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

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outline

- Goal of the work: modeling the wake-sleep cycle and study the effect of diversity / disorder / heterogeneity / noise

- Sleep, orexin, sleep-disorders (narcolepsy).

- Starting from the minimal 2-neuron model (1 LH + 1 PFC neuron) of Braun et al.

- Going on to the generalized model with *N* LH (or N-PFC) neurons.

- Effect of three different types of disorder on the response to a periodic signal:
  - Heterogeneity of neurons
  - Diversity of ion-channels within the same neuron
  - Noise

- Possible extensions of the model and work in progress.

modeling of sleep cycle

- Models describing the wake-sleep cycle as an interaction of two (dynamical) processes (no information about neuronal dynamics)

- Models based on a microscopic description of mental activity as a the result of the activity of a very large set of components.

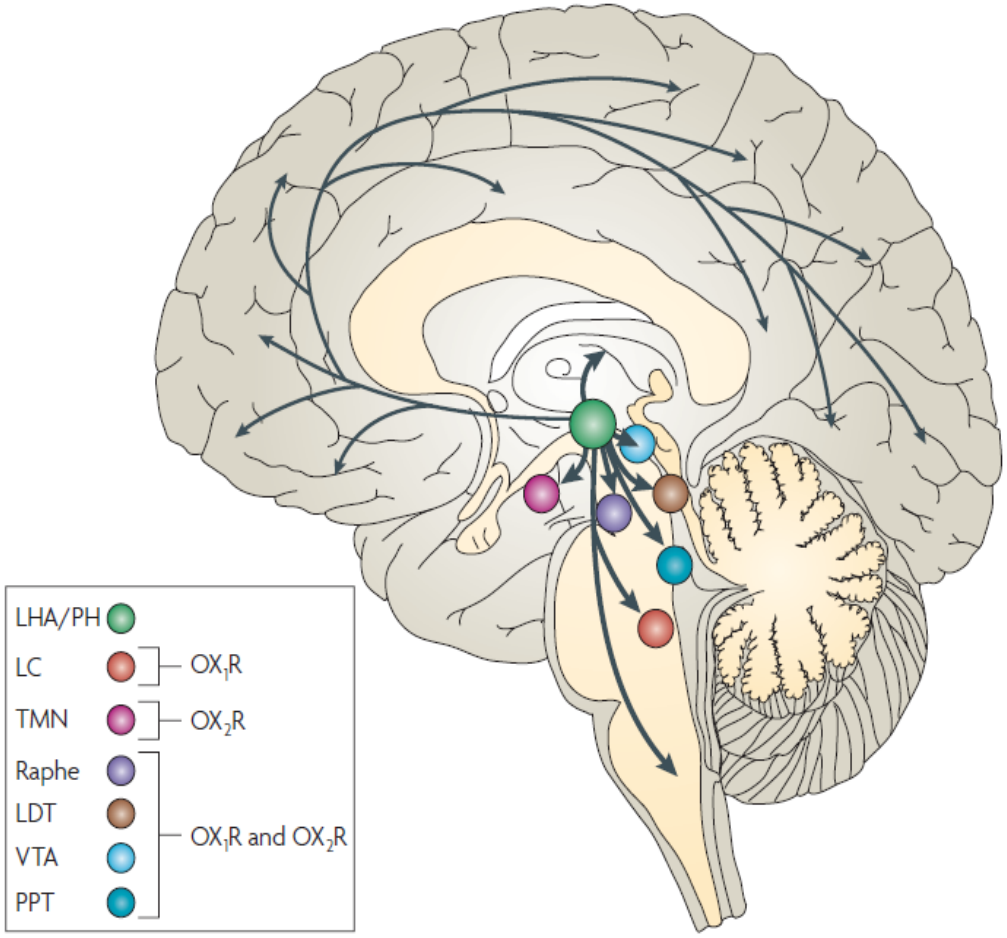
- (phenomenological) models with intermediate degrees of complexity

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.

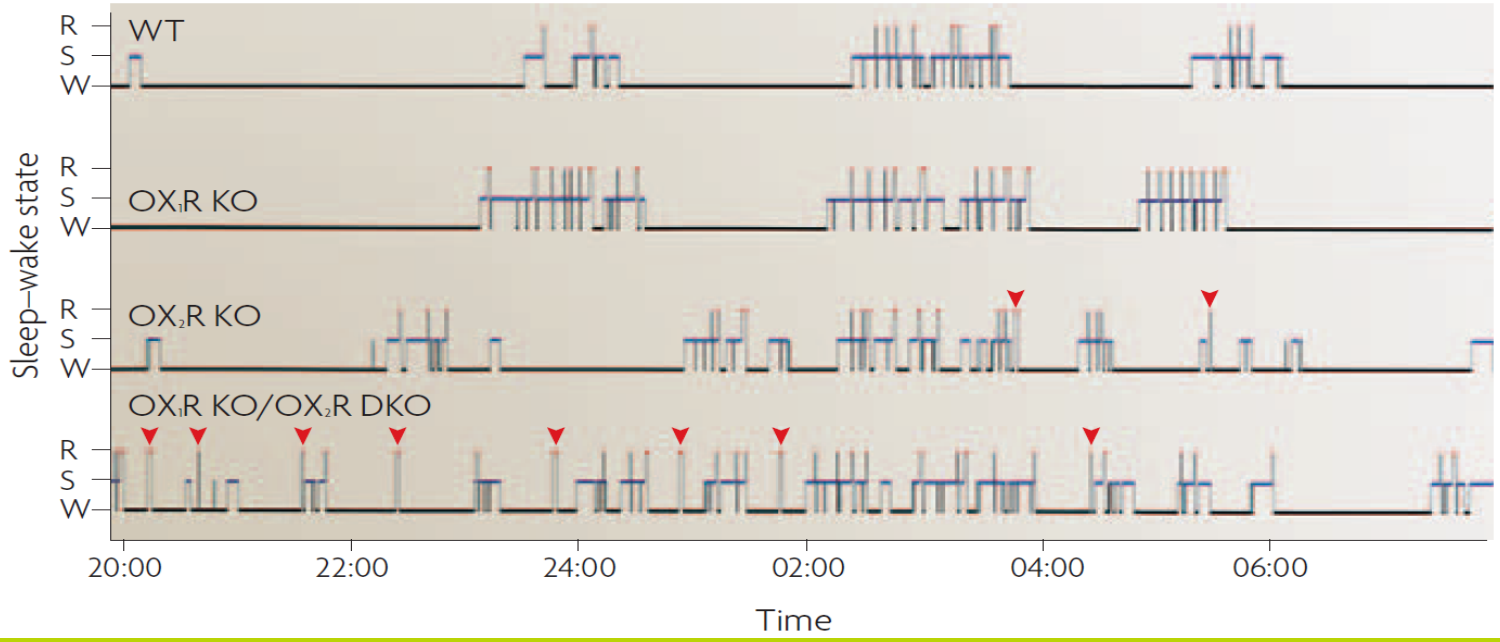


Narcolepsy:

- 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

More about Orexin [1]

- Injection of orexin increases wakefulness for hours. In mice, rats, and dogs, a lack of orexin/dysfunction of orexin receptors causes narcolepsy symptoms.

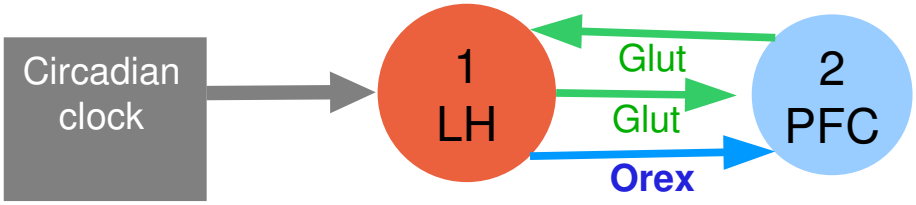
- Orexin producing neurons present a degree of heterogeneity much higher than the other types of neurons

- Among the several activators and inhibitors of orexin neurons, orexin neurons are tonically activated by glutamate: neurons containing orexin and glutamate form a positive feedback loop that may reinforce and coordinate their activity.

- The resting membrane potential of orexin neurons is close to their threshold for firing, even during synaptic blockade. This propensity for spontaneous activity may allow the orexin neurons to remain persistently active, thus helping maintain wakefulness over long periods of time, which can be important for the survival of the individual.

[1] Science editorial about T. Mochizuki and T.E. Scammell, Current Biology 13 (2003) R563

wake-sleep model of 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, A. Peters, H.A. Braun, *A Neuron-based Model of Sleep-Wake cycles: the role of orexin/hypocretin*, BioSim Preprint.

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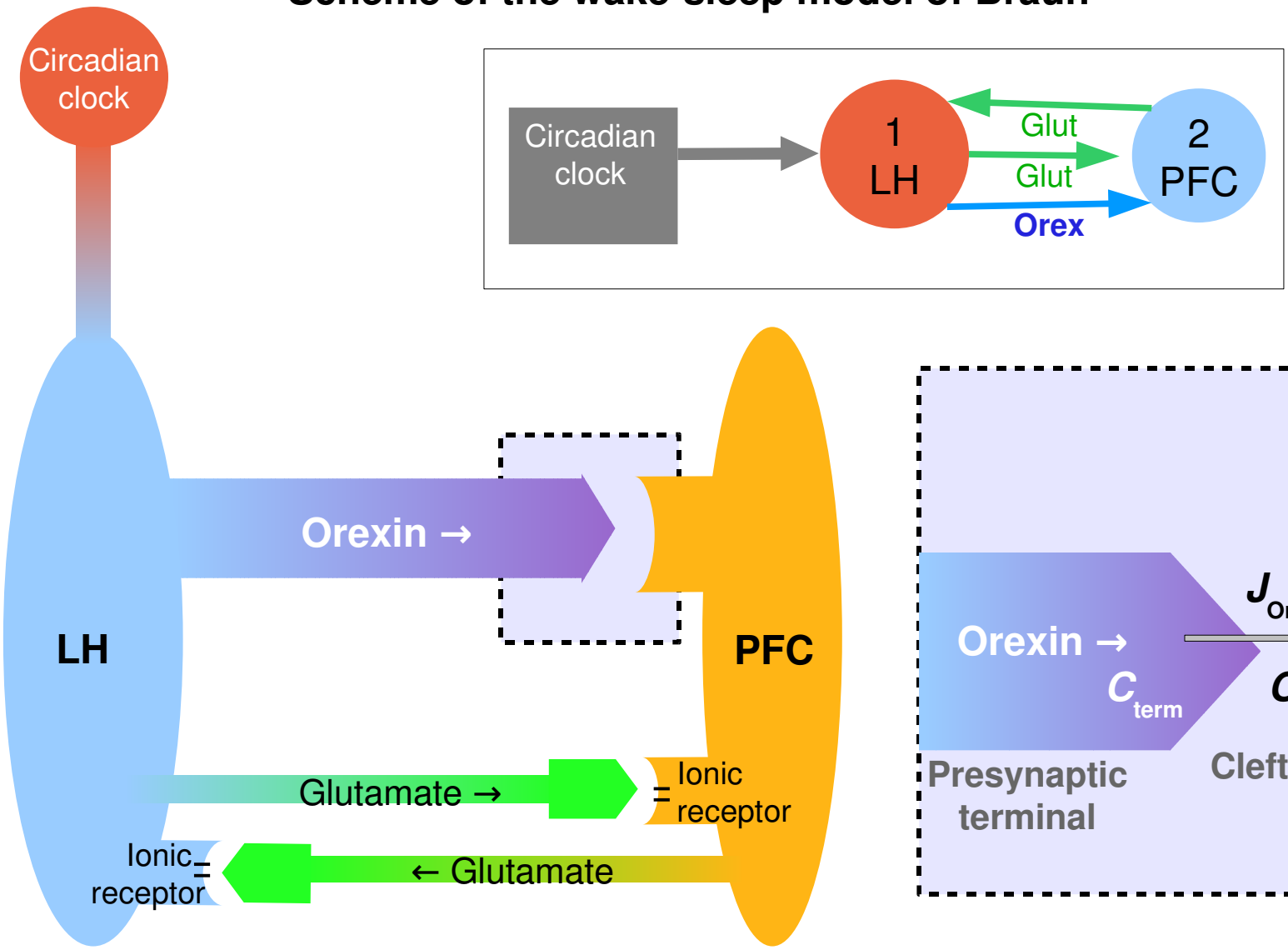
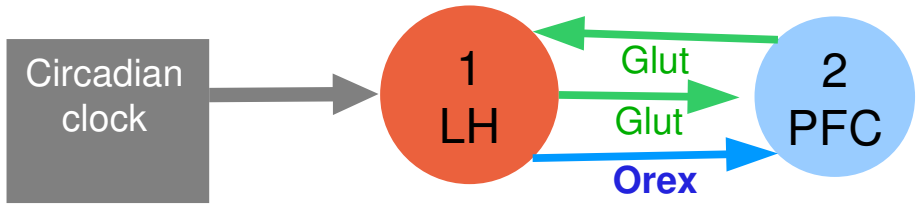
Scheme of the wake-sleep model of Braun



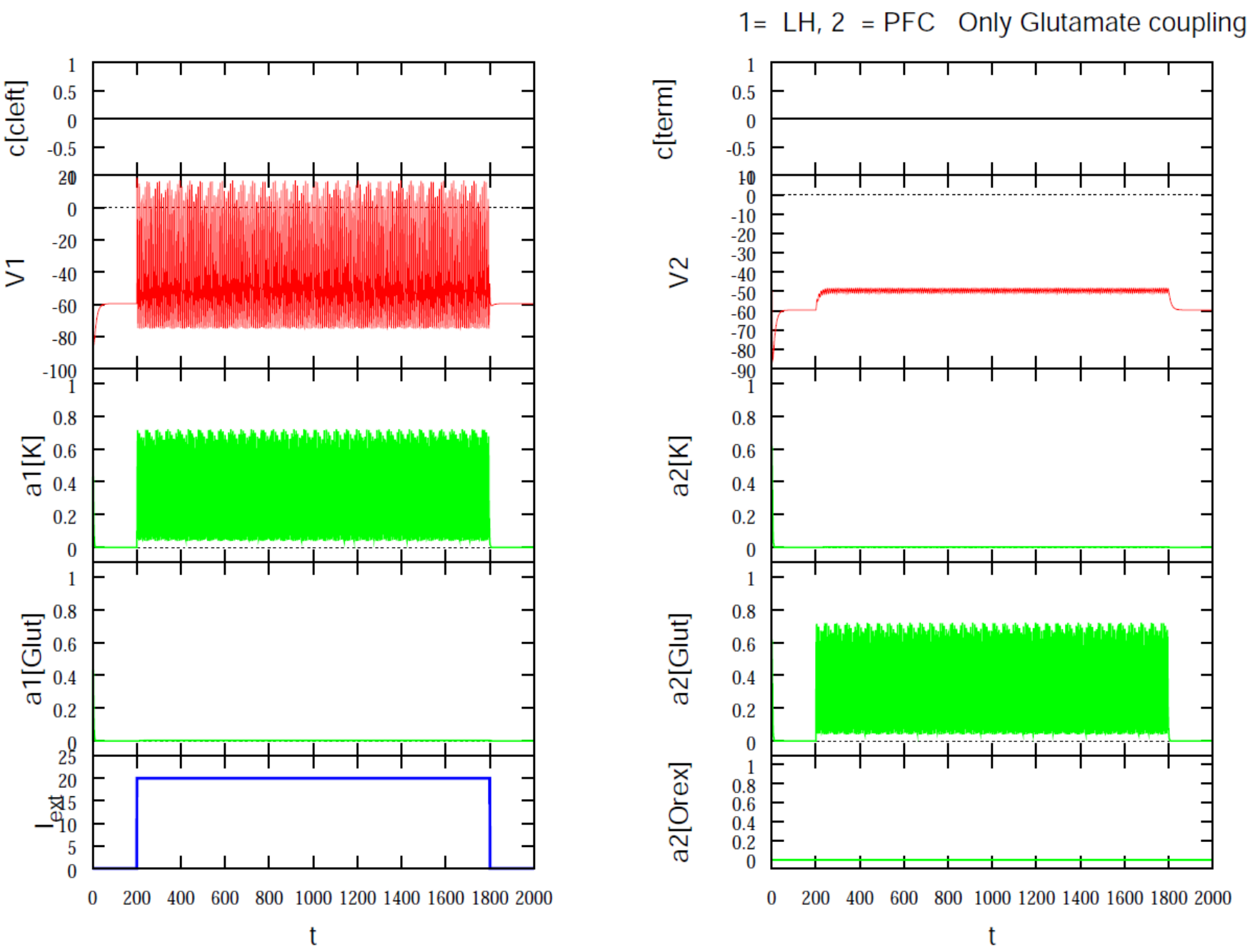


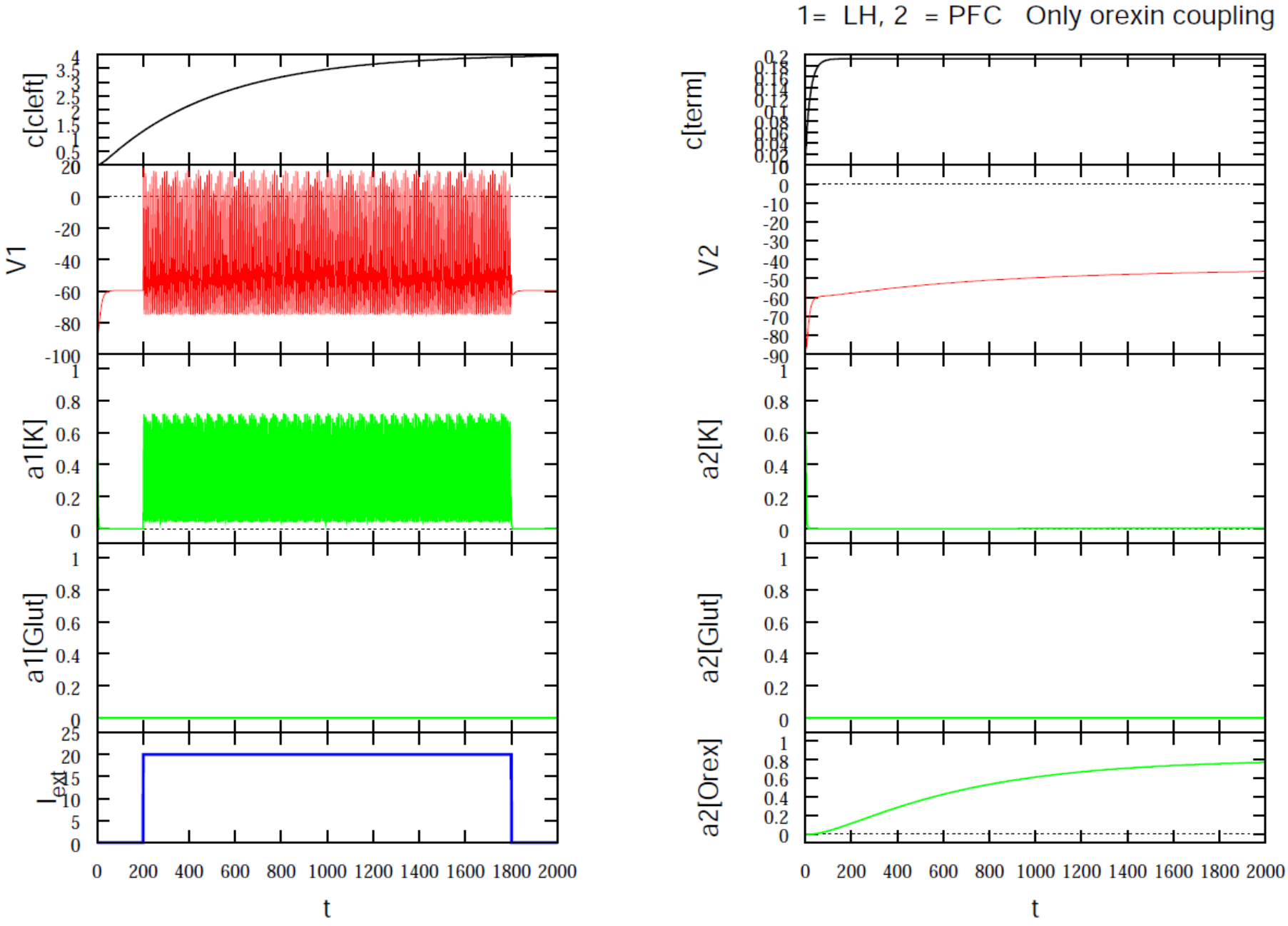
Mathematical formulation of the wake-sleep model of Braun

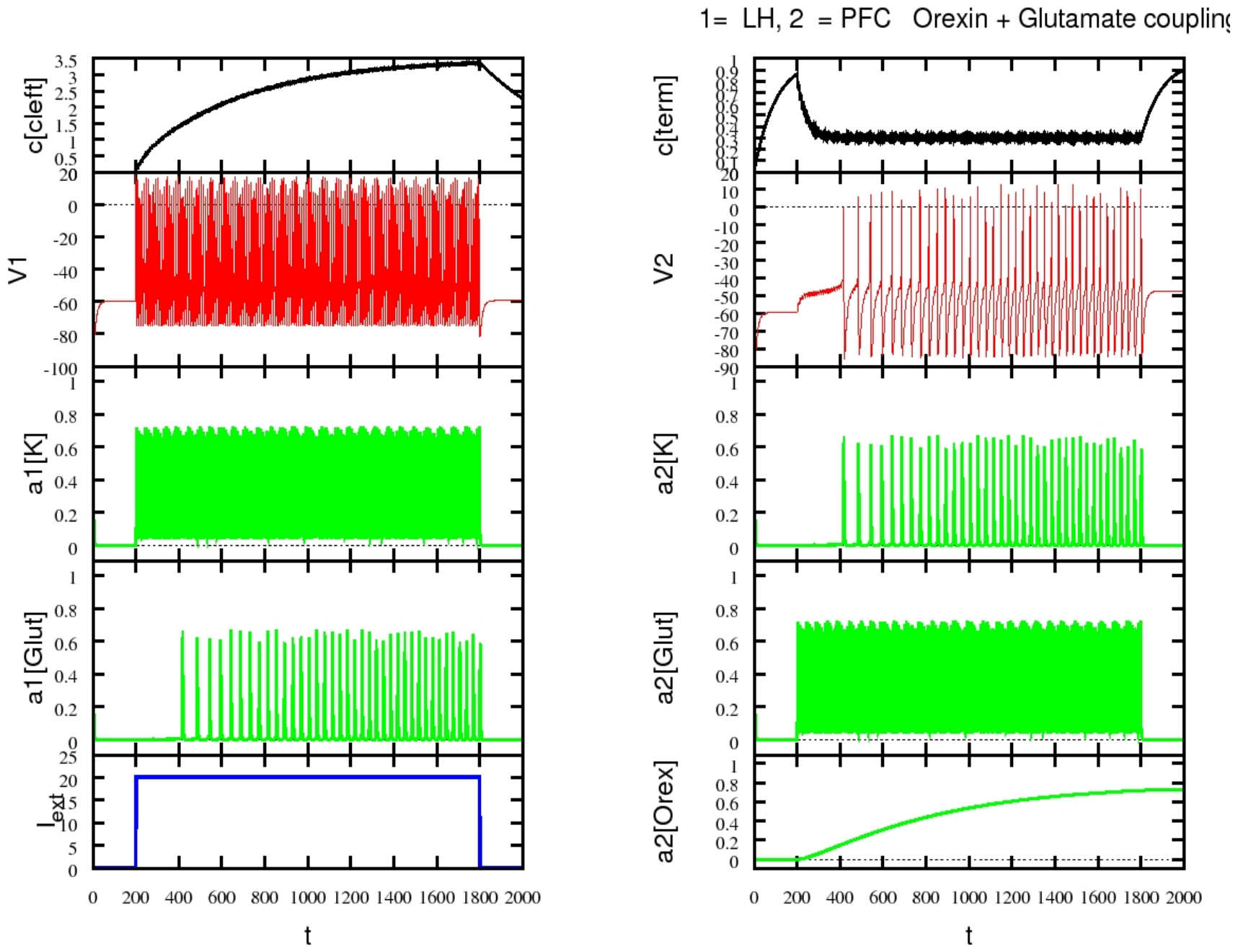
$$
\begin{aligned}
C_1 \frac{dV_1}{dt} &= -g_{\mathrm{L}}(V_1 - V_{\mathrm{L}}) - g_{\mathrm{Na}}\,(V_1 - V_{\mathrm{Na}})\,\bar{a}_{\mathrm{Na}}(V_1) - g_{\mathrm{K}}\,(V_1 - V_{\mathrm{K}})\,a_{1\mathrm{K}} \\
&\quad - g_{\mathrm{Glut}}\,(V_1 - V_{\mathrm{ref}})\,a_{1\mathrm{Glut}} + I_{\mathrm{ext}}(t)\,, \\
C_2 \frac{dV_2}{dt} &= -g_{\mathrm{L}}(V_2 - V_{\mathrm{L}}) - g_{\mathrm{Na}}\,(V_2 - V_{\mathrm{Na}})\,\bar{a}_{\mathrm{Na}}(V_2) - g_{\mathrm{K}}\,(V_2 - V_{\mathrm{K}})\,a_{2\mathrm{K}} \\
&\quad - g_{\mathrm{Glut}}\,(V_2 - V_{\mathrm{ref}})\,a_{2\mathrm{Glut}} - g_{\mathrm{Orex}}\,(V_2 - V_{\mathrm{ref}})\,a_{2\mathrm{Orex}}\,.
\end{aligned}
$$

$$
\begin{aligned}
\frac{da_{\mathrm{chann}}}{dt} &= -\frac{a_{\mathrm{chann}} - \bar{a}_{\mathrm{chann}}}{\tau_{\mathrm{chann}}} \\
\frac{da_{1\mathrm{Glut}}}{dt} &= -\frac{a_{1\mathrm{Glut}} - \bar{a}_{\mathrm{ref}}(V_2)}{\tau_{\mathrm{Glut}}}\,, \\
\frac{da_{2\mathrm{Glut}}}{dt} &= -\frac{a_{2\mathrm{Glut}} - \bar{a}_{\mathrm{ref}}(V_1)}{\tau_{\mathrm{Glut}}}\,,
\end{aligned}
\qquad
\begin{aligned}
\frac{da_{2\mathrm{Orex}}}{dt} &= -\frac{1}{\tau_{\mathrm{Orex}}}\left[a_{2\mathrm{Orex}} - \frac{C_{\mathrm{cleft}}}{C^0_{\mathrm{cleft}} + C_{\mathrm{cleft}}}\right] \\
\frac{dC_{\mathrm{cleft}}}{dt} &= J_{\mathrm{Orex}} - \frac{C_{\mathrm{cleft}}}{\tau_{\mathrm{cons}}} \\
\frac{dC_{\mathrm{term}}}{dt} &= -J_{\mathrm{Orex}} - \frac{C_{\mathrm{term}} - C^{\mathrm{max}}_{\mathrm{term}}}{\tau_{\mathrm{prod}}}
\end{aligned}
$$

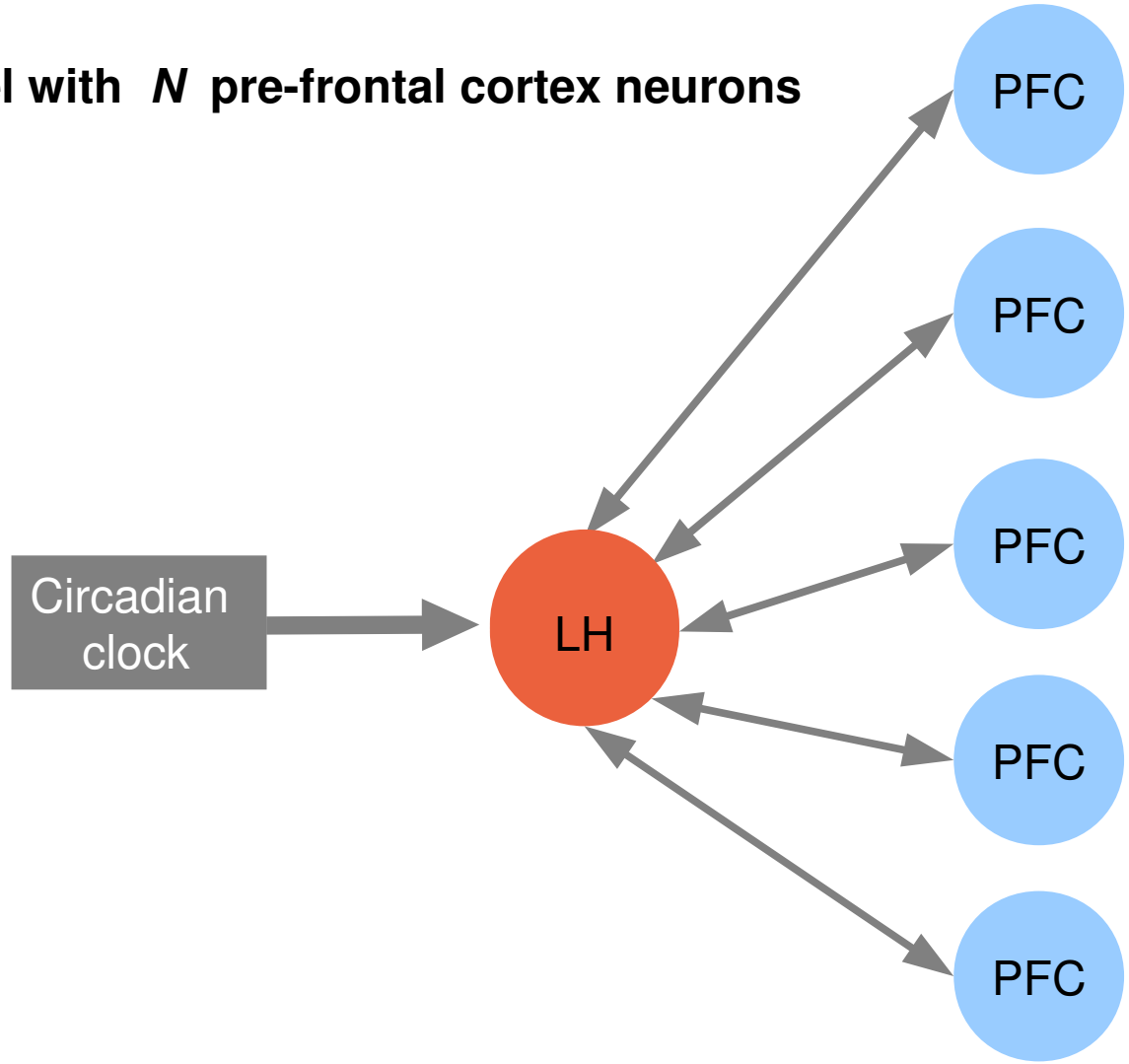
$$
\bar{a}_{\mathrm{chann}}(V) = \frac{1}{1 + \exp[-S_{\mathrm{chann}}\,(V - W_{\mathrm{chann}})]}\,,
\qquad
J_{\mathrm{Orex}} = r_{\mathrm{rel}}\,\bar{a}_{\mathrm{ref}}(V_1)\,\frac{C_{\mathrm{term}}}{C^{(0)}_{\mathrm{term}} + C_{\mathrm{term}}}
$$


1= LH, 2 = PFC Only Glutamate coupling
c[cleft]
V1
a1[K]
a1[Glut]
I_ext
c[term]
V2
a2[K]
a2[Glut]
a2[Orex]
t
t

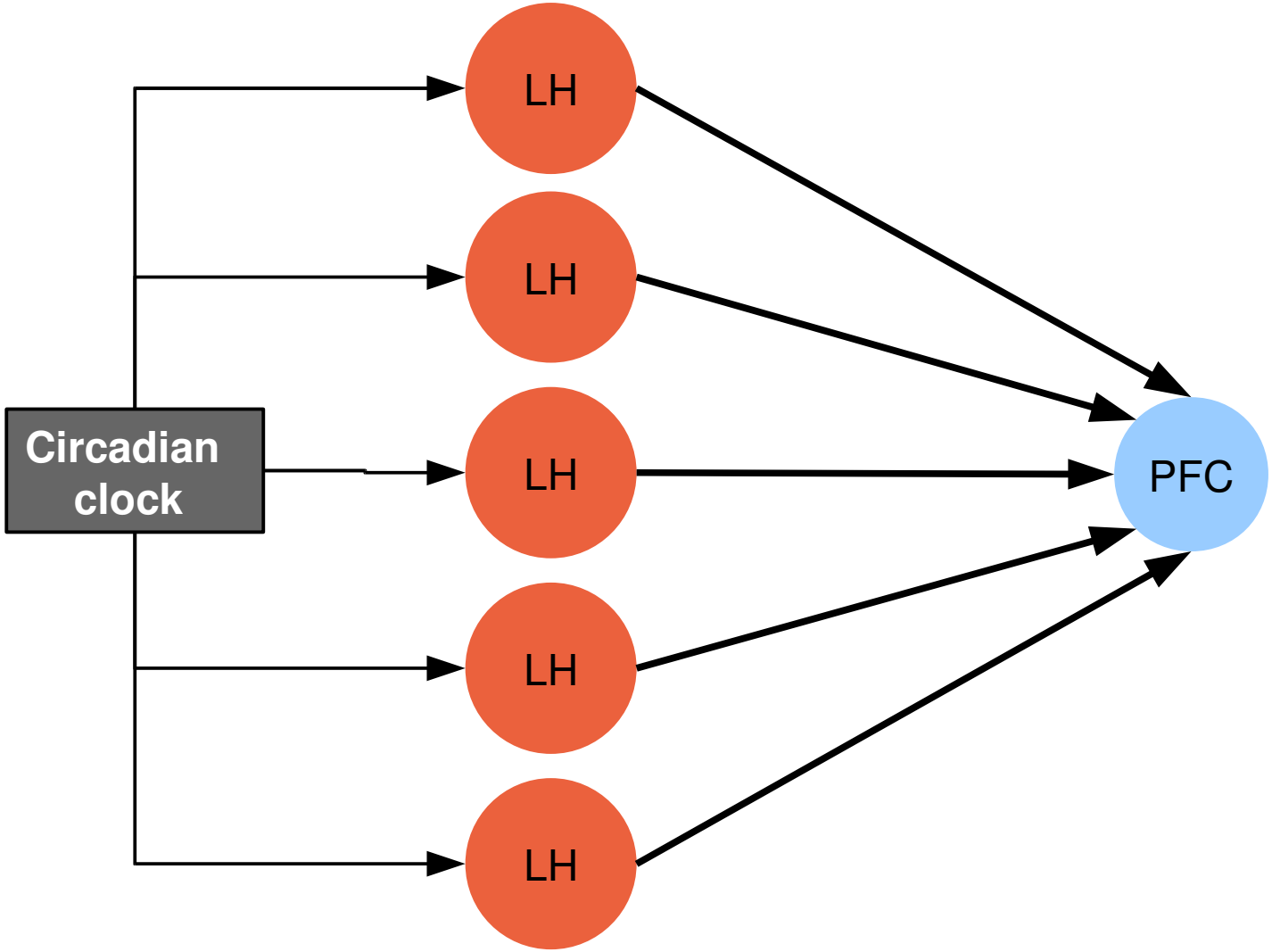

1= LH, 2 = PFC Only orexin coupling
c[cleft]
V1
a1[K]
a1[Glut]
I_ext
c[term]
V2
a2[K]
a2[Glut]
a2[Orex]
t
t


1= LH, 2 = PFC Orexin + Glutamate couplin
c[cleft]
V1
a1[K]
a1[Glut]
I_ext
t
c[term]
V2
a2[K]
a2[Glut]
a2[Orex]
t

Generalized model with *N* pre-frontal cortex neurons



Generalized model with *N* orexin-producing neurons



Effect of diversity in the activation threshold *W*

- Hp: the external signal has a noise component,

$I_{ext}(t) = I_0(t) + R(t)$; $R(t)$ = Gaussian noise

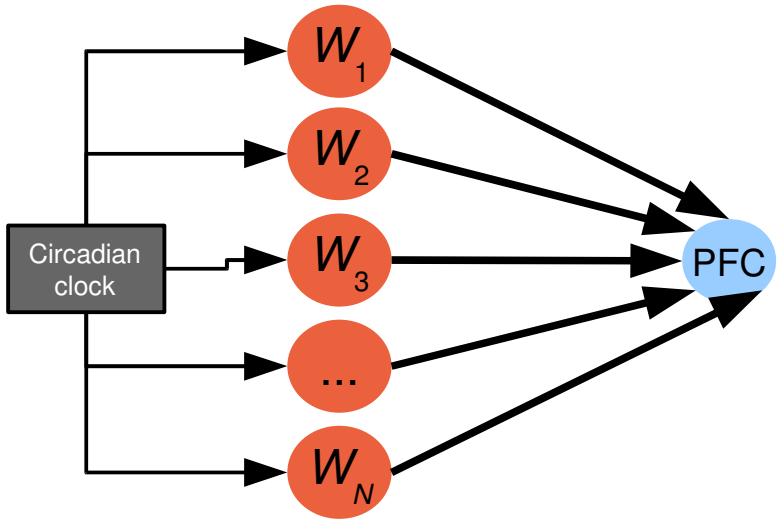
and its intensity is *kept constant.*

Diversity is introduced in the glutamate threshold potential *W* :

$f(W) \sim \exp[-(W - W_0)/2\sigma_W{}^2]$

σ_W = standard deviation

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



Effect of diversity in the activation threshold *W*

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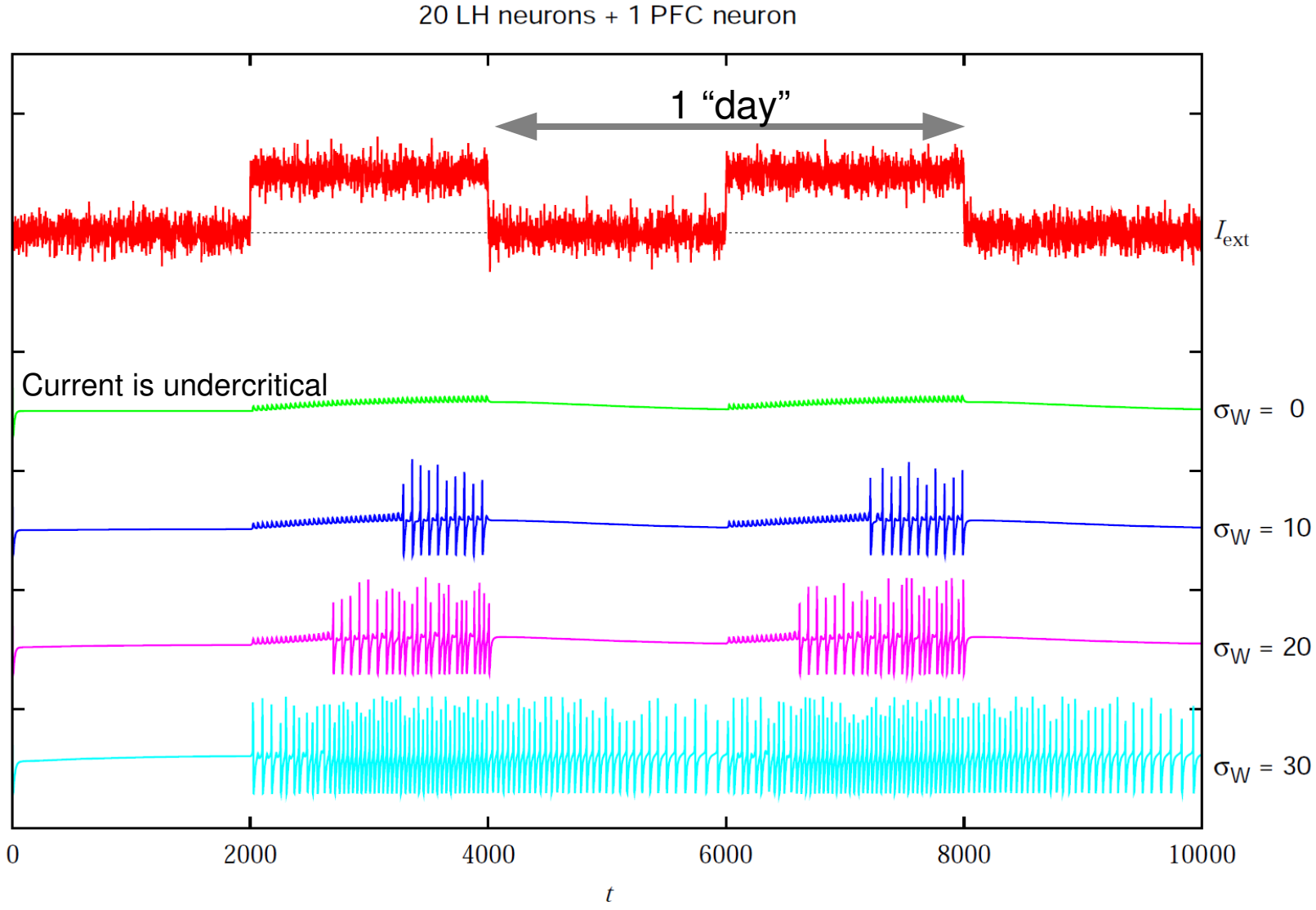
C. Tessone, C. Mirasso, R. Toral, J.D. Gunton,
Diversity-induced resonance,
Phys. Rev. Lett. 97, 194101 (2006)

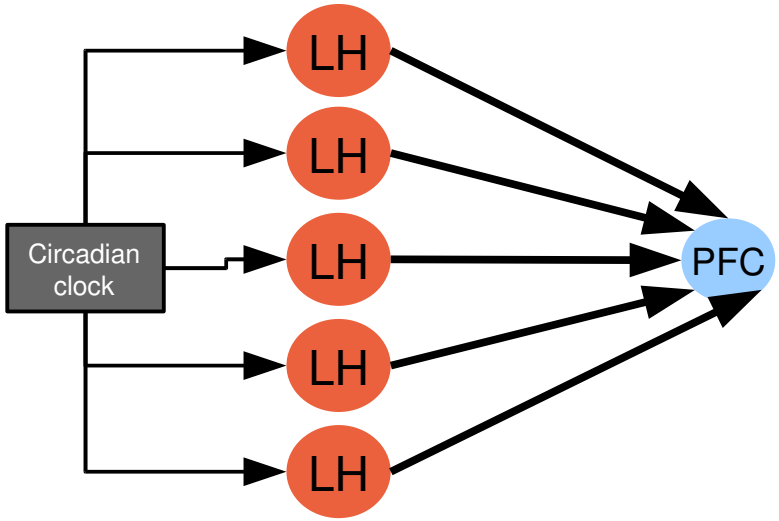


Effect of diversity of the activation of ion-channels

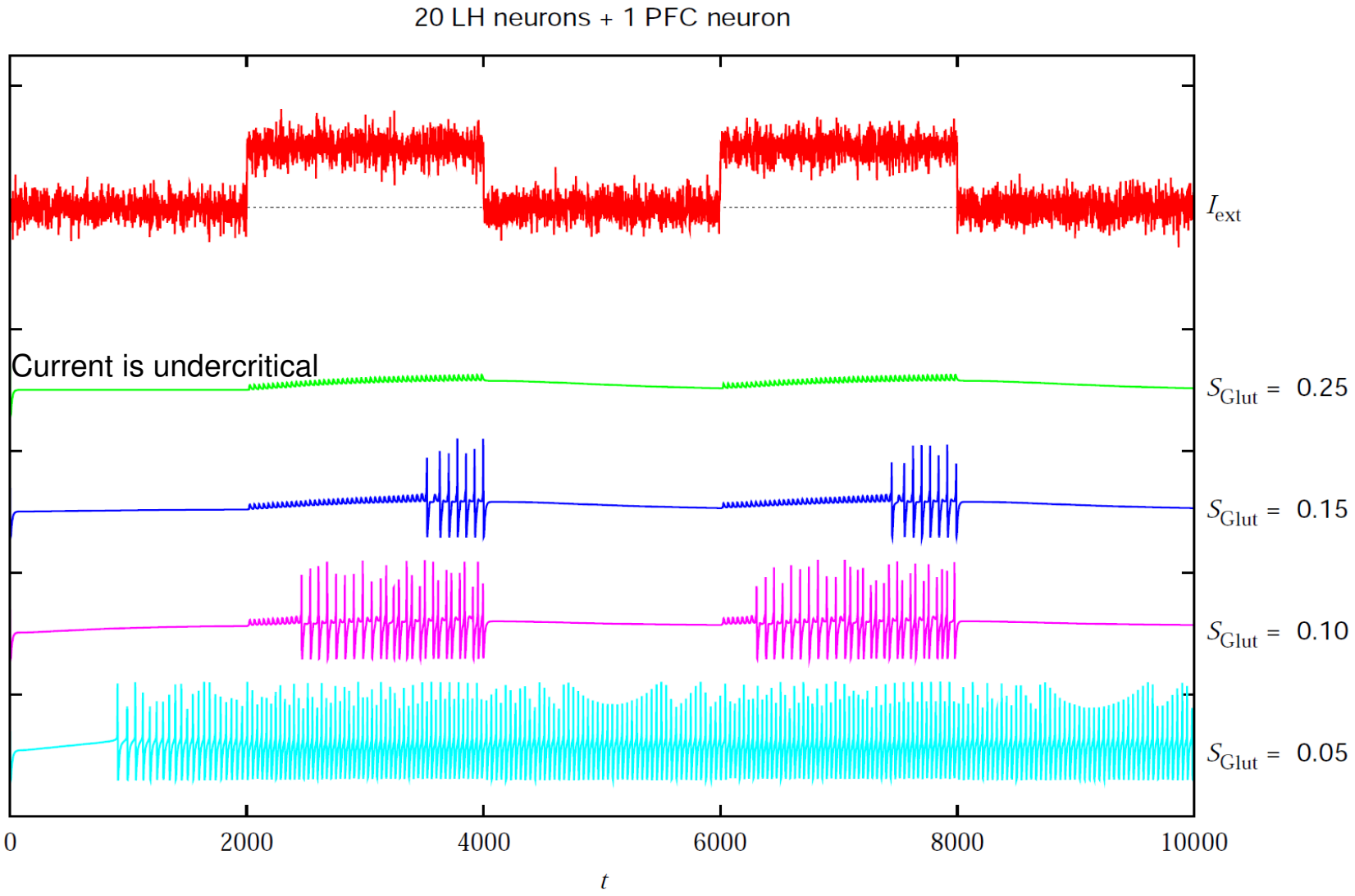
- external signal with noise, $I_{ext}(t) = I_0(t) + R(t)$; $R(t)$ = Gaussian noise

Diversity is introduced by decreasing the value of the glutamate smoothness parameter S_{glut} which represents the diversity of the ion-channels of a *same* neuron.

$$\bar{a}_{\ }(V) = \frac{1}{1+\exp[-S_{\ }(V-W_{\ })]},$$



Effect of diversity in the ion-channels (of a same neuron)

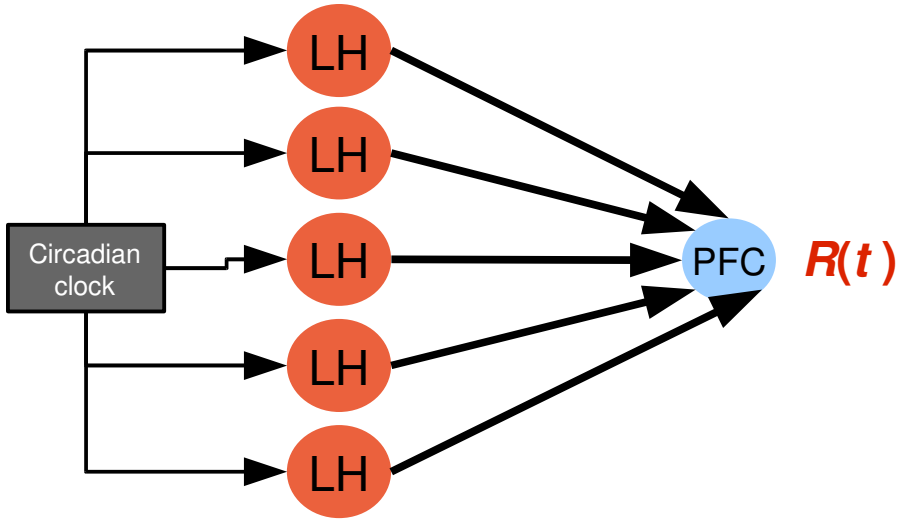


Stochastic Resonance (effect of noise = diversity/disorder in time)

$I_{ext}(t) = I_0(t)$ (deterministic)

but the PFC neuron currents contain an additional delta-correlated Gaussian noise term $R(t)$ representing a noise level / temperature T_B of the PFC neuron

$V_B(t) \rightarrow V_B(t) + R(t)$



Stochastic Resonance

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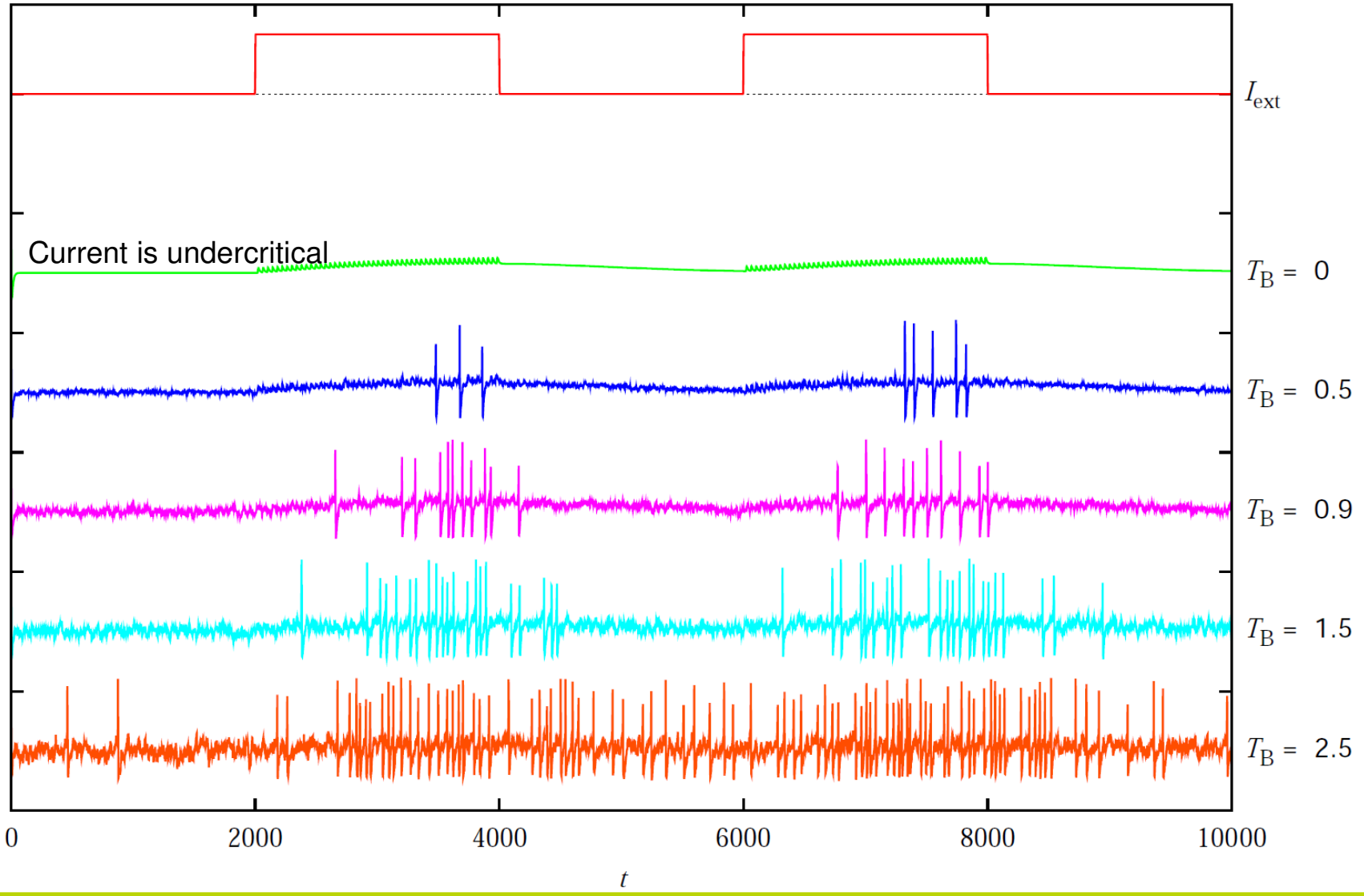
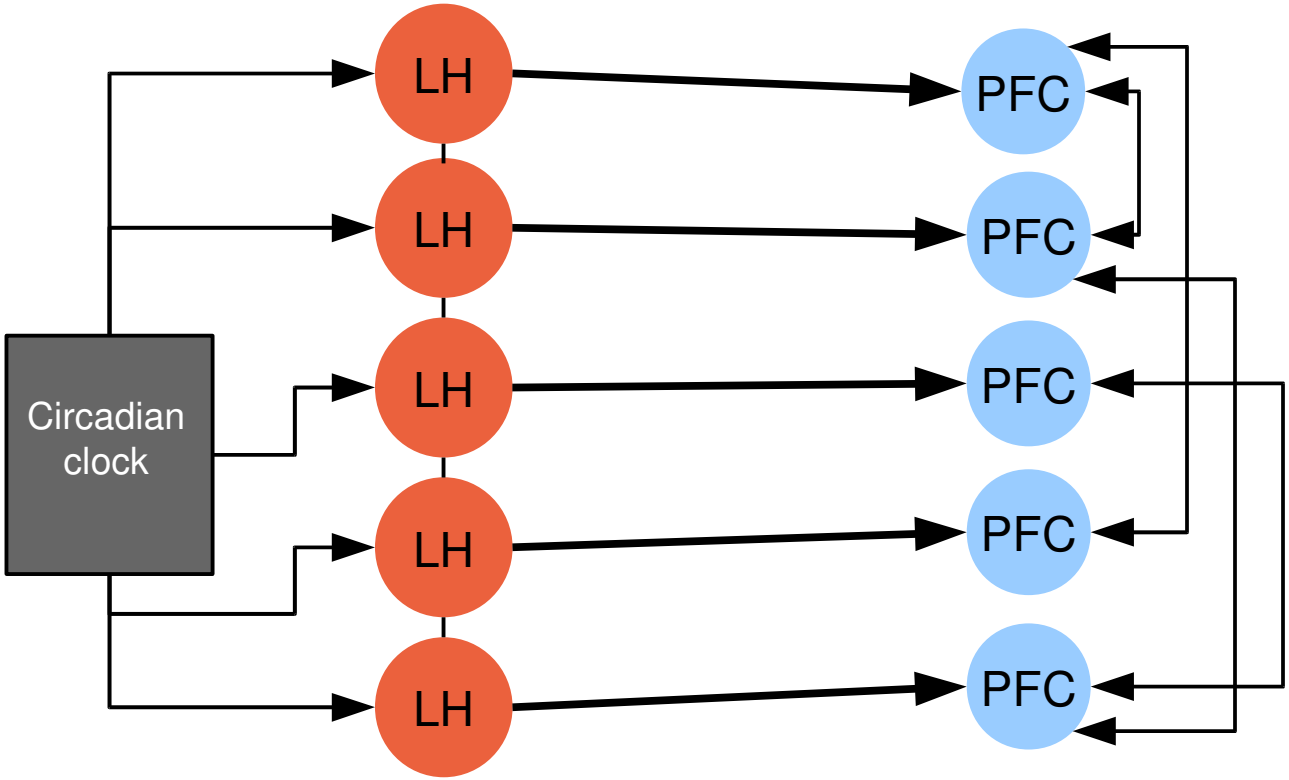
L.Gammaitoni,P. Hänggi, P. Jung, F. Marchesoni,
Stochastic resonance,
Rev.Mod.Phys.70 (1998) 223



Work in progress (more realistic model)

- Adding more neurons, constructing various network topologies
- Taking into account other neurotransmitters besides Glutamate and Orexin



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