Indraprastha Institute of Information Technology-Delhi

Computational neuroscience Assignment 3

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(1) What is the hypothesis, based on which 40Hz neuronal oscillations is modeled by Wang? (Xia-Jing Wang (1993), Ionic basis for intrinsic 40Hz neuronal oscillations Neuroreport, 5, 221-224).

The hypothesis based on which the 40Hz neuronal oscillations is modeled is that the subthreshold potential oscillations, arising at 40Hz frequency, could be caused by the intrinsic ion currents may which are capable of producing oscillatory activity.

(2) What do you understand by mixed-mode bursting and which neuron(s) display such dynamics?

Mixed-mode oscillations is the neuronal rhythmic acivity characterizd by an alternating pattern of large amplitude and small amplitude oscillations. Here, clusters of Na+ action potentials can be observed intersperced with durations of smaller amplitude subthreshold oscillations. The neurons that display such dynamics are generally from the the activated mammalian central nervous system. Guinea pig Layer 4 frontal cortex neurons are evidence of 2 subgroups of fast oscillatory neurons.

(3) What are the dynamical variable (s) responsible for mixed mode bursting and how it is concluded through the experiments?

The interplay of persistant sodium current I_Nap and a slow inactiviating I_Ks provides a suitable ionic mechanism for the 10Hz-50Hz oscillations and hence is responsible for the mixed mode bursting. It is shown through single neuron recordings and validated though neuronal model simulations.

(4) What is the nature of nonlinear ODE equation formulated to explain mixed mode bursting? What are the important terms in the equation and which term denotes the output resistance?

The ODE forms a 5D system first order differential equations. The system of equaltions are given below:

*dV/dt = (-g_L * (V - E_L) - I_Nap - I_Ks - I_Na - I_K + I_app) / C*

*I_Nap = g_Nap * m_inf1 * (V - E_Na)*

*I_Ks = g_Ks * m * (rho * h1 + (1 - rho) * h2) * (V - E_K)*

*I_Na = g_Na * (m_x ^ 3) * h * (V - E_Na)*

*I_K = g_K * (n ^ 4) * (V - E_K)*

$dh/dt = phi\_h * (alpha\_h * (1 - h) - beta\_h * h)$

$dn/dt = phi\_n * (alpha\_n * (1 - n) - beta\_n * n)$

$dh1/dt = phi\_h1 * (h1\_inf – h1)/tau\_h1$

$dh2/dt = phi\_h2 * (h2\_inf – h2)/tau\_h2$

$dm/dt = phi\_m * (m\_inf2 - m)/tau\_m$

The 4 currents follow the Hodgkin-Huxeley formalization.

The important parameters in the model include, the parameter **sigma**, for finetuning the action potential threshold, the parameter activation time **tau_m**, which is responsible for determining the oscillatory properties, the applied current **I_app**, which controls the oscillation amplitude. The bursting speed largely depends on the **I_Ks inactivation**. The minimal rhythmic frequency is determined by the passive time constant **tau_0** = C/g_L, also called the input resistance, which was fixed at 10ms. The output resistance is **tau_m** which is varied between 6 to 50ms.

(5) What is the parameter used to adjust the potential threshold and what are the consequence of varying this threshold in oscillatory dynamics?

The **sigma** parameter is used to adjust the potential threshold. It was seen that the subthreshold oscillations are only seen when this threshold value was high (obtained by setting sigma = 0). When the value was of the threshold was reduced, by setting sigma to -1, purely subthreshold oscillations did not occur and instead, the were single Na+ spikes separated by very small amplitude subthreshold oscillations.

(6) What are the inactivation constants for I_{ks} and what role do they play in oscillatory dynamics?

I_Ks has 2 inactivation variables, namely h1 and h2. Both of these have the same steady state function, however they have different time constants tau_h1 and tau_h2. As a result of these different values, the decline of h1 and h2 are slow, with h2 being slower, such that it can be considered almost constant. This results in the slow depolarization due to accumulated decrease in I_Ks, causing the Na+ spike clusters.

(7) What are the parameter values chosen for resting membrane potential (RMP), sodium, potassium, and leakage potentials, and which is close to RMP?

Values chosen for Resting membrane potential is -66.5 mV. Sodium potential V_Na = +55 mV, Potassium potential V_K = -90 mV and Leakage potential V_L = -60 mV. The Leakage potential is close to RMP.

(8) What is the bifurcation parameter chosen to simulate the dynamics? Does it influence the oscillatory dynamics?

The applied current I_app is used as the bifurcation parameter. The value of I_app is varied from 0 to 4 in the various experiements. The influence of I_app is that, the amplitude of the oscillations increase with increasing I_app. Further, the oscillation frequency and the number of spikes per burst increased with increasing I_app, these can be seen in the plots of Figure 2 and 3.

(9) What is the ionic mechanism responsible for mixed mode bursting and in particular for subthreshold oscillations? Explain this in detail in terms of depolarization-repolarization potentials and gating variables.

The ionic mechanism for mixed-mode oscillations is as follows:

1. The solw inactivation of I_Ks is responsible for the Na+ clusters. The inactivation terms h1 and h2 are slow, and the accumulated I_Ks decrease as a result, leads to depolarization, producing the Na+ clusters.
2. This is followed by repolarization, I_Ks deactivation phase. The interaction of the inward I_Nap and the outward I_Ks, a fast and slow timescale interaction, causeing subthreshold oscillations.

(10) In figure-2B what are the three different types of frequency described? How does the time constants affects the minimal rhythmic frequency of the oscillations?

Figure 2B shows 3 differents plot of oscillation frequency, bursting frequency and spike firing rate respectively. The oscillation frequency is the frequency of spikes in the plot of V vs time. The bursting frequency is the number of bursting patterns observed per unit of the spike firing rate time is the number of spikes per burst multiplied by the bursting frequency. It is observed that which the oscillation frequency varies almost linearly between 35 to 55 Hz, the bursting frequency remains almost a constant 3Hz and the spike firing rate gradually increases with I_app. The time constant **tau_0** and **tau_m** effects the minimal rhythmic frequency. With larger tau_m = 1, the minimal rhythmic frequency reduces to 11Hz from 35Hz (tau_0 is kept constant across all simulations).

(11) What are the main theoretical conclusions of the computational models ? What insight the modeling has provided about the experimental data?

The major conclusions from the computational models are:

1. Interactions between I_Nap and I_Ks generates 10-50Hz oscillations
2. The range of rhythmic frequencies can be changed by varying I_Nap-I_Ks kinetics, and depends critically on the time constanct of I_Ks
3. The 40Hz oscillations are mixed-mode with Na+ clusters, separated y subthreshold oscillations
4. The bursting frequency is independent of the applied current
5. At minimum rhythmic frequency of 10Hz, the frequency vs I_app curve begins with a plateau, followed by an increase with increasing I_app.

The modeling is in accordance with the layer V pyramindal neurons in the cat sensorimotor cortex. This further confirms the hypothesis that ionic currents can yield oscillations in mammalian CNS.

(12) Are the subthreshold oscillations visible in the electrophysiological recordings of the neuron? What do you understand phase-locked and synchronized rhythms? When phase locking rhythms become synchronized rhythm?

Literature states that intracellular single neurons recording revealed the existance of subthreshold oscillations and that SMPOs (subthreshold membrane potential oscillations) can be recorded in single neurons ref. However, in a population, the neurons are monitored by extracellular recordings, where the subthreshold oscillations are **not visible**. Phase locking refers to the property where a neuron spikes after a fixed delay following the onset of the periodic input. Synchronized rhythms refers to the synchronizations across neurons such that they spike at the same time. Synchronized analysis of mixed-mode oscillations shows iregular firing patters although phase-locked to the population rhythm. Synchronization depends on the synaptic transmission and phase locking rhythms become synchronized when phase resetting is performed to coordinate the various neurons. This can be achieved by cognitive strategies such as attention and motor coordination.

(13) Propose your own 2D model for mixed mode bursting, but assume silent phase instead of subthreshold oscillation. Explain various terms and show through nullclines various equilibrium points, their eigenvalues and types of bifurcation that occurs when bifurcation parameter is varied. What are various types of bursting? (Bonus point: How will you model mixed mode bursting using Hindmarsh-Rose equation or FHN model?)

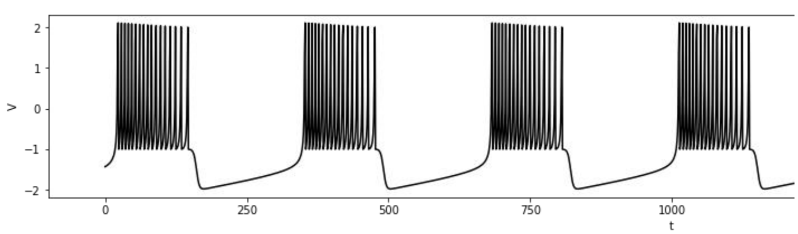
A 2 dimentional map based method ref with one fast and one slow variable, can be employed to model spiking bursting behaviour. The equations for the same are as follows:

$$x_{t+1} = f(x_t, y_t)$$

$$f(x_t, y_t) = \begin{cases} alpha / (1 - x_t) + y_t, \text{ when } x_t <= 0 \\ -1, \text{ when } x_t >= alpha + y_t \\ alpha + y_t, \text{ otherwise} \end{cases}$$

$$y_{t+1} = y_t - mu * (x_t + 1) + mu * sigma$$

The x vs t plot reveals bursting phenomenon:



BONUS:

Hindmarsh-Rose Model:

$$dx\_dt = y - a * (x ^\wedge 3) + b * (x ^\wedge 2) + I\_app - w$$

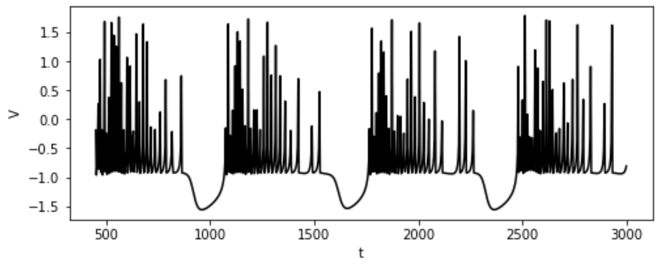
$$dy\_dt = c - d * (x ^\wedge 2) - y$$

$$dw\_dt = r * (s * (x - x1) - w)$$

The parameters are set as follows ref:

$a = 1, b = 3, c = 1, d = 5, r = 0.001, s = 4, I\_app = 2, x1 = -1.3$

The simulated output is as follows:



FitzHugh Nagumo Model:

$dV/dt = a\,(-v\,(v-1)\,(v-b) - w + I\_app)$, or more generally $f(v) - w + I\_app$

$dw/dt = v - c\,w$

Here, the f(V) is a cubic in V which. Self excitation is permitted via positive feedback. w on the other hand, has linear dynamics and provides a slower negative feedback.

To implement mixed mode bursting with clusters separated by silent phases in the FHN model, we can propose the following parameter setting ref:

$a = 10^5, c = 0.2, I\_app = 1,$ and vary b sinusoidally

The simulated output is as follows: