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[Re] Multiple dynamical modes of thalamic relay neurons: rhythmic bursting and intermittent phase-locking

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A reference implementation of

→ *Multiple dynamical modes of thalamic relay neurons: rhythmic bursting and intermittent phase-locking*, Wang, X-J, Neuroscience, 59(1), pg. 21–31, 1994.

Introduction

This work introduces a reference implementation of a neuron model for thalamocortical relay neurons, proposed by X-J Wang, [3]. The model is conductance-based and takes advantage of an interplay between a T-type calcium current and a non-specific cation sag current and thus, it is able to generate spindle and delta rhythms. Another feature of this model is the presence of an intermittent phase-locking phenomenon where action potentials of sodium take place in a non-periodic manner, despite the fact that they are phase-locked to the periodic input current. Finally, the model is capable of generating tonic spike patterns. The source code of reference implementation is written in Python (Numpy, Scipy, Matplotlib, and Scikit-image).

Methods

In this section, a detailed description of the model is given following the paradigm of Nordlie et al, [2]. Therefore, a brief description of the model, equations, parameters, and inputs are given in the form of tables.

Table 1 provides a description of the model, Table 2 provides information about simulations duration and temporal integration time steps, Table 3 gives a glimpse of the input signals used in this work. Table 4 introduces the equations of the model and finally Table 5 summarizes all the parameters for each figure (simulation). The neuron model is conductance-based consisting of four differential equations describing the dynamics of membrane potential and the kinetics of a T-Type calcium current, a Sag current channel and a Potassium channel. The rest currents are described by algebraic equations. The reference implementation has been done in a Python class (Python 3.5.1) along with Numpy (version 1.10.4), Scipy (version 0.17.0), Matplotlib (1.5.1) and Scikit-image (version 0.12.3). The numerical integration has been done using the *ode* method of Scipy *integrate* package. Three different methods have been tested in this work (*dopri5*, *Adams*, *BDF*, [1]). *dopri5* is the closest numerical method to the one used by the author in the original article (the author has numerically

Model Summary	
Populations	No population – one neuron model
Topology	–
Connectivity	–
Neuron Model	Hodgkin-Huxley conductance-based
Channel Models	
Synapse Model	–
Plasticity	–
Input	Constant current or periodic rectangular pulses
Measurements	Membrane potential, channels activation, phase plane

Table 1: Summary of the model

integrated the system of the four ODEs by using a fifth-order adaptive size Runge-Kutta method). *BDF* and *Adams* provide similar numerical results as the first one, but they are faster[1].

Simulation Time		
Figure	Simulation Time (s)	Integration Step (ms)
1	6	0.05
2	$15 \times period$, 2	0.05
3	6	0.05
4	1.5, 1.5, 1	0.05
5	5	0.05
6	2.5	0.05
7	40, 20	0.05

Table 2: Simulations Time

All simulations ran on a Dell OptiPlex 7040, equipped with a sixth generation i7 processor, 8 GB of physical memory and running Arch Linux. The total execution time of all simulations was 526 minutes and the peak consumed memory was 465 MB[2]. All the parameters used during simulations are given in Table 5.

[1] The user has the option to choose one of the three methods during class instantiating. We tested all three methods comparing, spike times, amplitudes and the coefficient of variation using as threshold value 0 mV. Spike events were overlapping, and $CV \simeq 1.5$ for all three methods. The membrane potential amplitude was sometimes different for the same spike events, however that difference was not too high as Figure 1 shows (up to 4 mV at maximum). Thus we decided to use the *Adams* method.

[2] Python memory profiler used (https://pypi.python.org/pypi/memory_profiler).

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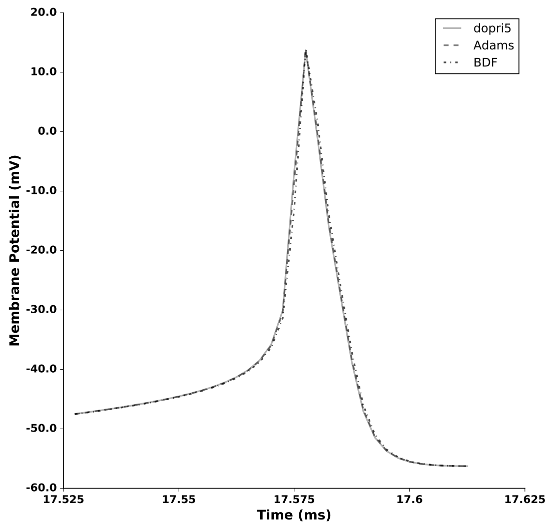

Figure 1: Spike waveform. Three integration methods: Runge-Kutta 5 (*dopri5*), *Adams*, and *BDF* where tested in order to identify potential numerical differences in our simulations (see text for more details). The amplitude for the three methods have no significant differences for the randomly picked up spike waveform shown in this figure (in general we detected differences up to $5\,\mathrm{mV}$, data not shown here). Continuous line – *dopri5*, dashed line – *Adams*, and dashed-dotted line – *BDF*.

		Input			
Figure	Type	Form	Frequency ($\frac{1}{P_0}$, Hz)	Duration (p, ms)	Amplitude (μA/cm^2)
Figure 1	Constant		–	–	-0.6
Figure 2	Periodic		5, 10	10, 40	-1.0 $+3.0$ 3
Figure 3	Constant		–	–	0.0 -0.45 -0.455 -0.47 -0.55 -0.6 -0.8 -1.3 -1.4 -2.1
Figure 4	Pulse/Constant		–	100	-1.25 0.25 -0.47
Figure 5	Constant		–	–	-0.95
Figure 6	Constant		–	–	$[-2, 0]$
Figure 7	Constant		–	–	$[-2, 0]$

Table 3: Description of the applied current I_{app}

Neuron Model	
Name	Thalamocortical relay neuron
Type	Conductance-based neuron
Membrane Potential	$C_{\mathrm{m}}\frac{dV(t)}{dt} = -I_{\mathrm{T}} - I_{\mathrm{h}} - I_{\mathrm{Na}} - I_{\mathrm{K}} - I_{\mathrm{Na(P)}} - I_{\mathrm{L}} + I_{\mathrm{app}}$
T-Type Calcium Current (I_T)	$I_{\mathrm{T}} = g_{\mathrm{T}} \cdot s_{\infty}^3(V) \cdot h \cdot (V - V_{\mathrm{Ca}})$ $s_{\infty}(V) = \frac{1}{1+\exp(-\frac{V+65}{7.8})}$ $\frac{dh(t)}{dt} = \phi_h \frac{h_{\infty}(V) - h}{\tau_h(V)}$ $h_{\infty}(V) = \frac{1}{1+\exp(\frac{V-\theta_h}{k_h})}$ $\tau_h(V) = h_{\infty}\exp(\frac{V+162.3}{17.8}) + 20$
Sag Current (I_h)	$I_h = g_h \cdot H^2 \cdot (V - V_h)$ $H_{\infty}(V) = \frac{1}{1+\exp(\frac{V+69}{7.1})}$ $\frac{dH(t)}{dt} = \phi_H \frac{H_{\infty}(V) - H}{\tau_H(V)}$
Hodgkin-Huxley Currents (I_K) and (I_{Na})	$I_{\mathrm{K}} = g_K \cdot n^4 \cdot (V - V_{\mathrm{K}})$ $\frac{dn(t)}{dt} = \phi_n \frac{n_{\infty}(V) - n(t)}{\tau_n(V)}$ $n_{\infty}(\sigma_{\mathrm{K}}, V) = \frac{\alpha_n(\sigma_{\mathrm{K}}, V)}{\alpha_n(\sigma_{\mathrm{K}}, V) + \beta_n(\sigma_{\mathrm{K}}, V)}$ $\tau_n(\sigma_{\mathrm{K}}, V) = \frac{1}{\alpha_n(\sigma_{\mathrm{K}}, V) + \beta_n(\sigma_{\mathrm{K}}, V)}$ $\alpha_n(\sigma_{\mathrm{K}}, V) = \frac{-0.01(V + 45.7 - \sigma_{\mathrm{K}})}{\exp(-0.1(V + 45.7 - \sigma_{\mathrm{K}})) - 1}$ $\beta_n(\sigma_{\mathrm{K}}, V) = 0.125\exp(-\frac{V + 55.7 - \sigma_{\mathrm{K}}}{80})$ $I_{\mathrm{Na}} = g_{\mathrm{Na}} \cdot m_{\infty}^3(\sigma_{\mathrm{Na}}, V) \cdot (0.85 - n) \cdot (V - V_{\mathrm{Na}})$ $m_{\infty}(V) = \frac{\alpha_m(\sigma_{\mathrm{Na}}, V)}{\alpha_m(\sigma_{\mathrm{Na}}, V) + \beta_m(\sigma_{\mathrm{Na}}, V)}$ $\alpha_m(\sigma_{\mathrm{Na}}, V) = -0.1\frac{V + 29.7 - \sigma_{\mathrm{Na}}}{\exp(-0.1(V + 54.7 - \sigma\mathrm{Na})) - 1}$ $\beta_m(\sigma_{\mathrm{Na}}, V) = 4\exp(-\frac{V + 54.7 - \sigma_{\mathrm{Na}}}{18})$
Persistent Sodium Currents ($I_{Na(P)}$)	$I_{\mathrm{Na(P)}} = g_{\mathrm{Na(P)}} \cdot m_{\infty}^3(\sigma_{\mathrm{Na(P)}}, V) \cdot (V - V_{\mathrm{Na}})$
Leak Current (I_L)	$I_L = g_L \cdot (V - V_L)$

Table 4: Description of the neuron model

Model Parameters							
Figure	V_0 (mV)	g_T (mS/cm^2)	θ_h (mV)	k_h (mV^{-1})	σ_{Na} (mV)	g_L (mS/cm^2)	V_L (mV)
1	−74	1	−79	−5	6	0.12	−70
2	−74	1	−81	6.25	3	0.1	−72
3	−74	0.3	−79	5	6	0.12	−70
4	−72/−64	1.0	−79	5	6	0.12	−70
5	−74	0.3	−75	5	6	0.08	−70
6	−74	1/0.7	−79	5	6	0.1/0.04	−70
7	−72	0.3/0.25	−81	6.25	3	0.1	−72
Common Parameters							
$C_m = 1\,\mu\mathrm{F/cm^2}$, $\phi_h = 2$, $V_{\mathrm{Ca}} = 120\,\mathrm{mV}$, $\phi_H = 1$, $g_h = 0.04\,\mathrm{mS/cm^2}$, $V_h = -40\,\mathrm{mV}$, $g_{\mathrm{K}} = 30\,\mathrm{mS/cm^2}$, $V_{\mathrm{K}} = -80\,\mathrm{mV}$, $g_{\mathrm{Ca}} = 42\,\mathrm{mS/cm^2}$ $V_{\mathrm{Ca}} = 55\,\mathrm{mV}$, $\phi_n = 28.5$, $\sigma_{\mathrm{K}} = 10\,\mathrm{mV}$, $V_{\mathrm{Na(P)}} = 55\,\mathrm{mV}$, $\sigma_{\mathrm{Na(P)}} = -5\,\mathrm{mV}$, $g_{\mathrm{Na(P)}} = 9\,\mathrm{mS/cm^2}$							

Table 5: Simulation Parameters

Results

We simulated the model described in Table 4 using the parameters given in Table 5 and the corresponding input (see Table 3). First, we examined what is the response of the reference implementation to rhythmic hyperpolarization. In [3] this is illustrated in Fig 1[3] of the original article. Thus, we applied a periodic current pulse of $-1\,\mu\text{A/cm}^2$ amplitude at several different frequencies ($\frac{1}{P_0}$ is the frequency in Hz and P_0 is the corresponding period in ms) ranging from 0.1 Hz to 15 Hz with a resolution (discretization) of 30 points. The same number of samples used for discretizing the duration for each frequency. The results are shown in Figure 2 left panel. Right panel shows three different simulations of the reference implementation at specific frequencies (10, 5, 0.5 Hz) and rations p/P_0 $(0.1, 0.6, 0.6)$, respectively (crossed area in Figure 2 reflects the transient, which is omitted in the rest of the figures in this work). It is apparent that right and left panels are in an agreement indicating that the reference model produces reliable results. The author in [3] shows in Fig 1 a shaded are where the number of spikes is 0.5. This number appears if one computes the average of suprathreshold and subthreshold spikes in one period.

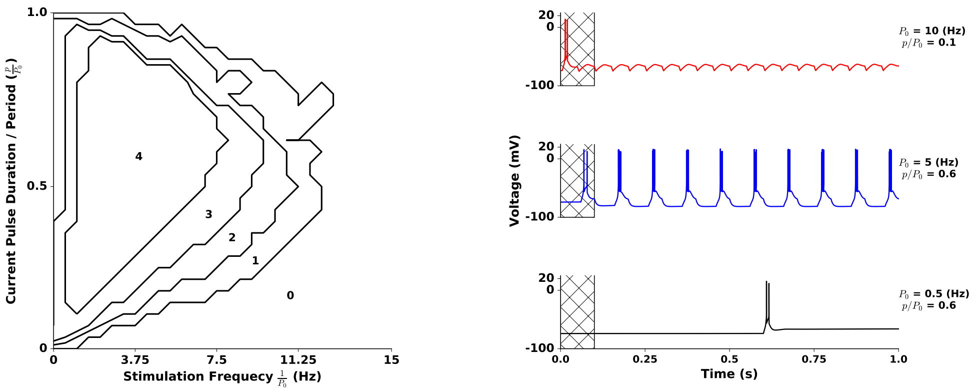

Figure 2: Responses to rhythmic hyperpolarizations. We stimulate the model with a periodic pulse with varying frequency $\frac{1}{P_0}$ in $[0.1, 15]Hz$ and ON pulse duration p. **Left Panel:** shows a range of frequencies $\frac{1}{P_0}$ from $0.1Hz$ to $15Hz$ versus the ratio $\frac{p}{P_0}$ in range $[0, 1]$. Numbers indicate the number of spikes per period. **Right Panels:** In all these plots the crossed area corresponds to the transient, and thus it has to be omitted. **Red** color demonstrates a case where only subthreshold spikes are generated, when the frequency of the periodic pulse is $\frac{1}{P_0} = 10Hz$ and $\frac{p}{P_0} = 0.1$. **Blue** indicates bursts of four spike, when the frequency is $\frac{1}{P_0} = 5Hz$ and $\frac{p}{P_0} = 0.6$. **Black** shows a case of two spikes bursts. Here the frequency is $\frac{1}{P_0} = 0.5Hz$ and $\frac{p}{P_0} = 0.6$.

Then we tested the transition from subthreshold to bursting oscillation via chaos. Therefore, we used a steady current varying only its amplitude keeping all the other parameters fixed. We used eight different values (exactly the same as in [3]),

$$I_{\text{app}} = 3.0, 0.0, -0.45, -0.455, -0.47, -0.55, -0.6, -0.8, -1.3, -1.4, -2.0\,\mu\text{A/cm}^2.$$

Results are depicted in Figure 3. This figure corresponds to Fig 3 of [3]. In this case, there was no difference between the reference implementation and the original one.

The next simulation we performed reproduces results related to hysteresis as in Fig 4 of [3]. First, we run a simulation where the input current I_{ext} varied from $-0.433\,\mu\text{A/cm}^2$ to $-0.55\mu A/cm^2$. At every iteration, we detected if there is subthreshold and/or suprathreshold activity in the membrane voltage trace. Thus we created the hysteresis diagram given in Figure 4, left panel. In addition, we tested the

[3] From now and then all the figures of the original article will be referred as Fig

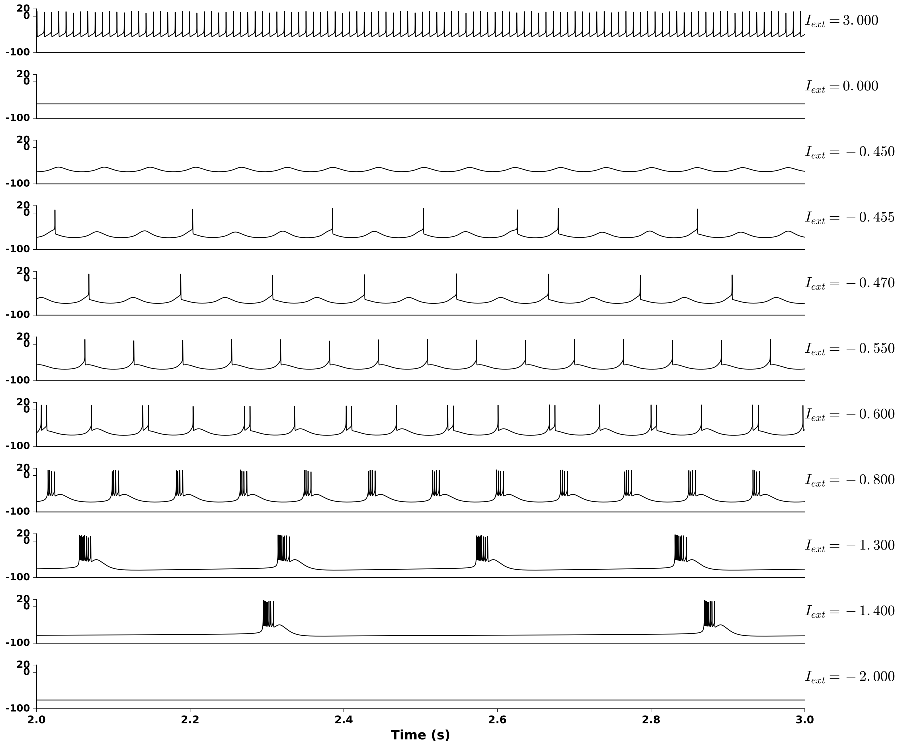

Figure 3: Dynamic behavior of neuron. Here we simulate the model with parameters given in Table 5. The only parameter that varies from panel to panel in this figure is the external current I_{ext}. These results correspond to Fig 3 of [3].

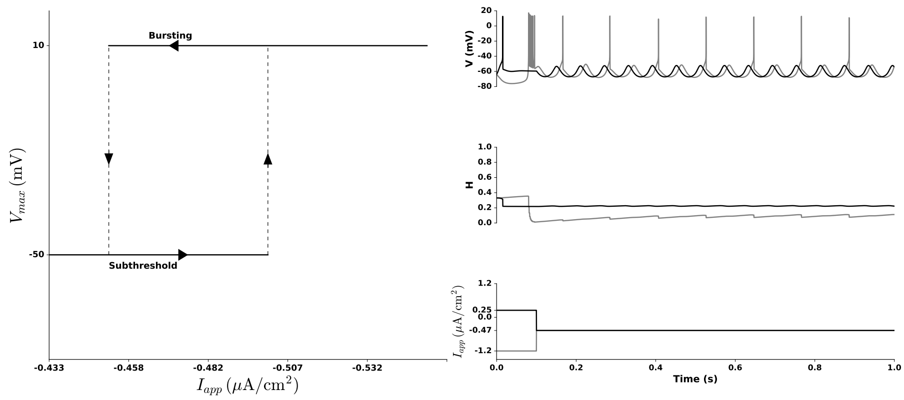

Figure 4: Hysteresis near the transition from the subthreshold to bursting oscillation. Left panel: Hysteresis diagram indicates a coexistence of bursting and subthreshold activity. **Upper right panel:** Bistability example shows how the same system can produce either subthreshold activity (black curve) or burst activity (gray curve). **Middle right panel:** shows the activation of H for the same simulation as in the upper panel. **Lower right panel:** Input to the model for this simulation is a brief current pulse at $0.25\,\mu\mathrm{A/cm}^2$ (black curve) and $-1.2\,\mu\mathrm{A/cm}^2$ (gray curve) followed by a steady current at $-0.47\,\mu\mathrm{A/cm}^2$ for both simulations.

bistability of the current model using the same protocol as in [3]. According to that protocol, we first apply a brief pulse (for 100 ms) of $0.25\,\mu\mathrm{A/cm}^2$ and $-1.2\,\mu\mathrm{A/cm}^2$ followed by a steady current at $-0.47\,\mu\mathrm{A/cm}^2$. This causes the state of the model to switch from a purely subthreshold activity pattern to a mixed sub- and suprathreshold activity pattern. The results are given in Figure 4, right panel.

Another interesting behavior of the model is the development of a "spiral" chaos (see Fig 6 in [3]). The reference implementation is capable of generating similar behavior as Figure 5 shows. In order to get these results we applied a constant external current with an amplitude of $-0.95\,\mu\mathrm{A/cm}^2$.

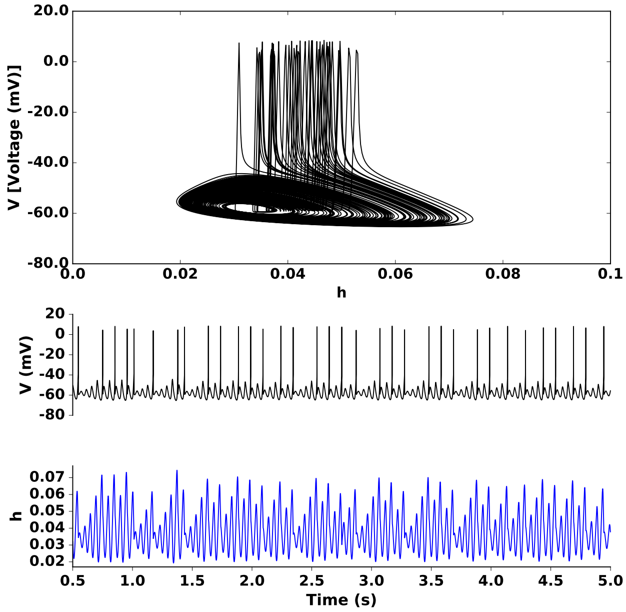

Figure 5: "Spiral Chaos". In this Figure we show that the model is capable of generating "spiral chaos" as it has been shown in Fig 6 in [3]. The external current in this simulation is constant ($-0.95\mu\mathrm{A/cm}^2$). **Top panel** shows the phase portrait of the membrane potential and the Sag current (V vs h). **Middle panel** illustrates the membrane potential (V) and, the **bottom panel** shows the h current over time.

The next simulation investigates how the bursting frequency is affected by the injected external current (see Fig 7 in [3], two bursting modes). To address this issue we captured data[4] values for the external current from Fig 7 of the original article (dots in Fig 7, pg. 27 in [3]) using a software called PlotDigitizer[5]. The results from our simulations are illustrated in Figure 6. Black curve represents the frequency in Hz and the blue one the period in sec. Provided results here are not as smooth as the original ones in [3]. Unfortunately there are no many details in the original article about these diagrams so we cannot reproduce them in full details.

The last simulation is related to Fig 2 of [3] and to an "intermittent" phase-locking phenomenon. A periodic pulse with frequency 10 Hz and ratio $\frac{p}{P_0} = 0.8$ is applied to the model as external input current. The response of the model is registered and sub- and supra-threshold spikes are counted. We applied six different current amplitudes and two different values for the T-type calcium conductance. $I_{app} = -1.4, -1.5, -1.6\,\mu\mathrm{A/cm}^2$ and $g_T = 0.3\,\mathrm{mS/cm}^2$ $I_{app} = -1.2, -1.5, -1.8\,\mu\mathrm{A/cm}^2$ and

[4] Data are available in the accompanying github repository of the present article.

[5] (http://plotdigitizer.sourceforge.net/)

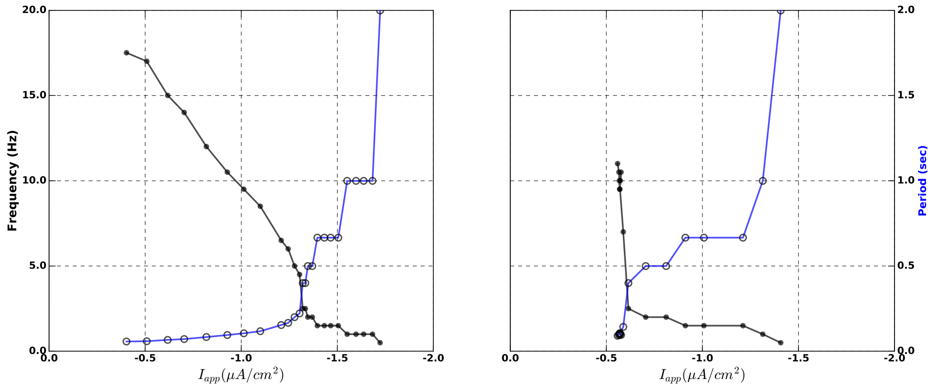

Figure 6: Frequency and period versus steady input current. This figure illustrates how the external current (ranging from 0 to $-2\,\mu\mathrm{A/cm^2}$ affects the bursts frequency (bursting mode) of the model. Black curve indicates the frequency in Hz and the blue curve the period in sec. The external current varies exactly as in Fig 7 in [3] (see text for more details).

$g_T = 0.25\,\mathrm{mS/cm^2}$. Figure 7 shows 2 seconds of membrane potential along with symbolic patterns of 0 (dark circles) and 1 (green line segments). Results given in Figure 7 are similar to the ones of Fig 2A and Fig 2B in [3].

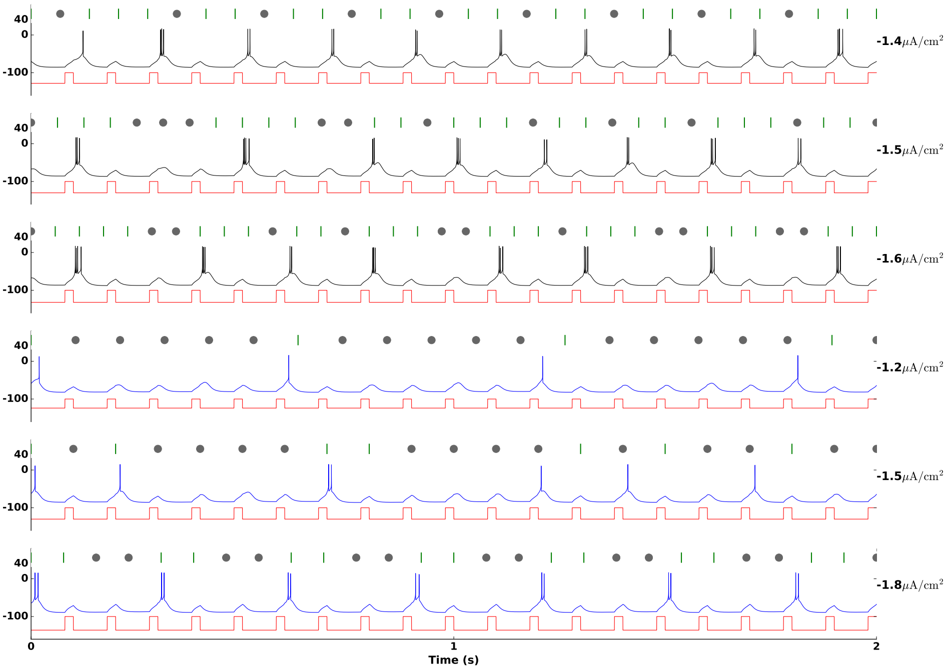

Figure 7: Symbolic patterns. Six different simulations are illustrated here ($I_{app} = -1.4, -1.5-1.6\,\mu\mathrm{A/cm^2}$ with $g_T = 0.3\,\mathrm{mS/cm^2}$) and ($I_{app} = -1.2, -1.5, -1.8\,\mu\mathrm{A/cm^2}$ with $g_T = 0.25\,\mathrm{mS/cm^2}$). Symbolic patterns are illustrated above membrane potential traces as green line segments – suprathreshold spikes and dark circles – subthreshold spikes. Red curve indicates the input periodic pulses.

Conclusion

A conductance-based model for relay thalamocortical neurons proposed by [3] was implemented in Python. The model tested thoroughly in several examples taken from the original article. In general, the original model was easy to be implemented since all the equations and the most of the parameters (except the initial time step of the integration method) are given. The reference implementation results are similar to the original ones. Unfortunately, we could not find any other implementation of the original model described in [3] to compare with.

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