Theoretical Neuroscience I
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Exercise 4: Hodgkin-Huxley Model

Introduction

In Hodgkin-Huxley Model, two new elements are introduced based on the single-compartment model (SCM) for simulating the generation of action potential, namely a transient voltage-dependent sodium conductance (g_{Na}) and a persistent voltage-dependent potassium conductance (g_K) (Fig. 1).

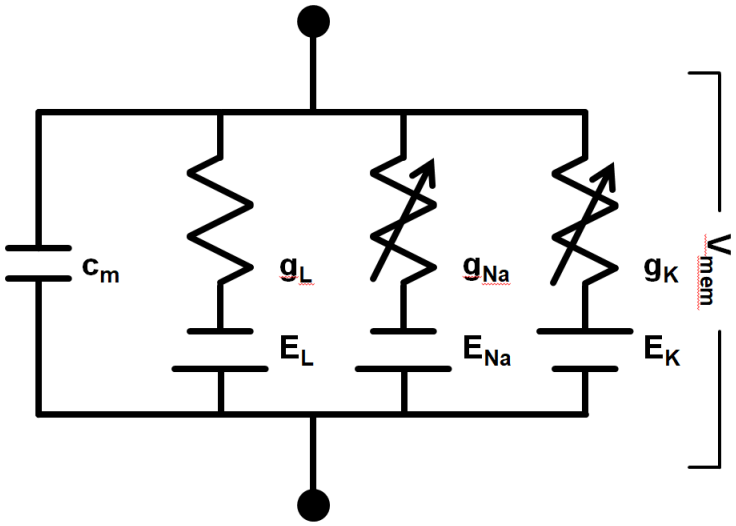

Fig. 1 Modified electrical circuit for Hodgkin-Huxley Model. Based on the SCM, two elements are added, namely a voltage-dependent sodium conductance (g_{Na}) and a voltage-dependent potassium conductance (g_K). All components are connected in parallel. The battery in serial with each resistor annotates the reversal potential of the corresponding conductance (E_L, E_{Na} or E_K).

These conductances depend on the maximum conductances $\bar{g}_{Na}$ and $\bar{g}_{Na}$ and also the activation variables *m(V)*, *h(V)* and *n(V)* as below:

$$g_{Na}(V) = \bar{g}_{Na} m(V)^3 h(V) \qquad g_K(V) = \bar{g}_K n(V)^4 \qquad m(V), h(V), n(V) \in [0,1]$$

Interestingly, the three activation variables showed different responses with changes in voltage (Fig. 2). On one hand, with an increasing membrane voltage, *h* decreases whereas *m* and *n* increase. On the other hand, the time constant of *m* is particularly small, which reveals its quick rate of change voltage. Only when membrane voltage reaches above -30*mV* do the time constants of *h* and *n* decrease to comparable levels. Base on the following equation,

$$\frac{dV}{dt} = \frac{1}{\tau_{eff}(V)} [V_\infty^{eff}(V) - V]$$

$$\tau_{eff}(V) = \frac{c_m}{\bar{g}_L + \bar{g}_{Na} m(V)^3 \mathrm{h(V)} + \bar{g}_K n(V)^4} \qquad V_\infty^{eff}(V) = \frac{\bar{g}_L E_L + \bar{g}_{Na} m(V)^3 \mathrm{h(V)} E_{Na} + \bar{g}_K n(V)^4 E_K + i_e}{\bar{g}_L + \bar{g}_{Na} m(V)^3 \mathrm{h(V)} + \bar{g}_K n(V)^4}$$

one can trace the kinetics of membrane voltage with a current injected. However, the challenge will be that the values of *m*, *h* and *n* also change along with membrane voltage.

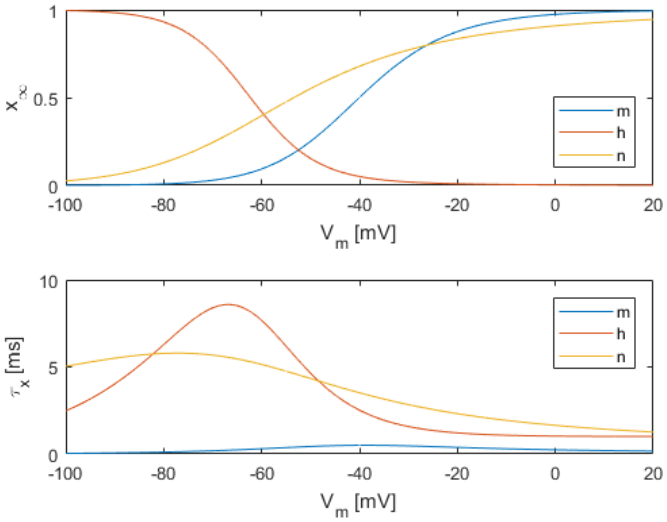

Fig. 2 Equilibrium states and time constants of the activation variables against membrane voltage. In the upper panel, *h* shows a decreasing trend when the membrane voltage increases; whereas *m* and *n* show increasing ones. In the lower panel, the time constant of *m* is particularly small, which reveals the quick rate of change in value whenever there is a change in voltage. That of *h* and *n* becomes comparable only when membrane voltage is above -30*mV*.

In this exercise, based on the SCM, the changes of membrane voltage (V_{mem}) and the activation variables (*m*, *h* and *n*) across the time were computed under different sets of their initial values and also different currents injected into the cell (I_e) using Matlab.

Method

In this exercise, different vectors were generated for illustrating Hodgkin-Huxley Model. Membrane capacity (c_m, also c_*m* in the code), maximal conductances (*g* in the code) and corresponding reversal potentials (*E* in the code) were saved at the very beginning, as they do not change in the whole exercise. *g* and *E* are both vectors in the code, each of which contains the values for leaky conductance ($\bar{g}_L$ & E_L), voltage-dependent sodium conductance ($\bar{g}_{Na}$ & E_{Na}) and voltage-dependent potassium conductance ($\bar{g}_K$ & E_K). They are saved as vectors as this design will speed up the calculation in the following parts. The values of these seven parameters are as below:

$$c_m = 10nF/mm^2;\ \bar{g}_L = 3\mu S/mm^2;\ \bar{g}_{Na} = 1200\mu S/mm^2;\ \bar{g}_K = 360\mu S/mm^2;$$

$$E_L = -54.402mV;\ E_L = 50mV;\ E_L = -77mV.$$

Since the aim of this exercise is to observe the changes of variables across the time, a time vector (*t* in the code) from 0 to 40*ms* with step-size (*dt* in the code) of 0.1*ms* was generated. Besides, because, in this time, all the situations of current injected I_e were constant only, a single variable for current (*i_e* in the code) was generated and reused in all situations.

Next, a function with a for-loop (HH_time.m) was used for the generation of dynamic variables, including the activation variables (*m*, *h* and *n* in the code), effective time constant of membrane voltage (τ_{eff}, also *V_eff* in the code), effective equilibrium state of membrane voltage (V_∞^{eff}, also *V_infty* in the code) and, most importantly, membrane voltage (*V*). For *m*, *h*, *n* and *V*, three variables were generated before the beginning of the for-loop with the initial value assigned in each situation. The corresponding values of τ_{eff} and V_∞^{eff} were then calculated, again, based on the following equations:

$$\tau_{eff}(t) = \frac{c_m}{\bar{g}_L + \bar{g}_{Na} m^3 \mathrm{h} + \bar{g}_K n^4} \qquad V_\infty^{eff}(t) = \frac{\bar{g}_L E_L + \bar{g}_{Na} m^3 \mathrm{h} E_{Na} + \bar{g}_K n^4 E_K + i_e}{\bar{g}_L + \bar{g}_{Na} m^3 \mathrm{h} + \bar{g}_K n^4}$$

In each round of the for-loop, the new equilibrium states (*x_infty* in the code, where x is m, h or n) and time constants (*tau_x* in the code, where x is m, h or n) for *m*, *h* and *n* were firstly generated using the function files provided (HH_equi_tau_m.m, HH_equi_tau_h.m and HH_equi_tau_n.m). Namely, by providing the old voltage value in these functions, the rates of activating (*α(V)*) and inactivating (*β(t)*) of each of the activation variables were calculated in the sub-function (e.g. HH_alpha_beta_m) in each of the files as below:

$$\alpha_m(V) = \frac{0.1/ms(V + 40mV)}{1 - e^{-0.1(V+40mV)}} \qquad \alpha_h(V) = \frac{0.07}{ms} e^{-0.05(V+65mV)} \qquad \alpha_n(V) = \frac{0.01/ms(V + 55mV)}{1 - e^{-0.1(V+55mV)}}$$

$$\beta_m(V) = \frac{4}{ms} e^{-0.0556(V+65mV)} \qquad \beta_h(V) = \frac{1/ms}{1 + e^{-0.1(V+35mV)}} \qquad \beta_n(V) = \frac{0.125}{ms} e^{-0.0125(V+65mV)}$$

Then new *x_infty* and *tau_x* were calculated:

$$x_\infty(V) = \frac{\alpha_x(V)}{\alpha_x(V) + \beta_x(V)} \qquad \tau_x(V) = \frac{1}{\alpha_x(V) + \beta_x(V)}$$

Using these new values, the new value of *m*, *h* and *n* were calculated and added to the vectors as followed:

$$x(\mathrm{i}+1) = x_\infty(V) + [x(i) - x_\infty(V)] e^{\frac{-dt}{\tau_x(V)}}$$

Afterwards, the new τ_{eff} and V_∞^{eff} were calculated with the new value of *m*, *h* and *n* as above, and saved. At the end, the new *V* was computed as below and saved:

$$V(\mathrm{i}+1) = V_\infty^{eff}(t) + [V(i) - V_\infty^{eff}(t)] e^{\frac{-dt}{\tau_{eff(t)}}}$$

In the three situations, the i_e and initial values of *V*, *m*, *h* and *n* were as below:

	1st situation	2nd situation	3rd situation
i_e (nA/mm^2)	0	100	62
V (*mV*)	-70	Ending of 1st situation	-65
m	0	Ending of 1st situation	0.08
h	0	Ending of 1st situation	0.5
n	0.3	Ending of 1st situation	0.37

Results & Discussion

Calculation of τ_{eff} and V_{∞}^{eff}

In Hodgkin-Huxley model, the dynamic equation becomes:

$$c_m \frac{dV(t)}{dt} = -i_L - i_{Na} - i_K + i_e$$

in which:

$$i_L = \bar{g}_L(V(t) - E_L) \qquad i_{Na} = \bar{g}_{Na} m^3 h(V(t) - E_{Na}) \qquad i_K = \bar{g}_K n^4 (V(t) - E_K)$$

Therefore,

$$c_m \frac{dV(t)}{dt} = (\bar{g}_L E_L + \bar{g}_{Na} m^3 h E_{Na} + \bar{g}_K n^4 E_K + i_e) - (\bar{g}_L + \bar{g}_{Na} m^3 h + \bar{g}_K n^4)[V(t)]$$

$$\frac{dV(t)}{dt} = \frac{\bar{g}_L + \bar{g}_{Na} m^3 h + \bar{g}_K n^4}{c_m} \{ \frac{\bar{g}_L E_L + \bar{g}_{Na} m^3 h E_{Na} + \bar{g}_K n^4 E_K + i_e}{\bar{g}_L + \bar{g}_{Na} m^3 h + \bar{g}_K n^4} - [V(t)] \}$$

$$\therefore \tau_{eff}(t) = \frac{c_m}{\bar{g}_L + \bar{g}_{Na} m^3 \mathrm{h} + \bar{g}_K n^4} \qquad V_{\infty}^{eff}(t) = \frac{\bar{g}_L E_L + \bar{g}_{Na} m^3 \mathrm{h} E_{Na} + \bar{g}_K n^4 E_K + i_e}{\bar{g}_L + \bar{g}_{Na} m^3 \mathrm{h} + \bar{g}_K n^4}$$

Activation variables and voltage reached steady state when no current is injected

Without any current input, the membrane voltage and activation variables (*m*, *h* and *n*) eventually achieved their respective plateaus (Fig. 3). In the upper panel, with the initial values of activation variables, the $V_{\infty}^{eff}(0)$ was -65.5*mV*, which was higher than *V(0)*. This difference caused the increase in *V*. Similar situations happened to the three activation variables in the lower panel of Fig. 3. Refer to Fig. 2, the value of $m_{\infty}(-65.5)$, $h_{\infty}(-65.5)$ and $n_{\infty}(-65.5)$ were 0.03, 0.75 and 0.25, which were different than the initial value. Among the three, *h* had the most significant different and time constant at *t*=0, which therefore showed the greatest rate of change.

Despite so, it is interesting that it is actually *n*, which has the least difference between *n(0)* and $n_{\infty}(0)$, that promoted the change in V_{∞}^{eff} (Data not shown). This may because $\bar{g}_K$ was relatively smaller that $\bar{g}_{Na}$, and hence a slight change in the *n* caused a more significant effect on the denominator in the equation of V_{∞}^{eff} (see above). With an almost unnoticeable decrease in *n*, driven by the difference with the equilibrium state, V_{∞}^{eff} showed an increase. However, with a sustained increase in *V*, the equilibrium state of *n* also increased, and thus V_{∞}^{eff} decreased. Eventually, the difference between *V* and V_{∞}^{eff} gradually diminished, causing the achievement of equilibrium state of all the variables, which are also the values in a resting neuron.

Spiked change generated in membrane voltage under sufficient current input

With a current of 100nA/mm^2, spiked patterns were observed in membrane voltage (Fig. 4). In each cycle, a slow depolarisation was initially observed. Once the membrane voltage reached around -50mV, an overshooting pattern followed by a repolarisation phase (i.e. the spike), appeared. Correspondingly, in the depolarisation phase, *m* and *h* were generally increasing, whereas *n* was decreasing. In the overshooting phase, at the very beginning *m* increased drastically, causing the increasing of g_{Na}, and so as V_{∞}^{eff}. However, soon after so, *h* decreased with the rise of membrane voltage and therefore counteracted the increase of *m*. At the same time, *n* increased and caused an increase of g_{Na}. These two factors contributed to the slowdown of overshooting and repolarising phase of *V*.

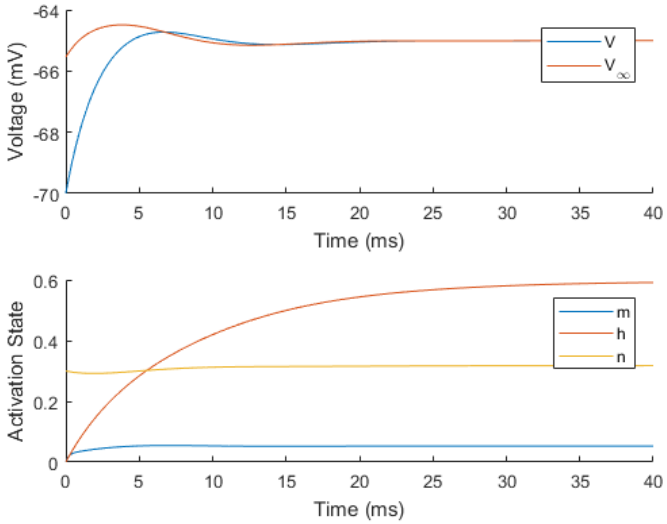

Fig. 3 Voltage and activation variables stabilised across time without any current input. In the both panel, the variables eventually reached plateau. Despite insignificant in terms of value, the change in *n* (lower panel) synchronised with that in V_{∞}^{eff} (upper panel).

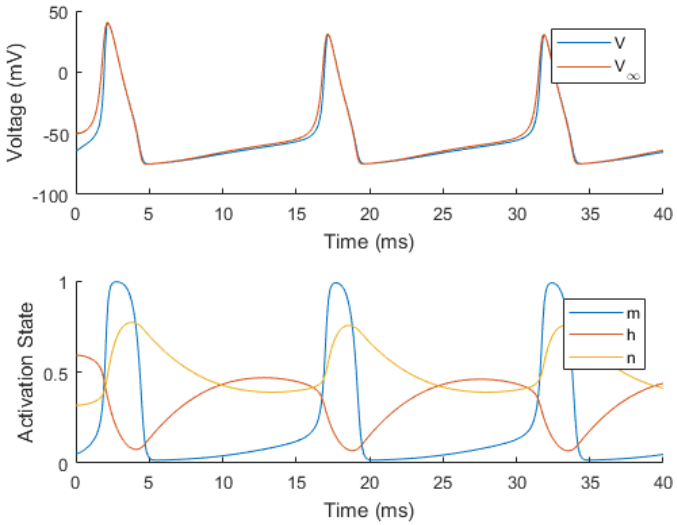

Fig. 4 Voltage and activation variables across time under a current input of 100nA/mm². In the upper panel, membrane voltage showed a spiky pattern similar to the sharp of action potentials.

Spike generation in membrane voltage depends on the amount of current input

With a current of 62nA/mm^2, spiked patterns were observed in a similar manner as in the case of 100nA/mm^2 (Fig. 5). However, the inter-spike interval was longer with a lower input current. Interestingly, with an even lower current input of 61nA/mm^2, despite the successful generation of one spike, the membrane voltage and also the activation variables evenutally stabilised. This may due to the reduced difference between V andV_∞^{eff}, thus the value of m could not reach to its exponential increasing phase as in Fig. 2. These results showed that the generation of action potential depends on how much the current is given to a neuron. On contrary, an extreme high current (e.g 1000nA/mm^2) also distorted the formation of spikes (Data not shown).

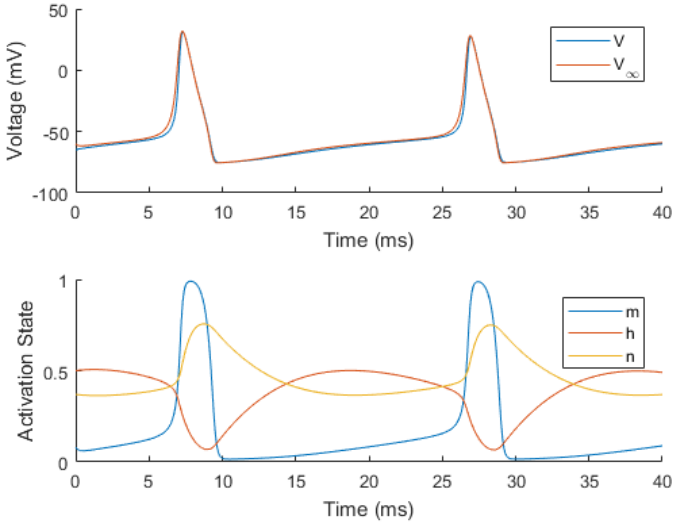

Fig. 5 Voltage and activation variables across time under a current input of 62nA/mm^2. In the upper panel, membrane voltage showed a similar result as Fig. 4, but in a slower rate, i.e. larger inter-spike intervals.

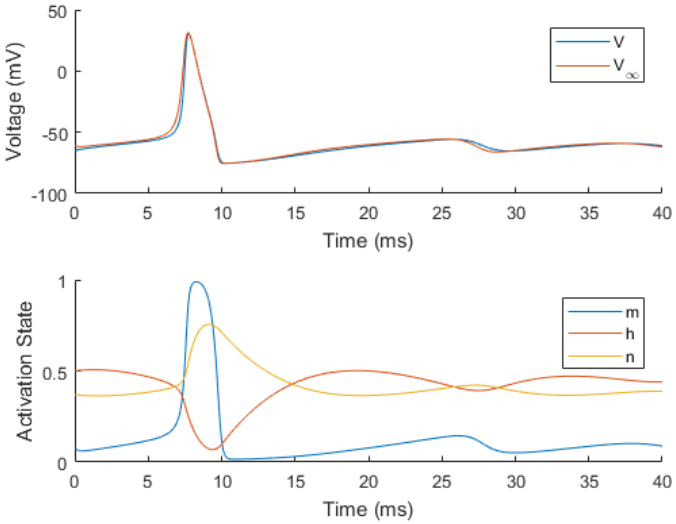

Fig. 6 Voltage and activation variables across time under a current input of 61nA/mm^2. In the upper panel, membrane voltage showed a spike, but afterwards stabilise. Similar pattern occurred to the activation variables.