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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 reference implementation in this work does not aim to reproduce all the results of the original article, but some of them in order to test if the model can be easily reproduced and at what degree the original results are reproducible. 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 all the simulation times 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 used in this

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

work (*dopri5*, *Adams*, *BDF*, [1]). *dopri5* is quite close to the one used by the author in the original article (the author has numerically integrated the system of the four ODEs by using a fifth-order adaptive size Runge-Kutta method). *BDF* and *Adams* provide exactly the same numerical results as the first one, but they are faster[1].

Simulation Time		
Figure	Simulation Time (s)	Integration Step (ms)
1	$2, 5 \times period$	0.05
2	2	0.05
3	8	0.05
4	2.5	0.05
5	2	0.05

Table 2: Simulations Time

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

Input					
Figure	Type	Form	Frequency ($\frac{1}{P_0}$,Hz)	Duration (p, ms)	Amplitude ($\mu A/cm^2$)
Figure 1	Periodic		5, 10	10, 40	-1.0 $+3.0$
Figure 2	Constant		–	–	0.0 -0.5 -0.55 -0.6 -0.8 -1.3 -2.1
Figure 3	Constant		–	–	-0.95
Figure 4	Constant		–	–	$[-2, 0]$
Figure 5	Constant		–	–	$[-2, 0]$

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

[1]The user has the option to choose one of the three methods. Initially, we tested all three methods and since there is no any numerical difference on our results we decided to use *BDF*, since its much faster than *dopri5*.

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

Neuron Model	
Name	Thalamocortical relay neuron
Type	Conductance-based neuron
Membrane Potential	$C_m \frac{dV(t)}{dt} = -I_T - I_h - I_{Na} - I_K - I_{Na(P)} - I_L + I_{\text{app}}$
T-Type Calcium Current (I_T)	$I_T = g_T \cdot s_\infty^3(V) \cdot h \cdot (V - V_{Ca})$ $s_\infty(V) = \frac{1}{1+\exp(-\frac{V+65}{7.8})}$ $\frac{dh(t)}{dt} = \phi_h \frac{h_\infty(V) - h}{\tau_h(V)}$ $h_\infty(V) = \frac{1}{1+\exp(\frac{V-\theta_h}{k_h})}$ $\tau_h(V) = h_\infty \exp(\frac{V+162.3}{17.8}) + 20$
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})	$I_K = g_K \cdot n^4 \cdot (V - V_K)$ $\frac{dn(t)}{dt} = \phi_n \frac{n_\infty(V) - n(t)}{\tau_n(V)}$ $n_\infty(\sigma_K, V) = \frac{\alpha_n(\sigma_K, V)}{\alpha_n(\sigma_K, V) + \beta_n(\sigma_K, V)}$ $\tau_n(\sigma_K, V) = \frac{1}{\alpha_n(\sigma_K, V) + \beta_n(\sigma_K, V)}$ $\alpha_n(\sigma_K, V) = \frac{-0.01(V + 45.7 - \sigma_K)}{\exp(-0.1(V + 45.7 - \sigma_K)) - 1}$ $\beta_n(\sigma_K, V) = 0.125 \exp(-\frac{V + 55.7 - \sigma_K}{80})$ $I_{Na} = g_{Na} \cdot m_\infty^3(\sigma_{Na}, V) \cdot (0.85 - n) \cdot (V - V_{Na})$ $m_\infty(V) = \frac{\alpha_m(\sigma_{Na}, V)}{\alpha_m(\sigma_{Na}, V) + \beta_m(\sigma_{Na}, V)}$ $\alpha_m(\sigma_{Na}, V) = -0.1 \frac{V + 29.7 - \sigma_{Na}}{\exp(-0.1(V + 54.7 - \sigma Na)) - 1}$ $\beta_m(\sigma_{Na}, V) = 4 \exp(-\frac{V + 54.7 - \sigma_{Na}}{18})$
Persistent Sodium Currents ($I_{Na(P)}$)	$I_{Na(P)} = g_{Na(P)} \cdot m_\infty^3(\sigma_{Na(P)}, V) \cdot (V - V_{Na})$
Leak Current (I_L)	$I_L = g_L \cdot (V - V_L)$

Table 4: Description of the neuron model

Model Parameters						
Currents Type	Common	Figure 1	Figure 2	Figure 3	Figure 4	Figure 5
Membrane Potential	$C_m = 1\mu F/cm^2$ $V_0 = -74mV$					
T-Type Calcium Current	$\phi_h = 2$ $V_{Ca} = 120mV$	$g_T = 1mS/cm^2$ $\theta_h = -81mV$ $k_h = 6.25mV^{-1}$	$g_T = 0.3mS/cm^2$ $\theta_h = -79mV$ $k_h = 5mV^{-1}$	$g_T = 0.3mS/cm^2$ $\theta_h = -75mV$ $k_h = 5mV^{-1}$	$g_T = 0.3/0.25/0.2mS/cm^2$ $\theta_h = -81mV$ $k_h = 6.25mV^{-1}$	$g_T = 1.0/0.7mS/cm^2$ $\theta_h = -79mV$ $k_h = 5mV^{-1}$
Sag Current	$\phi_H = 1$ $g_h = 0.04mS/cm^2$ $V_h = -40mV$					
Hodgkin-Huxley Currents	$g_K = 30mS/cm^2$ $V_K = -80mV$ $g_{Ca} = 42mS/cm^2$ $\phi_n = 28.5$ $V_{Ca} = 55mV$ $\sigma_K = 10$	$\sigma_{Na} = 3mV$	$\sigma_{Na} = 6mV$	$\sigma_{Na} = 6mV$	$\sigma_{Na} = 3mV$	$\sigma_{Na} = 6mV$
Persistent Sodium Currents	$V_{Na(P)} = 55mV$ $\sigma_{Na(P)} = -5$ $g_{Na(P)} = 9mS/cm^2$					
Leak Current		$g_L = 0.1mS/cm^2$ $V_L = -72mV$	$g_L = 0.12mS/cm^2$ $V_L = -70mV$	$g_L = 0.08mS/cm^2$ $V_L = -70mV$	$g_L = 0.08mS/cm^2$ $V_L = -70mV$	$g_L = 0.12/0.04mS/cm^2$ $V_L = -70mV$

Table 5: Simulations Parameters

Results

We simulated the model described in Table 4 using the parameters given in Table 5 and the corresponding input (see Table 3). The first test case is the simulation of burst responses. In this case, we examined if the model is able to generate different types of burst responses such as in Fig[3] 1 of the original article. Thus, we applied a periodic current pulse of $-1\mu A/cm^2$ 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 $0.1Hz$ to $15Hz$ with a resolution (discretization) of 150 points. The same number of samples used for discretizing the duration for each frequency. The results are shown in Figure 1 left panel. Our right panel is slightly different from the original one. In order to produce this diagram, we simulated the model using different frequencies and duration pulses and we counted spikes in one period of each iteration (one frequency out of 150 and one duration out of 150). The author in [3] shows in Fig 1 a shaded are where the number of spikes is 0.5. By simple counting this is impossible. However, if one takes the average of suprathreshold and subthreshold spikes in one period can obtain some numbers like these.

In addition, we picked up three specific frequencies $\frac{1}{P_0} = 10, 5, 0.5$ and pulse duration $p = 10, 120, 1200ms$ ($\frac{p}{P_0} = 0.1, 0.6, 0.6$) in order to test if the model can reproduce the upper panel of Fig 1 of [3]. The first frequency that we used is not used in the original article, so we do not further discuss it. For the two other frequencies, we have that the corresponding periods in ms are $200ms$ and $2000ms$, respectively. Now, if we compute the ON duration of each pulse (this is the p), we get $p = P_0 \times 0.6$ and this gives $p = 120ms$ ($5Hz$) and $p = 1200ms$ ($0.5Hz$). These numbers are different from the ones given in the caption of Fig 1 in [3]. Also according to the parameters diagram in the left panel original of Fig 1, the frequency $frac1P_0 = 5Hz$ and the ratio $\frac{p}{P_0} = 0.6$ generate a burst of two (2) spikes. This is in contradiction, with what is presented in the same figure on the upper right panel, where there is a burst of one (1) spike. This does not happen in our implementation, where the results on the right panels of Fig 1 are in agreement with the parameters diagram on the left panel.

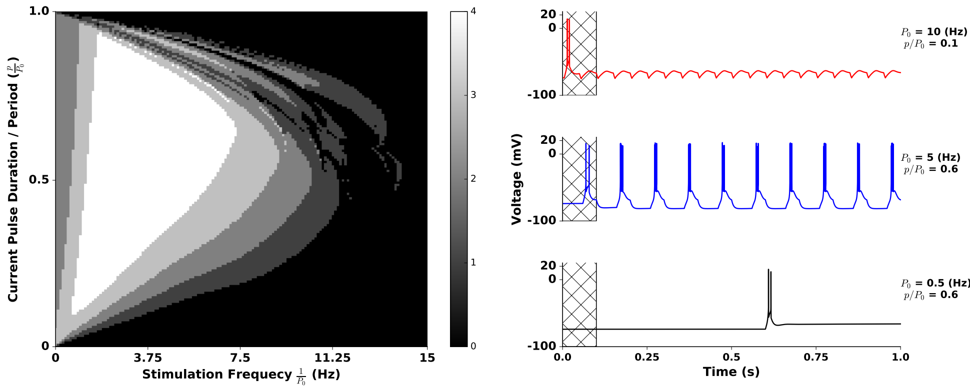

Figure 1: Responses to rhythmic hyperpolarizations. We stimulate the model with a periodic pulse with varying frequency $\frac{1}{P_0}$ in $[0.1, 15]Hz$ and ON pulse duration p. **Left Panel:** shows a range of frequencies $\frac{1}{P_0}$ from $0.1Hz$ to $15Hz$ versus the ratio $\frac{p}{P_0}$ in range $[0, 1]$. **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 $\frac{p}{P_0} = 0.6$.

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

The second test case implies a steady (constant) current. Thus, we used a steady current varying only its amplitude keeping all the other parameters fixed. We used eight different values, $I_{\text{app}} = 3.0, 0.0, -0.47, -0.6, -0.8, -1.3, -1.4, -2.0 \mu A/cm^2$. The results of these simulations are depicted in Figure 2. This figure corresponds to Fig 3 of [3]. In this case, there was no difference between the reference implementation and the original one.

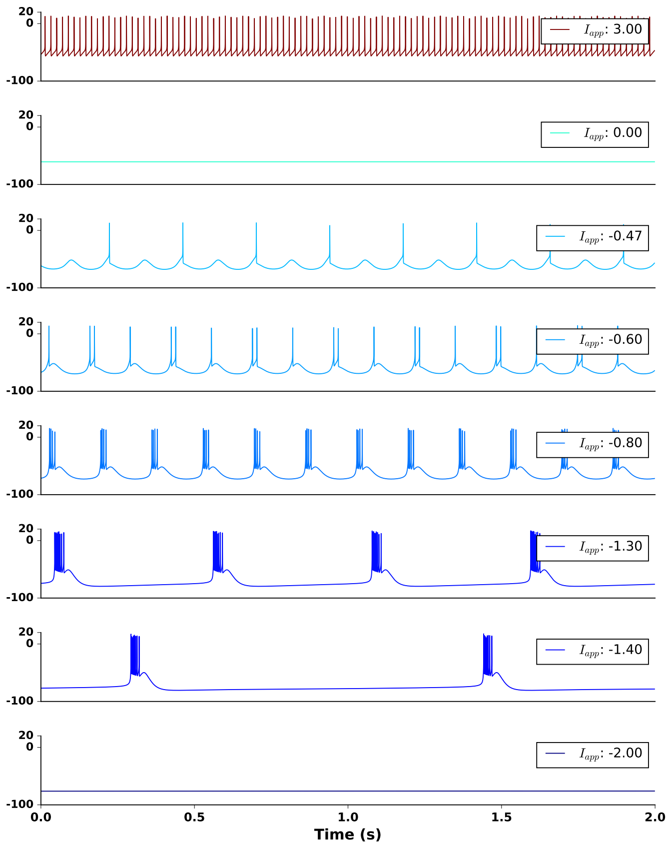

Figure 2: Dynamic behavior of neuron. Here we simulate the model with parameters given in Table 5. The only parameter that varies from panel to panel in this figure is the external current I_{app}. The jet colormap indicates the different current values. For instance, we obtain, repetitive spiking when we apply a constant current at $3\mu A/cm^2$, or a periodic bursting response, when we apply an external current of $-1.3\mu A/cm^2$. These results correspond to Fig 3 of [3].

In the third test case, we simulated the Fig 6 of [3]. In this test-case the neuron receives a constant external current at $-0.95\frac{\mu A}{cm^2}$ and as Figure 3 points out “spiral chaos” is generated as in the original article. In this case, no differences found between reference and original implementations.

The fourth test case has to do with the amplitude of the injected external current and its relation to the frequency of the generated spike bursts. In order to be as precise as possible, we captured the data[4] values for the external current from Fig 7 of the original article (dots in Fig 7, pg. 27 in [3]) using the software PlotDigitizer[5].

[4] Data are available in the accompanying github repository of the present article.
[5] (http://plotdigitizer.sourceforge.net/)

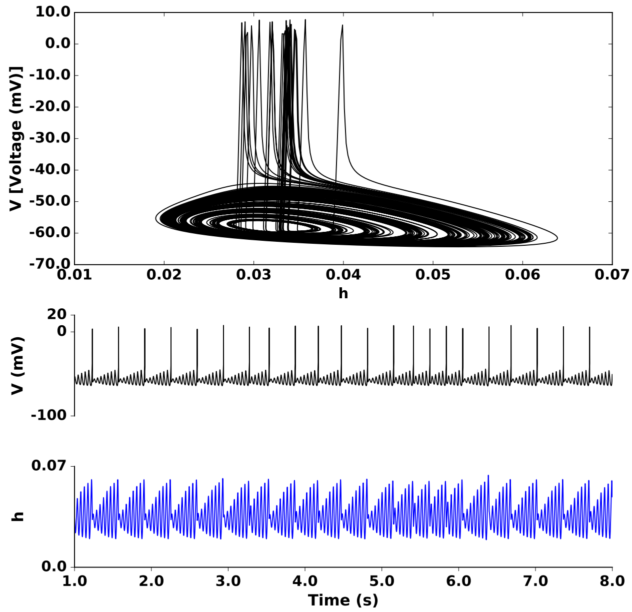

Figure 3: "Spiral Chaos". In this Figure we show that the model is capable of generating "spiral chaos" as it has been shown in Fig 6 in [3]. The external current in this simulation is constant ($-0.95\mu A/cm^2$). **Top Panel** shows the phase portrait of the membrane potential and the Sag current (V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

We run a simulation using as external current the numerical values that we captured from the original article and the results are shown in Figure 4 upper row. The black axis represent the frequency (we measured the frequency using the FFT provided by Numpy) and the blue axis indicates the period ($\frac{1}{\text{frequency}}$). Our results are pretty close to the ones in Fig 7 of the original article. Because the results presented in the original article look as a result of a regression method[6], we simulated the same test case but using a much higher resolution (using 100 sample values for the injected current (0 to $-2.0\mu A/cm^2$). The results are shown in Figure 4 lower panels and indicate that these simulations are quantitatively similar to the original ones but the curves are coarse and not so much smooth.

The final test case is related to Fig 2 in [3]. In this case, a periodic pulse with frequency $10Hz$ and ratio $\frac{p}{P_0} = 0.8$ is applied to the model as external current. The response of the model is registered and then the subthreshold and suprathreshold spikes are counted. We applied six different current amplitudes as in Fig 2A and 2B in [3] and we illustrate (i) the entire temporal trace of the membrane potential, (ii) a specific are of the whole trace (magnification) and (iii) a "symbolic" pattern of zeros and ones.

The results are shown in Figure 5, where the left panels show the whole trace of six different simulations for six different current amplitudes and two different values of g_T ($-1.4, -1.5, -1.6\mu A/cm^2$ along with $g_T = 0.2975mS/cm^2$ - black traces, and $-1.2, -1.5, -1.8\mu A/cm^2$ for $g_T = 0.252mS/cm^2$ - blue traces). The right panels, show a magnification of a specific temporal window of the whole trace along with a "symbolic" pattern. The symbolic pattern represents zeros (dark discs) and ones (green line segments). By examining these patterns, we conclude that the reference

[6] If one take a good look at the plots of Fig 7, they will see that the curve is not exactly on the data points, implying that a regression method has been used

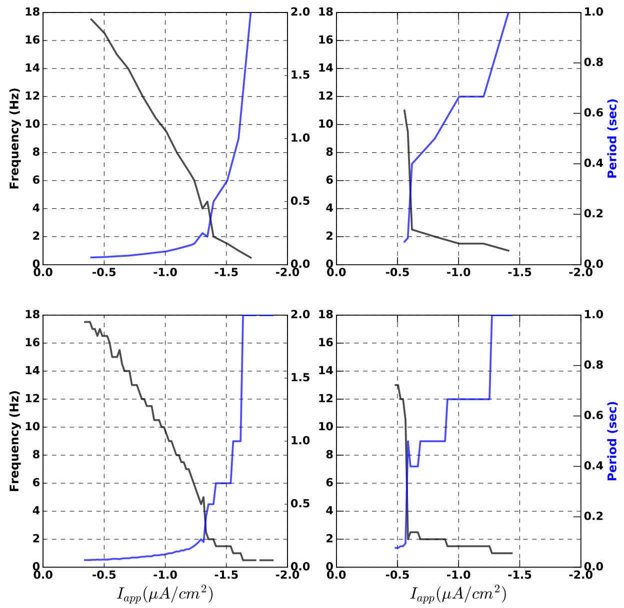

Figure 4: Frequency and period versus steady input current. Top Row: Indicates the external current (ranging from 0 to $-2\mu A/cm^2$ versus the spike bursts frequency in Hz (black axis) and the period in sec (blue axis). The external current varies exactly as in Fig 7 in [3] (see text for more details). **Bottom Row:** Same simulations but using a finer discretization for the external current values range (100 samples).

model is able to reproduce all the original patterns except from these generated by a current of $-1.5\mu A/cm^2$ in any case. In addition, we slightly changed the values of g_T in order to achieve similar results with the original implementation.

In this case, we observed something odd. The frequency for these simulations was set to $10Hz$ implying a period of $100ms$. This leads to a choice of $p = 80ms$ in order to achieve a ratio $\frac{p}{P_0} = 0.8$. This means that the symbolic patterns appear in the original article are not generated per period, since the period is too short to have symbolic patterns such as 0301. In addition, it seems that these symbolic patterns emerge from a longer duration signal ($\sim 2ms$, the scale in Fig 2 is $500ms$) and not from one period. Furthermore, as we show in our simulations in Figure 5, the whole trace is more complicated and in some cases it seems that these patterns are not repeated across the whole trace[7].

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. Some of them were successfully reproduced and some other had some differences from their original implementations. In general, the original model was easy to implemented since all the equations and the most of the parameters (except the initial time step of the integration method) are given or are almost accurate. Unfortunately, we could not find any other implementation of this model to compare with ours.

[7] We ran long simulations in order to verify this. Data not shown here.

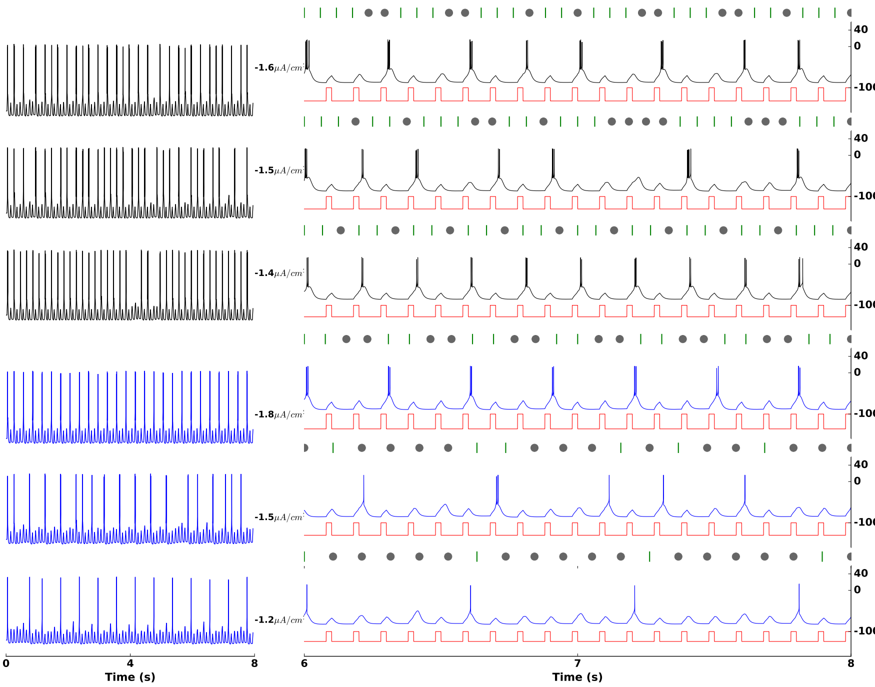

Figure 5: Symbolic patterns. This figure illustrates membrane potential traces (in mV) for two different simulations. In the first simulation $g_T = 2.2975 mS/cm^2$ and $I_{\text{app}} = -1.4, -1.5$ and $-1.6 \mu A/cm^2$ (black traces). For the second simulation, $g_T = 0.252 mS/cm^2$ and $I_{\text{app}} = -1.2, -1.5$ and $-1.8 \mu A/cm^2$. **Left Panel** shows the whole trace ($8 sec$ of total simulation time). **Right Panel** illustrates a magnification of the right panel (6 to 8 seconds) along with a symbolic representation of supra- and sub-thresholds spikes (green line segments and dark circles, respectively). The red curve depicts the external pulse current.

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