

Effects of Several Classes of Voltage-Gated Ion Channel Conductances on Gamma and Theta Oscillations in a Hippocampal Microcircuit Model

Chris Olteanu¹^{*}, Forough Habibollahi^{1,2*}, and Chris French³

 ¹ Melbourne Brain Centre, The University of Melbourne, Victoria, Australia
 ² Department of Biomedical Engineering, The University of Melbourne, Victoria, Australia
 ³ Department of Medicine, The Royal Melbourne Hospital, The University of Melbourne, Victoria, Australia

Correspondence: Chris French frenchc@unimelb.edu.au

SUPPLEMENTARY MATERIALS

In this section, we will introduce the mathematical details of the utilized model and introduce the equations and parameters that derive the PING network in this work.

1 NEURON MODELS

We use the following models for each type of the neurons in our study:

• E-Cells: Based on the model of Olufsen et al. (2003) and extending it to incorporate the persistent sodium conductance (g_{NaP}) of the E-Cells as well, we use:

$$C\frac{dV}{dt} = g_{Na}m_{\infty}V^{3}h(V_{Na} - V) + g_{k}n^{4}(V_{k} - V) + g_{L}(V_{L} - V) + g_{NaP}r_{\infty}(V_{NaP} - V) + I \quad (1)$$

$$\frac{dh}{dt} = \frac{h_{\infty}(V) - h}{\tau_h(V)} \tag{2}$$

$$\frac{dn}{dt} = \frac{n_{\infty}(V) - n}{\tau_n(V)} \tag{3}$$

where we have:

$$x_{\infty}(V) = \frac{\alpha_x(V)}{\alpha_x(V) + \beta_x(V)} \qquad for \ x = m, h, or \ n$$
(4)

*Both authors contributed equally to this manuscript.

and

$$\tau_x(V) = \frac{1}{\alpha_x(V) + \beta_x(V)} \qquad for \ x = h \ or \ n \tag{5}$$

In the above equations, the letters C, V, t and τ , g, and I denote capacitance density, voltage, time, conductance density, and current density, respectively. The corresponding units for these quantities are $\frac{\mu F}{cm}$, mV, ms, $\frac{mS}{cm}$, and $\frac{\mu A}{cm}$. For this part of the model, we use the following parameters: C = 1, $g_{Na} = 100$, $g_K = 80$, $g_L = 0.1$, $V_{Na} = 50$, $V_K = -100$, $V_L = -67$. Finally, for the α_x and β_x parameters we have:

$$\alpha_m(V) = \frac{0.32(V+54)}{1-exp(-(V+54)/4)}$$

$$\beta_m(V) = \frac{0.28(V+27)}{exp((V+27)/5) - 1}$$

$$\alpha_h(V) = 0.128exp(-(V+50)/18)$$

$$\beta_h(V) = \frac{4}{1+exp(-(V+27)/5)}$$

$$\alpha_n(V) = \frac{0.032(V+52)}{1-exp(-(V+52)/5)}$$

$$\beta_n(V) = 0.5exp(-(V+57)/40)$$

(6)

Finally, with the addition of persistent sodium conductance based on Li and Cleland (2013), we have:

$$r_{\infty} = \frac{1}{1 + \exp(-(V + 50)/5)} \tag{7}$$

• I-Cells: Based on Wang and Buzsáki (1996), we follow the below equations for modeling the I-cells in this work:

$$C\frac{dV}{dt} = g_{Na}m_{\infty}V^{3}h(V_{Na} - V) + g_{k}n^{4}(V_{k} - V) + g_{L}(V_{L} - V) + I$$
(8)

$$\frac{dh}{dt} = \frac{h_{\infty}(V) - h}{\tau_h(V)} \tag{9}$$

$$\frac{dn}{dt} = \frac{n_{\infty}(V) - n}{\tau_n(V)} \tag{10}$$

where we have:

$$x_{\infty}(V) = \frac{\alpha_x(V)}{\alpha_x(V) + \beta_x(V)} \qquad for \ x = m, h, or \ n$$
(11)

and

$$\tau_x(V) = \frac{0.2}{\alpha_x(V) + \beta_x(V)} \qquad for \ x = hor \ n \tag{12}$$

where we have the rate functions as the following:

$$\alpha_m(V) = \frac{0.1(V+35)}{1-exp(-(V+35)/10)}$$

$$\beta_m(V) = 4exp(-(V+60)/18)$$

$$\alpha_h(V) = 0.07exp(-(V+58)/20)$$

$$\beta_h(V) = \frac{1}{exp(-0.1(V+28))+1}$$

$$\alpha_n(V) = \frac{0.01(V+34)}{1-exp(-0.1(V+34))}$$

$$\beta_n(V) = 0.125exp(-(V+44)/80)$$

(13)

The parameters utilized, are in the same units as for the E-cells and we have C = 1, $g_{Na} = 35$, $g_K = 9$, $g_L = 0.1$, $V_{Na} = 55$, $V_K = -90$, $V_L = -65$.

• **O-Cells:** We refer to the model of Tort et al. (2007) for defining the O-cells which is itself a reduction of the multi-compartmental model in Saraga et al. (2003). Therefore, we get:

$$C\frac{dV}{dt} = g_{Na}m^{3}h(V_{Na} - V) + g_{k}n^{4}(V_{k} - V) + g_{A}ab(V_{A} - V) + g_{h}r(V_{h} - V)g_{L}(V_{L} - V) + I$$
(14)

with

$$\frac{dx}{dt} = \frac{x_{\infty}(V) - x}{\tau_x(V)} \qquad for \ x = m, h, n, a, b, r$$
(15)

For x = m, n, h the functions $x_{\infty}(V)$ and $\tau_x(V)$ are the same as in Equations 4 and 5, and now the rate functions can be defined as follows:

$$\alpha_m(V) = \frac{0.1(V+38)}{exp(-(V+38)/10) - 1}$$

$$\beta_m(V) = 4exp(-(V+65)/18)$$

$$\alpha_h(V) = 0.07exp(-(V+63)/20)$$

$$\beta_h(V) = \frac{1}{exp(-(V+33)/10) + 1}$$

$$\alpha_n(V) = \frac{0.018(V-25)}{1 - exp(-(V-25)/25)}$$

$$\beta_n(V) = \frac{0.0036(V-35)}{exp((V-35)/12) - 1}$$

(16)

Eventually, for x = a, b, r, we present the $x_{\infty}(V)$ and $\tau_x(V)$ as below:

$$a_{\infty}(V) = \frac{1}{1 + exp(-(V + 14)/16.6)}$$

$$\tau_{a}(V) = 5$$

$$\alpha_{h}(V) = 0.07exp(-(V + 63)/20)$$

$$b_{\infty}(V) = \frac{1}{1 + exp((V + 71)/7.3)}$$

$$\tau_{b}(V) = \frac{1}{\frac{0.000009}{exp((V - 26)/18.5)} + \frac{0.014}{0.2 + exp(-(V + 70)/11)}}$$

$$r_{\infty}(V) = \frac{1}{1 + exp((V + 48)/10.2)}$$

$$\tau_{r}(V) = \frac{1}{exp(-14.59 - 0.086V) + exp(-1.87 + 0.0701V)}$$

(17)

The parameter values for the above equations are C = 1.3, $g_L = 0.05$, $g_{Na} = 30$, $g_K = 23$, $g_A = 16$, $g_h = 12$, $V_{Na} = 90$, $V_K = -100$, $V_A = -90$, $V_h = -32.9$, $V_L = -70$.

Next, we move on to modeling the synapses in this network.

2 SYNAPTIC MODEL

The utilized synaptic model in this work is adopted from Ermentrout and Kopell (1998). We represent the synaptic gating variable for each synapse associated with the presynaptic neuron with s where $0 \le s \le 1$. This variable obeys:

$$\frac{ds}{dt} = \rho(V)\frac{1-s}{\tau_R} - \frac{s}{\tau_D}$$
(18)

Here, τ_R and τ_D are the rise and decay time constants, respectively and ρ denotes a smoothed Heaviside function as the following:

$$\rho(V) = \frac{1 + tanh(\frac{V}{4})}{2} \tag{19}$$

The synaptic input to every given neuron j from a neuron i in the model must be added to the right-hand side of the equation which governs the membrane potential V_j . This term is added in the form of:

$$g_{ij}s_i(t)(V_{srev} - V_j) \tag{20}$$

where g_{ij} denotes the maximal conductance associated with the synapse, s_i represents the gating variable associated with neuron *i*, and V_{srev} is the synaptic reversal potential. For *AMPA* receptor-mediated synapses, we have $\tau_R = 0.1$, $\tau_D = 3$, and $V_{srev} = 0$; for *GABA_A* receptor-mediated synapses, $\tau_R = 0.2$, $\tau_D = 20$, and $V_{srev} = -80$, if the synapse originates from an O-cell.

3 PARAMETER SET

Here we bring the parameter values utilized in this work to model the hippocampal network which behaves as a PING network with nested gamma and theta rhythms. The model LFP exhibits mixed gamma and theta oscillations as observed experimentally in coronal slices of hippocampus Gloveli et al. (2005). Let us represent the number of E, I, and O-cells with N_E , N_I , and N_O . We denote the maximal conductance of the synaptic connection between cell type X and cell type Y with G_{XY} .

$$G_{XY} = \frac{g_{XY}}{N_X}, \qquad X, Y = O, I, E.$$
(21)

the employed g_{XY} for each synapse type between different cell types are: $g_{II} = 0.1$, $g_{OI} = 0.15$, $g_{IO} = 0.5$, $g_{IE} = 0.08$, $g_{OE} = 0.15$, $g_{EI} = 0.05$, and $g_{EO} = 0.01$ in $\frac{mS}{cm^2}$. All unspecified parameters are equal to zero.

4 ADDITIONAL RESULTS

In this section, we further explored the fluctuation of the network oscillations in response to variations in the drive currents I_E and I_I . We investigate the current value range between 0.2 and 1 $\frac{\mu A}{cm^2}$ for both I_E and I_I . In this section, we only include the simultaneous effect of varying these currents concurrently with varying g_A , g_H , and g_{KDRe} conductances as sample case studies. Due to the increased complexity with the addition of drive current variations, further analysis of these results is out of the scope of this study.

Figures 1 and 2, represent the results comparing network oscillations in theta and gamma ranges while varying drive currents to E-cells and I-cells as well as g_A , g_H , and g_{KDRe} . The theta range oscillations show higher vulnerability to drive current changes compared to gamma oscillations. This difference is more significant in the case of varying drive currents concurrently with g_{KDRe} where the theta peak is nearly lost at many variations of I_E and I_I (Figures 1f and 2f). However, the power of the peak at gamma range is much less impacted by the changes in drive currents and this peak seems to be more robust in the network in all study cases of g_A , g_H , and g_{KDRe} . These figures also confirm the expectations from a PING network discussed in the Introduction section where very weak I_E or strong I_I values abolish the PING rhythms and disturb the network activity.

Due to the extra complexity by the addition of drive current variations, we leave further discussions about the clear impact of this variable in our model to future works.

REFERENCES

- Ermentrout, G. B. and Kopell, N. (1998). Fine structure of neural spiking and synchronization in the presence of conduction delays. *Proceedings of the National Academy of Sciences* 95, 1259–1264
- Gloveli, T., Dugladze, T., Rotstein, H. G., Traub, R. D., Monyer, H., Heinemann, U., et al. (2005). Orthogonal arrangement of rhythm-generating microcircuits in the hippocampus. *Proceedings of the National Academy of Sciences* 102, 13295–13300
- Li, G. and Cleland, T. A. (2013). A two-layer biophysical model of cholinergic neuromodulation in olfactory bulb. *Journal of Neuroscience* 33, 3037–3058
- Olufsen, M. S., Whittington, M. A., Camperi, M., and Kopell, N. (2003). New roles for the gamma rhythm: population tuning and preprocessing for the beta rhythm. *Journal of computational neuroscience* 14, 33–54
- Saraga, F., Wu, C., Zhang, L., and Skinner, F. (2003). Active dendrites and spike propagation in multicompartment models of oriens-lacunosum/moleculare hippocampal interneurons. *The Journal* of physiology 552, 673–689
- Tort, A. B., Rotstein, H. G., Dugladze, T., Gloveli, T., and Kopell, N. J. (2007). On the formation of gamma-coherent cell assemblies by oriens lacunosum-moleculare interneurons in the hippocampus. *Proceedings of the National Academy of Sciences* 104, 13490–13495
- Wang, X.-J. and Buzsáki, G. (1996). Gamma oscillation by synaptic inhibition in a hippocampal interneuronal network model. *Journal of neuroscience* 16, 6402–6413



e) Frequency changes with I_E and g_{KDRe} variations

f) Power changes with I_E and g_{KDRe} variations

Figure 1. Effects of changing I_E **and conductances simultaneously.** The black asterisks represent baseline conductance values at each I_E level and the red asterisks indicate all variables (conductances and drive currents) being at baseline. Graphs also display three adjusted drive currents for each conductance level for (a,b) g_A , (c,d) g_H , and (e,f) g_{KDRe} . Fluctuations in peak frequency (left) and power (right) are given at each conductance and current pair for theta (top) and gamma (bottom) rhythms.





e) Frequency changes with I_I and g_{KDRe} variations

f) Power changes with I_I and g_{KDRe} variations

Figure 2. Effects of changing I_I **and conductances simultaneously.** The black asterisks represent baseline conductance values at each I_I level and the red asterisks indicate both conductances and drive currents being at baseline. Graphs also display three adjusted drive currents for each conductance level for (a,b) g_A , (c,d) g_H , and (e,f) g_{KDRe} . Fluctuations in peak frequency (left) and power (right) are given at each conductance and current pair for theta (top) and gamma (bottom) rhythms.