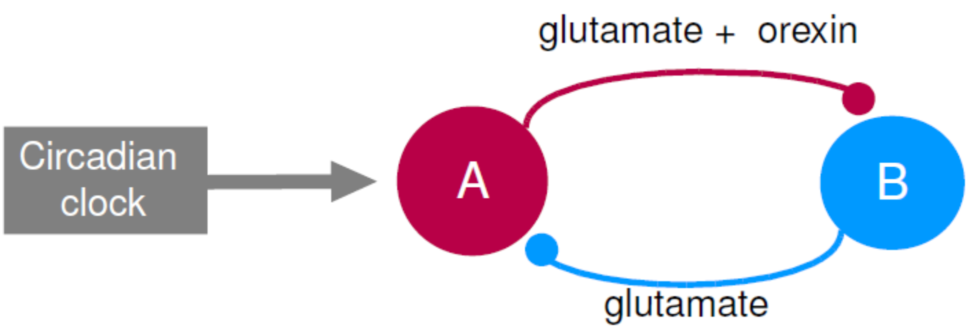
Scheme of the wake-sleep model



Mathematical model

$$C\frac{dV_{\mathrm{A}}(t)}{dt} = -g_{\mathrm{L}}[V_{\mathrm{A}}(t)-E_{\mathrm{L}}] - g_{\mathrm{Na}}[V_{\mathrm{A}}(t)-E_{\mathrm{Na}}]a_{\mathrm{Na}} - g_{\mathrm{K}}[V_{\mathrm{A}}(t)-E_{\mathrm{K}}]a_{\mathrm{K}}(t) - g_{\mathrm{gl}}[V_{\mathrm{A}}(t)-E_{\mathrm{gl}}]a_{\mathrm{gl}}(t) + I_{\mathrm{circ}}(t)$$

$$C\frac{dV_{\mathrm{B}}(t)}{dt} = -g_{\mathrm{L}}[V_{\mathrm{B}}(t)-E_{\mathrm{L}}] - g_{\mathrm{Na}}[V_{\mathrm{B}}(t)-E_{\mathrm{Na}}]b_{\mathrm{Na}} - g_{\mathrm{K}}[V_{\mathrm{B}}(t)-E_{\mathrm{K}}]b_{\mathrm{K}}(t) - g_{\mathrm{gl}}[V_{\mathrm{B}}(t)-E_{\mathrm{gl}}]b_{\mathrm{gl}}(t) - g_{\mathrm{or}}[V_{\mathrm{B}}(t)-E_{\mathrm{or}}]b_{\mathrm{or}}(t)$$



Mathematical model

$$C\frac{dV_\mathrm{A}(t)}{dt} = -\, g_\mathrm{L}[V_\mathrm{A}(t)-E_\mathrm{L}] - g_\mathrm{Na}[V_\mathrm{A}(t)-E_\mathrm{Na}]a_\mathrm{Na} - g_\mathrm{K}[V_\mathrm{A}(t)-E_\mathrm{K}]a_\mathrm{K}(t) - g_\mathrm{gl}[V_\mathrm{A}(t)-E_\mathrm{gl}]a_\mathrm{gl}(t) + I_\mathrm{circ}(t)$$

$$C\frac{dV_\mathrm{B}(t)}{dt} = -\, g_\mathrm{L}[V_\mathrm{B}(t)-E_\mathrm{L}] - g_\mathrm{Na}[V_\mathrm{B}(t)-E_\mathrm{Na}]b_\mathrm{Na} - g_\mathrm{K}[V_\mathrm{B}(t)-E_\mathrm{K}]b_\mathrm{K}(t) - g_\mathrm{gl}[V_\mathrm{B}(t)-E_\mathrm{gl}]b_\mathrm{gl}(t) - g_\mathrm{or}[V_\mathrm{B}(t)-E_\mathrm{or}]b_\mathrm{or}(t)$$

$$a_\mathrm{Na} \equiv \Phi(S_\mathrm{Na}(V_\mathrm{A} - W_\mathrm{Na}))$$

$$b_\mathrm{Na} \equiv \Phi(S_\mathrm{Na}(V_\mathrm{B} - W_\mathrm{Na}))$$

$$\Phi(S(V-W)) = \frac{1}{1+\exp[-S(V-W)]}$$

Mathematical model

$$C\frac{dV_A(t)}{dt} = -g_L[V_A(t)-E_L] - g_{Na}[V_A(t)-E_{Na}]a_{Na} - g_K[V_A(t)-E_K]a_K(t) - g_{gl}[V_A(t)-E_{gl}]a_{gl}(t) + I_{circ}(t)$$

$$C\frac{dV_B(t)}{dt} = -g_L[V_B(t)-E_L] - g_{Na}[V_B(t)-E_{Na}]b_{Na} - g_K[V_B(t)-E_K]b_K(t) - g_{gl}[V_B(t)-E_{gl}]b_{gl}(t) - g_{or}[V_B(t)-E_{or}]b_{or}(t)$$

$$\frac{da_K}{dt} = -\frac{1}{\tau_K}[a_K - \Phi(V_A; S_K, W_K)]$$

$$\frac{db_K}{dt} = -\frac{1}{\tau_K}[b_K - \Phi(V_B; S_K, W_K)]$$

$$\Phi(S(V-W)) = \frac{1}{1+\exp[-S(V-W)]}$$

Mathematical model

$$C\frac{dV_A(t)}{dt} = -g_L[V_A(t)-E_L] - g_{Na}[V_A(t)-E_{Na}]a_{Na} - g_K[V_A(t)-E_K]a_K(t) - g_{gl}[V_A(t)-E_{gl}]a_{gl}(t) + I_{circ}(t)$$

$$C\frac{dV_B(t)}{dt} = -g_L[V_B(t)-E_L] - g_{Na}[V_B(t)-E_{Na}]b_{Na} - g_K[V_B(t)-E_K]b_K(t) - g_{gl}[V_B(t)-E_{gl}]b_{gl}(t) - g_{or}[V_B(t)-E_{or}]b_{or}(t)$$

$$\frac{da_{gl}}{dt} = -\frac{1}{\tau_{gl}}\left[a_{gl} - \Phi(V_B; S_{gl}, W_{gl})\right]$$

$$\frac{db_{gl}}{dt} = -\frac{1}{\tau_{gl}}\left[b_{gl} - \Phi(V_A; S_{gl}, W_{gl})\right]$$

$$\Phi(S(V-W)) = \frac{1}{1+\exp[-S(V-W)]}$$

Mathematical model

$$C\frac{dV_{\rm A}(t)}{dt} = - g_{\rm L}[V_{\rm A}(t) - E_{\rm L}] - g_{\rm Na}[V_{\rm A}(t) - E_{\rm Na}]a_{\rm Na} - g_{\rm K}[V_{\rm A}(t) - E_{\rm K}]a_{\rm K}(t) - g_{\rm gl}[V_{\rm A}(t) - E_{\rm gl}]a_{\rm gl}(t) + I_{\rm circ}(t)$$

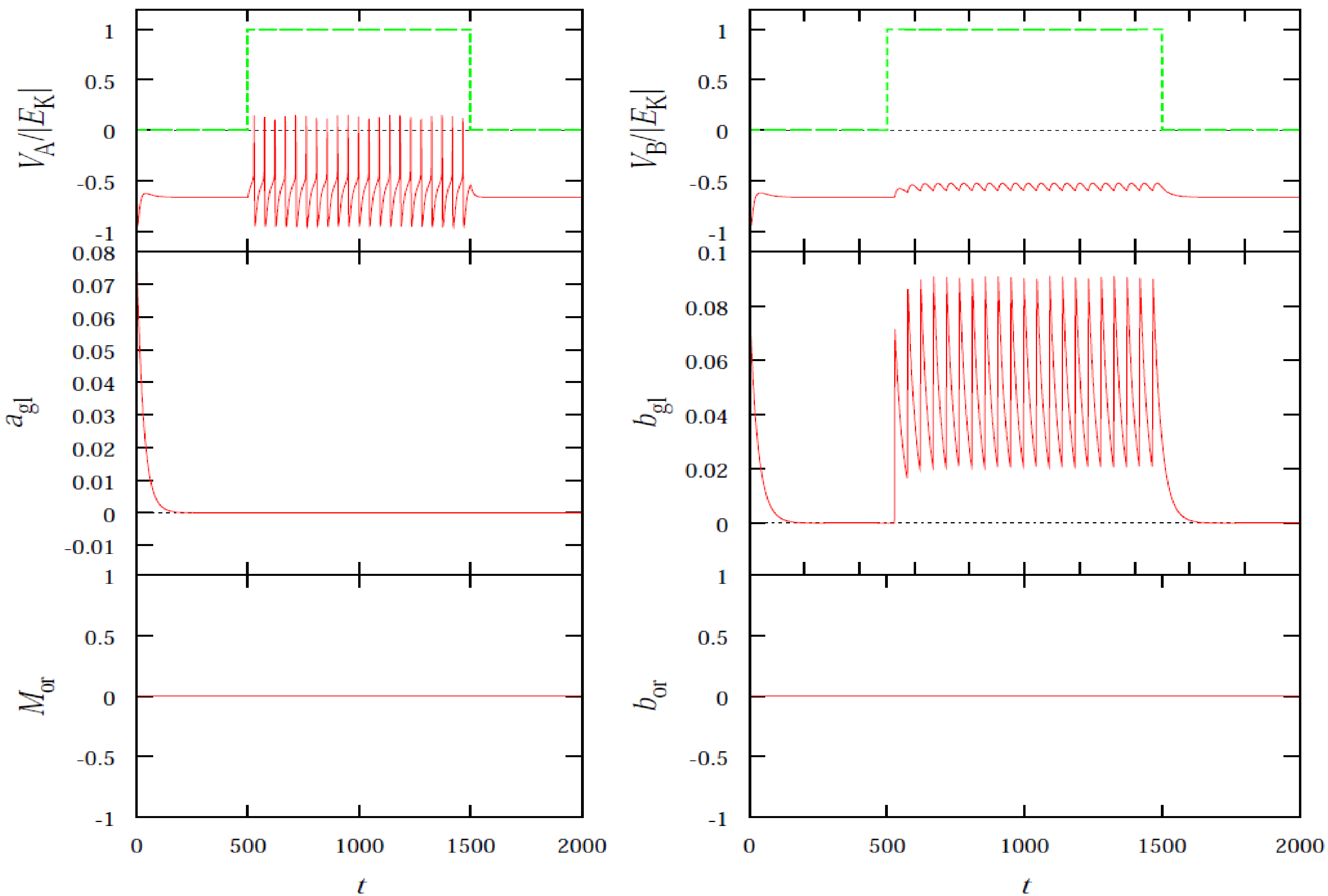
$$C\frac{dV_{\rm B}(t)}{dt} = - g_{\rm L}[V_{\rm B}(t) - E_{\rm L}] - g_{\rm Na}[V_{\rm B}(t) - E_{\rm Na}]b_{\rm Na} - g_{\rm K}[V_{\rm B}(t) - E_{\rm K}]b_{\rm K}(t) - g_{\rm gl}[V_{\rm B}(t) - E_{\rm gl}]b_{\rm gl}(t) - g_{\rm or}[V_{\rm B}(t) - E_{\rm or}]b_{\rm or}(t)$$

$$\frac{db_{\rm or}}{dt} = -\frac{1}{\tau_{\rm or}}[b_{\rm or} - M_{\rm or}\Phi(V_{\rm A}; S_{\rm or}, W_{\rm or})]$$

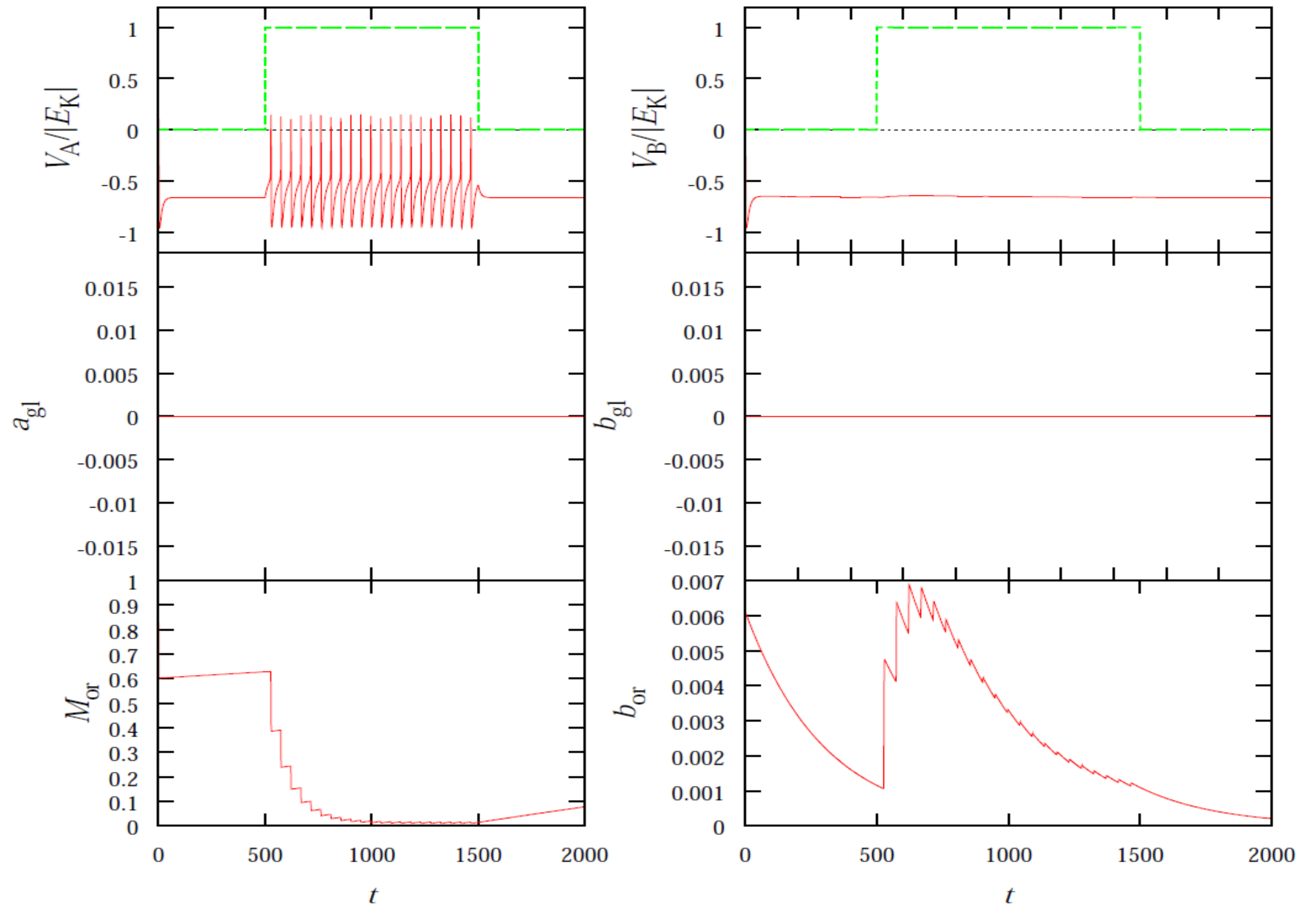
$$\frac{dM_{\rm or}}{dt} = -\frac{1}{\tau_+}(1 - M_{\rm or}) - \frac{1}{\tau_-}M_{\rm or}\Phi(V_{\rm A}; S_{\rm or}, W_{\rm or})$$

$$\Phi(S(V - W)) = \frac{1}{1 + \exp[-S(V - W)]}$$

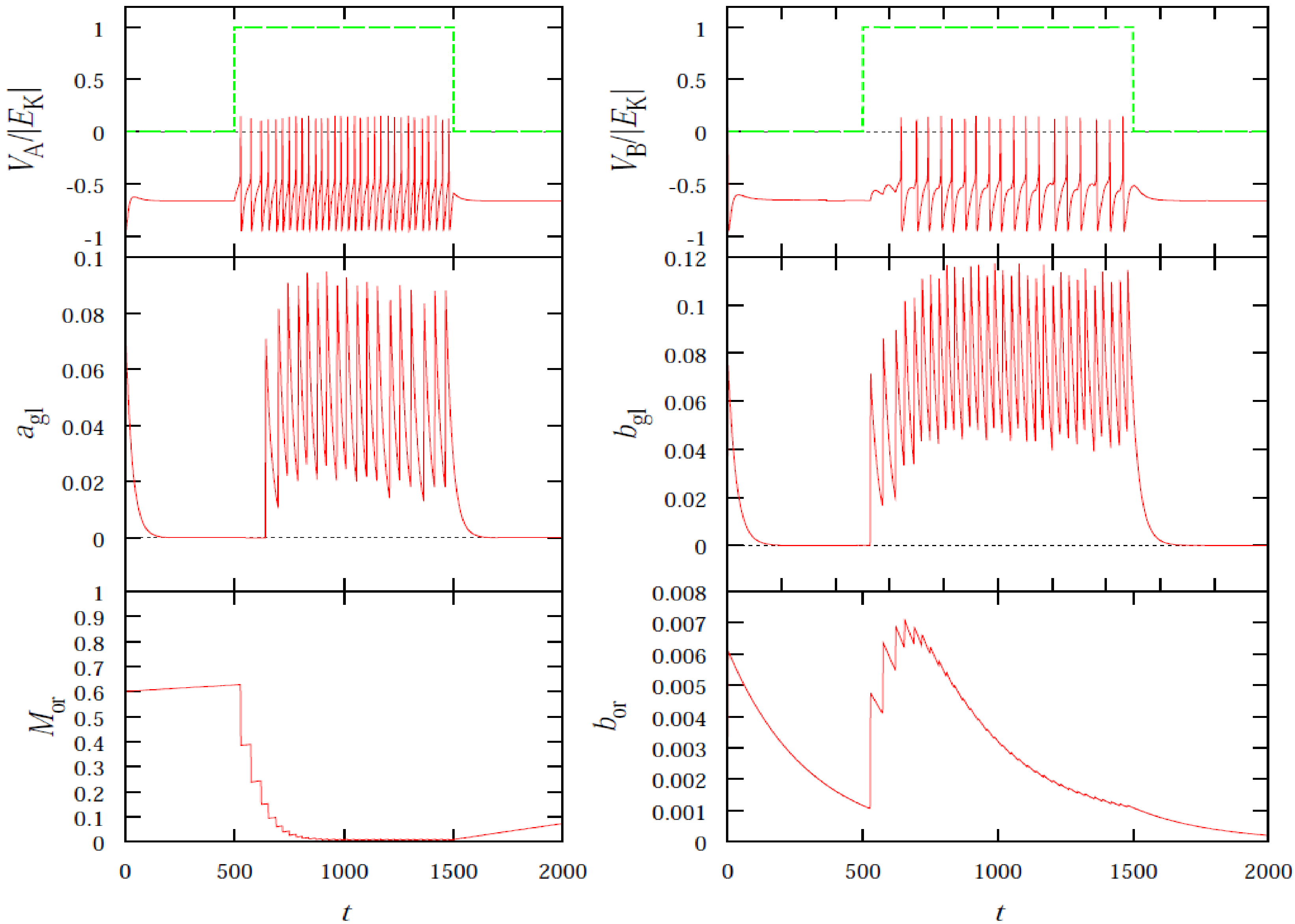
Only glutamate A --> B and B--> A



Only Orexin A --> B

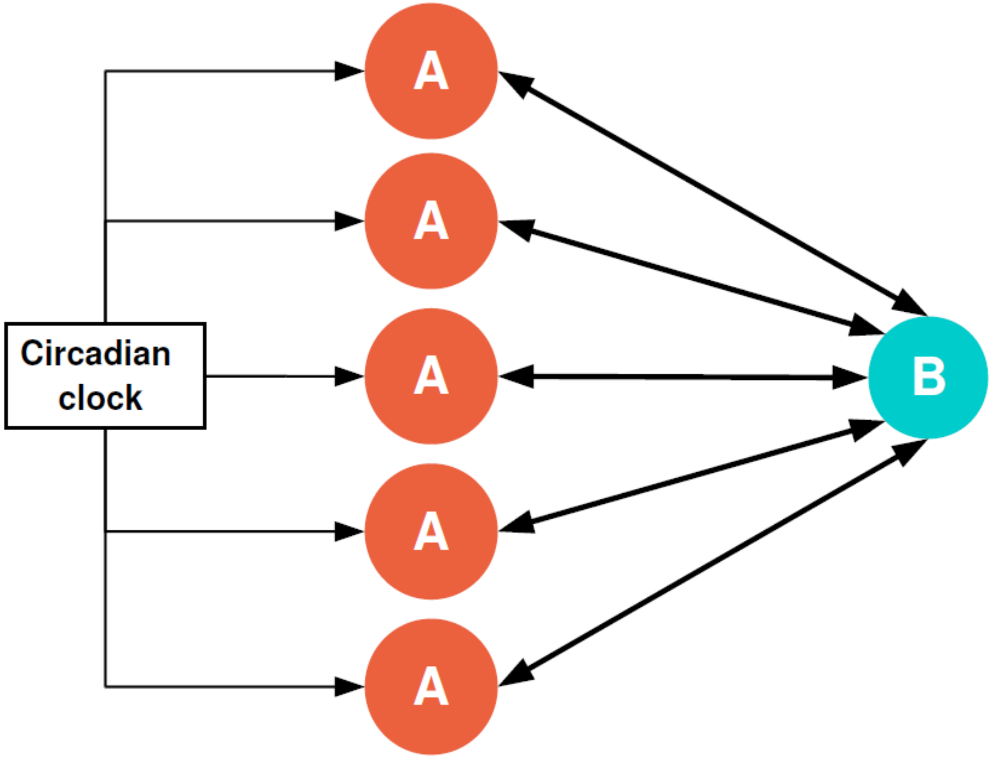


Orexin + Glutamate A --> B and Glutamate B → A



Generalized model with *N* orexin-producing neurons

N_A A-units + 1 B-unit



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Diversify Leakage Potentials

$$C\frac{dV_{\mathrm{A}}^{(i)}(t)}{dt} = -\,g_{\mathrm{L}}[V_{\mathrm{A}}^{(i)}(t)-E_{\mathrm{L}}^{(i)}] - g_{\mathrm{Na}}[V_{\mathrm{A}}^{(i)}(t)-E_{\mathrm{Na}}]a_{\mathrm{Na}}^{(i)} - g_{\mathrm{K}}[V_{\mathrm{A}}^{(i)}(t)-E_{\mathrm{K}}]a_{\mathrm{K}}^{(i)}(t) - g_{\mathrm{gl}}[V_{\mathrm{A}}^{(i)}(t)-E_{\mathrm{gl}}]a_{\mathrm{gl}}^{(i)}(t) + I_{\mathrm{circ}}(t)$$

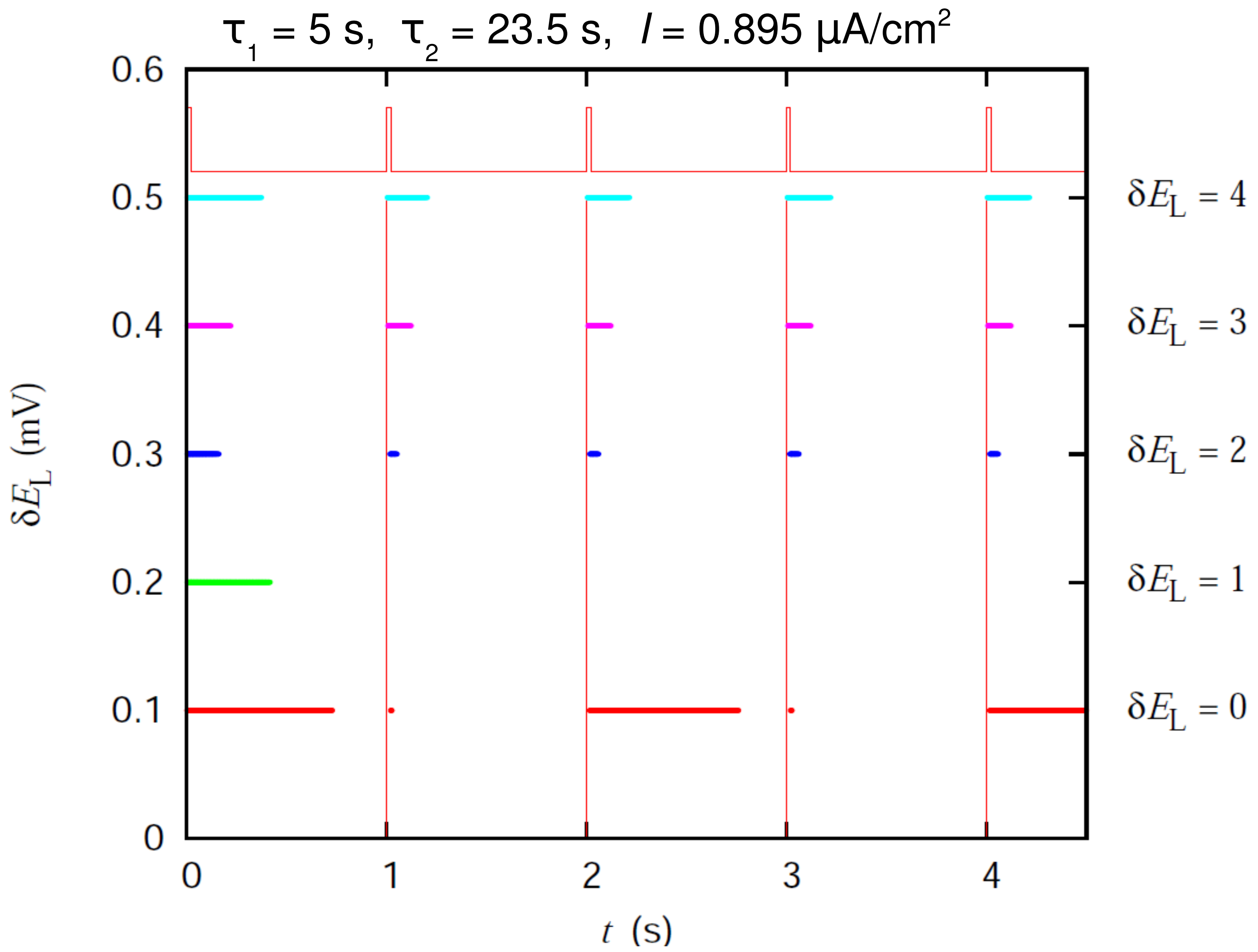
$$C\frac{dV_{\mathrm{B}}(t)}{dt} = -\,g_{\mathrm{L}}[V_{\mathrm{B}}(t)-E_{\mathrm{L}}] - g_{\mathrm{Na}}[V_{\mathrm{B}}(t)-E_{\mathrm{Na}}]b_{\mathrm{Na}} - g_{\mathrm{K}}[V_{\mathrm{B}}(t)-E_{\mathrm{K}}]b_{\mathrm{K}}(t) - g_{\mathrm{gl}}[V_{\mathrm{B}}(t)-E_{\mathrm{gl}}]b_{\mathrm{gl}}(t) - g_{\mathrm{or}}[V_{\mathrm{B}}(t)-E_{\mathrm{or}}]b_{\mathrm{or}}(t)$$

- Same average value $\langle E_L \rangle$ = - 60 mV as in the 2-unit model
- Dispersion δE_L around the average value

Diversity in inner parameters: Leakage potential E_L

$<E_L> = -60$ mV

Short but normal-periodic sleep-wake cycle



Undercritical current, excessive sleeping, double-periodicity!

Diversify Leakage Potentials

$$C\frac{dV_A^{(i)}(t)}{dt} = -g_L[V_A^{(i)}(t)-E_L^{(i)}] - g_{Na}[V_A^{(i)}(t)-E_{Na}]a_{Na}^{(i)} - g_K[V_A^{(i)}(t)-E_K]a_K^{(i)}(t) - g_{gl}[V_A^{(i)}(t)-E_{gl}]a_{gl}^{(i)}(t) + I_{circ}(t)$$

$$C\frac{dV_B(t)}{dt} = -g_L[V_B(t)-E_L] - g_{Na}[V_B(t)-E_{Na}]b_{Na} - g_K[V_B(t)-E_K]b_K(t) - g_{gl}[V_B(t)-E_{gl}]b_{gl}(t) - g_{or}[V_B(t)-E_{or}]b_{or}(t)$$

$$\frac{db_{gl}}{dt} = -\frac{1}{\tau_{gl}}\left[b_{gl} - \frac{1}{N_A}\sum_{i=1}^{N_A}\Phi(V_A^{(i)}; S_{gl}, W_{gl}^{(i)})\right]$$

- Same average value $\langle W_{gl} \rangle$ = - 20 mV as in the 2-unit model
- Dispersion δW_{gl} around the average value

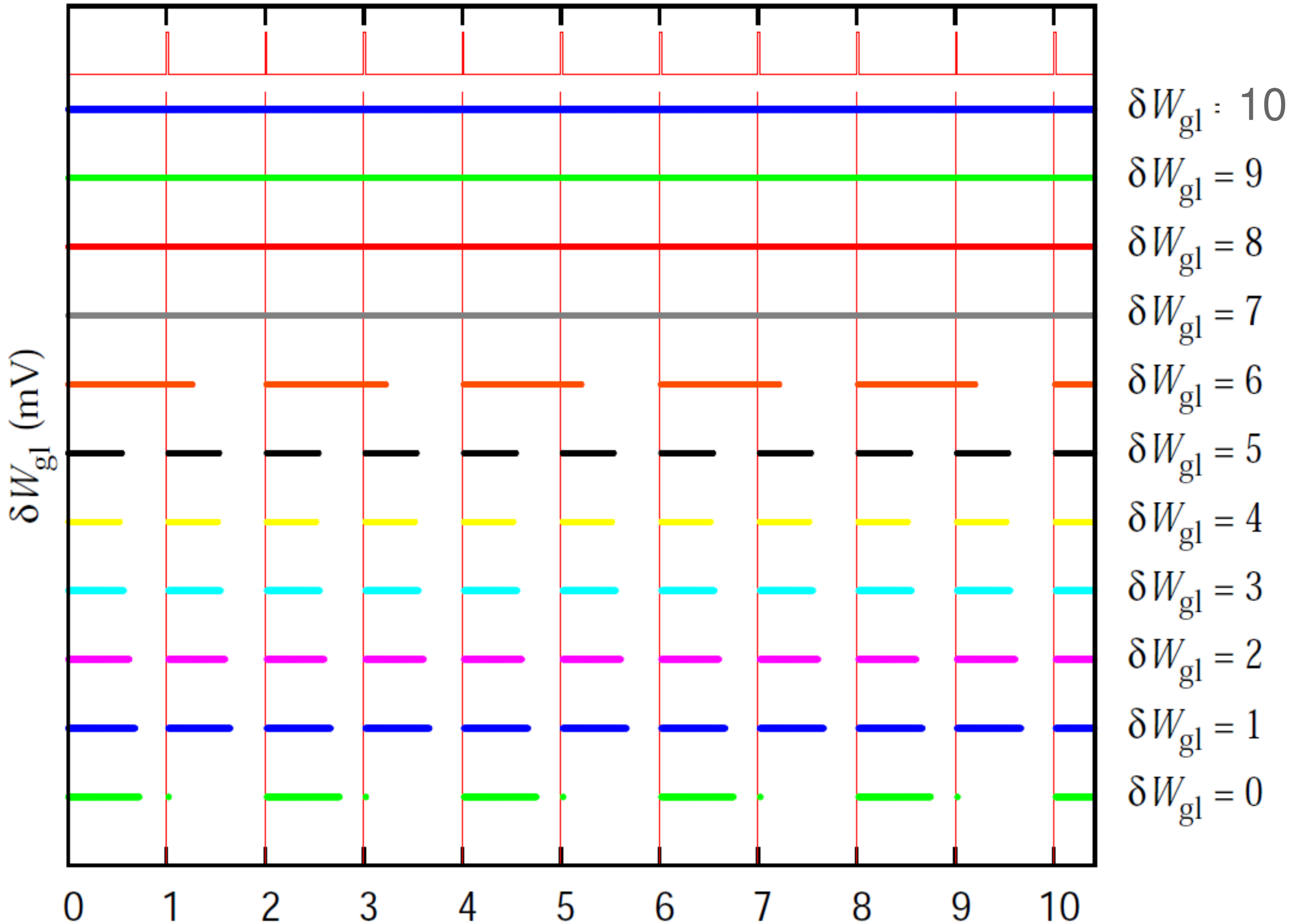
Diversity in coupling parameters: activation threshold W_{gl}

τ_1 = 5 s, τ_2 = 23.5 s, I = 0.895 μA/cm^2 $\langle W_{gl} \rangle$ = - 20 mV

Excessive wakefulness, double-periodicity

Normal sleep-wake cycle

Undercritical current, double-periodicity!



C.Tessone, C.Mirasso, R.Toral, J.D.Gunton, ***Diversity-induced resonance***, Phys.Rev.Lett. 97, 194101 (2006)

Mathematical model

$$C\frac{dV_A(t)}{dt} = -g_L[V_A(t)-E_L] - g_{Na}[V_A(t)-E_{Na}]a_{Na} - g_K[V_A(t)-E_K]a_K(t) - g_{gl}[V_A(t)-E_{gl}]a_{gl}(t) + I_{circ}(t)$$

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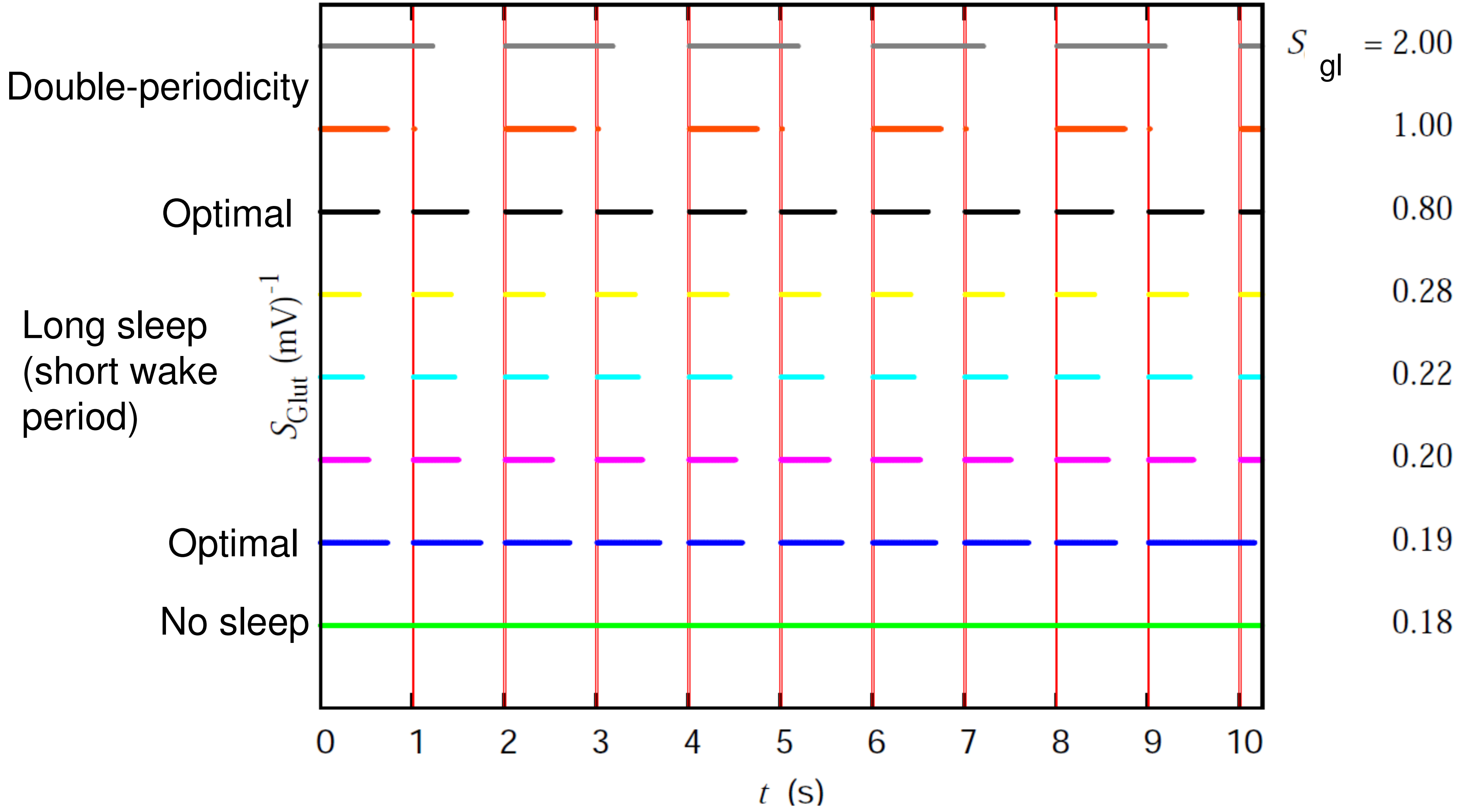
$$\frac{da_{gl}}{dt} = -\frac{1}{\tau_{gl}}[a_{gl} - \Phi(V_B; S_{gl}, W_{gl})]$$

$$\frac{db_{gl}}{dt} = -\frac{1}{\tau_{gl}}[b_{gl} - \Phi(V_A; S_{gl}, W_{gl})]$$

$$\Phi(S(V-W)) = \frac{1}{1+\exp[-S(V-W)]}$$

Diversity in the ion-channels of a same neuron: varying S_{gl}



- Minimal models with few neurons already present *strong dependence* on diversity

- An *optimal* amount – not too small or large – of diversity seems produce an optimal configuration

- Example of a collective effect.

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