M2 Biology

TD2b: Models of Neurons III

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TD material is available at:

`https://github.com/Elieoriol/2122_UlmM2_ThNeuro/tree/master/TD2b`

In the following we will consider the parameters:

C	g_l	E_l	g_K	E_K	g_{Na}	E_{Na}
$1\mu\text{F/cm}^2$	0.3mS/cm^2	-54.4mV	36mS/cm^2	-77mV	120mS/cm^2	50mV

1 The Hodgkin-Huxley model of spiking neurons

In the leaky integrate-and-fire model, spikes occur as a simple threshold crossing of the voltage variable; the biophysical mechanisms for spike generation are not directly described. In the Hodgkin-Huxley model, spikes are generated by the cooperative activity of two voltage dependent channels (sodium Na and potassium K), which open and close with different time scales. The equation which regulates the time evolution of the membrane potential is given by:

$$C\,\frac{\mathrm{d}V}{\mathrm{d}t} = g_l(E_l - V) + g_K n^4(E_{\text{K}} - V) + g_{Na} m^3 h(E_{\text{Na}} - V) + I \tag{1}$$

where the second term on the right-hand-side describes the current due to the K-channel and the third term the current due to the Na-channel.

The channel variables h, m, n all follow first-order kinetics, i.e. rate equations of the form

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \alpha_x(V)(1-x) - \beta_x(V)x \tag{2}$$

and the open and closing rates, $\alpha(V)$, and $\beta(V)$ are channel-specific and voltage-dependent.

$$\begin{aligned}
\alpha_n(V) &= \frac{55+V}{100(1-e^{-(55+V)/10})} \\
\beta_n(V) &= e^{(65+V)/80}/8 \\
\alpha_m(V) &= \frac{40+V}{10(1-e^{-(40+V)/10})} \\
\beta_m(V) &= 4e^{-(65+V)/18} \\
\alpha_h(V) &= 0.07e^{-(65+V)/20} \\
\beta_h(V) &= \frac{1}{(e^{-(35+V)/10}+1)}
\end{aligned}$$

1. **num** Implement numerically this model with $I = 10$ using Euler's method.
2. **num** Vary the value of the external input. At which value I_C does the neuron start firing?
3. **num** What is the value of the firing rate for $I \sim I_C$? How does this differ from a LIF neuron?

2 Sub-threshold resonance

From experiments it is observed that some neurons display a resonance of their membrane potential at a particular frequency upon injection of a small oscillating current.

We now consider the behaviour of the Hodgkin-Huxley model close to the leak potential V_L. The sodium channels are therefore closed and can be ignored.

$$\begin{aligned} C\,\frac{\mathrm{d}V}{\mathrm{d}t} &= -g_L(V-V_L) - g_K n^4 (V-V_K) \\ \tau_n(V)\,\frac{\mathrm{d}n}{\mathrm{d}t} &= -n + n_\infty(V) \end{aligned} \tag{3}$$

1. We suppose that there is an equilibrium point at V_{eq} and n_{eq}, where:

$$\frac{\mathrm{d}V}{\mathrm{d}t} = 0 \qquad \frac{\mathrm{d}n}{\mathrm{d}t} = 0 \tag{4}$$

We aim at studying the stability of this solution. We consider a small perturbation away from the equilibrium, and we analyse its time evolution.

Linearize the equations around this equilibrium point so as to show that the response to a small perturbation $V(t) = V_{eq} + \delta V(t)$, $n(t) = n_{eq} + \delta n(t)$ follows:

$$\frac{\mathrm{d}(\delta V)}{\mathrm{d}t} = -a\delta V - b\delta n \qquad \frac{\mathrm{d}(\delta n)}{\mathrm{d}t} = c\delta V - d\delta n \tag{5}$$

where:

$$\begin{aligned} a &= (g_l + g_k n_{eq}^4)/C \\ b &= 4 g_k n_{eq}^3 (V_{eq} - V_K)/C \\ c &= n'_\infty(V_{eq})/\tau_n(V_{eq}) \\ d &= 1/\tau_n(V_{eq}) \end{aligned} \tag{6}$$

To linearize means that we only keep terms in δV and δn (but not in $\delta V \delta n$).

$$\begin{aligned} C\,\frac{\mathrm{d}V}{\mathrm{d}t} &= C\,\frac{\mathrm{d}(V_{eq}+\delta V)}{\mathrm{d}t} = C\,\frac{d\delta V}{\mathrm{d}t} \\ &= -g_L(V_{eq}+\delta V - V_L) - g_K(n_{eq}+\delta n)^4(V_{eq}+\delta V - V_K) \\ &= -g_L(V_{eq}-V_L) - g_L\delta V - g_K(n_{eq}^4 + 4n_{eq}^3\delta n)(V_{eq}-V_K+\delta V) \\ &= -g_L(V_{eq}-V_L) - g_K n_{eq}^4(V_{eq}-V_K) - g_K 4n_{eq}^3\delta n(V_{eq}-V_K) - (g_L + g_K n_{eq}^4)\delta V \\ C\,\frac{\mathrm{d}(\delta V)}{\mathrm{d}t} &= -4g_K(V_{eq}-V_K)n_{eq}^3\delta n - (g_L + g_K n_{eq}^4)\delta V \\ \tau_n(V)\,\frac{\mathrm{d}n}{\mathrm{d}t} &= \tau_n(V_{eq}+\delta V)\frac{\mathrm{d}(n_{eq}+\delta n)}{\mathrm{d}t} = (\tau_n(V_{eq}) + \delta V \tau'_n(V_{eq}))\frac{\mathrm{d}(\delta n)}{\mathrm{d}t} = \tau_n(V_{eq})\frac{\mathrm{d}(\delta n)}{\mathrm{d}t} \\ &= -n + n_\infty(V) = -n_{eq} - \delta n + n_\infty(V_{eq}+\delta V) \\ &= -n_{eq} - \delta n + n_\infty(V_{eq}) + \delta V n'_\infty(V_{eq}) \\ \tau_n(V_{eq})\,\frac{\mathrm{d}(\delta n)}{\mathrm{d}t} &= -\delta n + \delta V n'_\infty(V_{eq}) \end{aligned}$$

2. Determine the time evolution of the first-order perturbations. Under what conditions will the system return to the equilibrium point when it is perturbed?

   We can consider the evolution of the vector $X = (\delta V, \delta n)$.

   Using the vector notation we have:

   $$\frac{\mathrm{d}X}{\mathrm{d}t} = \begin{pmatrix} -a & -b \\ c & -d \end{pmatrix} X = MX$$

   To obtain the behaviour of the system, we consider the eigenvectors X_0, X_1 *and eigenvalues* λ_0, λ_1 *of the matrix* M *such that* $X_0 M = \lambda_0 X_0$, $X_1 M = \lambda_1 X_1$.

   We decompose X *according to the eigenvectors:*

   $$\begin{aligned} X(t) &= x_0(t)X_0 + x_1(t)X_1 \\ \frac{\mathrm{d}X}{\mathrm{d}t} &= x_0'(t)X_0 + x_1'(t)X_1 \\ &= x_0(t)MX_0 + x_1(t)MX_1 = x_0(t)\lambda_0 MX_0 + x_1(t)\lambda_1 MX_1 \\ x_0'(t) &= \lambda_0 x_0(t) \\ x_1'(t) &= \lambda_1 x_1(t) \\ X(t) &= x_0(0)\exp(\lambda_0 t)X_0 + x_1(0)\exp(\lambda_1 t)X_1 \end{aligned}$$

   The system returns to the equilibrium point after a small perturbation if and only if the real parts of both eigenvalues are negative.

   The product of eigenvalues is given by the determinant of the matrix $ad + bc > 0$ *therefore the eigenvalues have the same sign.*

   The sum of eigenvalues is given by the trace of the matrix $-a - d < 0$ *therefore both eigenvalues are negative.*

   We can also explicitly calculate the eigenvalues. They satisfy:

   $$\begin{aligned} \det \begin{pmatrix} -a-\lambda & -b \\ c & -d-\lambda \end{pmatrix} = 0 &= (-a-\lambda)(-d-\lambda) - c(-b) \\ &= \lambda^2 + \lambda(a+d) + ad + bc \end{aligned}$$

   The determinant of this equation is given by:

   $$\begin{aligned} \Delta &= (a+d)^2 - 4(ad+bc) = a^2 + d^2 + 2ad - 4ad - 4bc \\ &= (a-d)^2 - 4bc \end{aligned}$$

   - *if* $4bc < (a-d)^2$, *then* $\Delta > 0$ *and the eigenvalues are given by:*

     $$\lambda_0 = \frac{-(a+d) - \sqrt{\Delta}}{2} < 0$$
     $$\lambda_1 = \frac{-(a+d) + \sqrt{\Delta}}{2} < 0$$

   - *if* $4bc < (a-d)^2$, *then* $\Delta < 0$, *the system is oscillatory and the complex eigenvalues are given by:*

     $$\lambda_0 = \frac{-(a+d) - i\sqrt{-\Delta}}{2}$$
     $$\lambda_1 = \frac{-(a+d) + i\sqrt{-\Delta}}{2}$$

   In both cases the real parts of both eigenvalues are negative so perturbations do not get amplified.

3. Consider the system dynamics close to the equilibrium state. Show that the response to a small oscillating current is:

$$V_0 \exp(i\phi_V) = \frac{I_0(d+i\omega)}{bc + (d+i\omega)(a+i\omega)}$$

We consider only the $\exp(i\omega t)$ *terms:*

$$\begin{aligned}
I(t) &= I_0 \exp(i\omega t) \\
\delta V(t) &= V_0 \exp(i\phi_V)\exp(i\omega t) \\
\delta n(t) &= n_0 \exp(i\phi_n)\exp(i\omega t) \\
i\omega n_0 \exp(i\phi_n) &= cV_0 \exp(i\phi_V) - dn_0 \exp(i\phi_n) \\
n_0 \exp(i\phi_n) &= \frac{cV_0 \exp(i\phi_V)}{d+i\omega} \\
i\omega V_0 \exp(i\phi_V) &= -aV_0 \exp(i\phi_V) - bn_0 \exp(i\phi_n) + I_0 \\
&= -aV_0 \exp(i\phi_V) - b\frac{cV_0 \exp(i\phi_V)}{d+i\omega} + I_0 \\
V_0 \exp(i\phi_V) &= \frac{I_0}{i\omega + a + \frac{bc}{d+i\omega}} \\
&= \frac{I_0(d+i\omega)}{bc + (d+i\omega)(a+i\omega)}
\end{aligned}$$

4. Does the voltage response necessarily decrease as the input frequency ω increases?

   For simplicity, consider the case $a = 0$. Show that there is resonance if $bc/d^2 > \sqrt{2} - 1$.

   For $a = 0$*:*

$$\begin{aligned}
\left(\frac{V_0}{I_0}\right)^2 &= \frac{\| d + i\omega \|^2}{\| bc - \omega^2 + id\omega \|^2} \\
&= \frac{d^2+\omega^2}{(bc-\omega^2)^2 + (d\omega)^2} = \frac{d^2 + W}{(bc)^2 + W(d^2 - 2bc) + W^2} \\
\frac{d\left(\frac{V_0}{I_0}\right)^2}{dW} &\propto (bc)^2 + W(d^2-2bc) + W^2 - (d^2+W)(d^2-2bc+2W) \\
&= W^2(1-2) + W(d^2 - 2bc - (d^2-2bc) - 2d^2) + (bc)^2 - d^2(d^2-2bc) \\
&= -W^2 - 2d^2W - d^4 + 2d^2bc + (bc)^2
\end{aligned}$$

There is resonance if and only if there is $W > 0$ *such that this derivative is zero. This happens if and only if:*

$$\begin{aligned}
-d^4 + 2d^2bc + (bc)^2 > 0 \quad &\Leftrightarrow \quad \left(\frac{bc}{d^2}\right)^2 + 2\frac{bc}{d^2} - 1 > 0 \\
&\Leftrightarrow \quad \frac{bc}{d^2} > \sqrt{2} - 1
\end{aligned} \tag{7}$$