M2 Biology **15/10/18**

TD2: Models of Neurons II

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`https://github.com/Elieoriol/2021_UlmM2_ThNeuro/tree/master/TD2`

1 Refractory period

Additional rules can be added to account for other observed features of real spikes, also called action potentials. One of the observed features is a refractory period; immediately after a spike the neuron cannot produce another spike for a short period of time called the refractory period. The refractory period can be included in models of neurons in a number of ways.

1.1 Forced voltage clamp

The voltage is fixed at its reset value following a spike for the duration of the refractory period τ_{ref}.

1. What is the maximal firing rate f with this method?

   The maximal firing rate is obtained when the neuron fires immediately after the refractory period. Thus:

$$max\ f = \frac{1}{\tau_{ref}} \tag{1}$$

   A disadvantage of this method is that as the firing rate of the neuron increases, the neuron spends a greater proportion of its time in the refractory period with the membrane potential at its low reset value. Therefore, the mean membrane potential decreases with increased input in such a model, in contrast to the behavior of real neurons.

1.2 Refractory conductance

A solution closer to biology is to add a large conductance g_K at spike time, producing an outward hyperpolarizing current. In real neurons, such a late current can most often be related to potassium channels.

2. Explain why a large conductance can replace the LIF reset mechanism. Propose a differential equation for g_K to enable the neuron to spike again after the refractory period. Does this model solve the previous problem?

   A large conductance is associated to a small relaxation time. If a large conductance associated to a low reversal potential is induced when the membrane potential reaches its threshold value, it will be forced to decrease strongly. This way it can be brought back close to its reset value and remain there as long a required. We now need a second ingredient defining the time the system will stay in the refractory period. For our neuron to spike we needed g_K to be null. A way to make it spike again after a given time is to make g_K decay to 0 with a relaxation time corresponding to the refractory period τ_{ref}. Finally:

$$\frac{\mathrm{d}g_K}{\mathrm{d}t} = -g_K/\tau_{ref} \qquad \textit{after a spike, } g_K \to g_K + \Delta g$$

Now the potassium current produced by this refractory conductance yields an additional term to the membrane potential equation $g_K(t)\,(E_K - V_m(t))$.

The time spent at the reset value depends on the strength of other currents entering the neuron; the stronger the other inputs, the more quickly they overcome the decaying refractory current. As such the mean membrane potential increases with increased input.

Note: This is a first step towards the Hodgkin-Huxley model of spiking neurons. The difference resides in that instead of roughly adding a decaying conductance at spike time, this conductance is made non-linearly voltage-dependent: when the membrane potential reaches high values, this conductance becomes large and brings the potential down.

1.3 Raised threshold

A third alternative could be to consider that the neuron does not really go into a refractory period but instead becomes less prone to spiking by raising its threshold.

3. By analogy with the previous method, can you think of a way to implement a raised threshold method?

   Following a spike the voltage threshold can be raised and allowed to decay back to its baseline constant:

$$\frac{\mathrm{d}V_{th}(t)}{\mathrm{d}t} = -\frac{V_{th}^{(0)} - V_{th}(t)}{\tau_{ref}} \qquad \textit{after a spike, } V_{th} \to V_{th} + \Delta V_{th}$$

   This method has the advantage that the refractory period is not absolute: the greater the input, the sooner the membrane potential will reach the decaying threshold.

4. **num** Implement numerically the three previous methods.

2 Non linear models

Linear models cannot reproduce all the behaviors of biological neurons. We propose to study a nonlinear model of neurons and show how it can display a richer repertoire of behaviors.

The model we consider is the *quadratic integrate and fire* (QIF) model:

$$\begin{aligned} \frac{\mathrm{d}V}{\mathrm{d}t} &= V^2 + b \\ \text{if } V > V_{peak}&\text{ , then } V \to V_{reset} \end{aligned} \tag{2}$$

We consider here the potential V and the quantity b to be adimensional (through normalization for instance). b can be a function of time (a varying current), but we consider it constant for the moment.

5. Would you describe V_{peak} as a threshold?

   V_{peak} *is not exactly a threshold, it corresponds to the peak value of the spike (not the threshold value at which it is initiated).*

2.1 $b > 0$

6. Describe the behavior of the neuron in this case.

If $b > 0$, then the derivative of V is always strictly positive. This means we will observe periodic oscillations of the neuron. We can compute their period:

$$\begin{aligned} &\frac{\mathrm{d}V}{b+V^2} = \mathrm{d}t \\ \implies &\int_{V_{reset}}^{V_{peak}} \frac{\mathrm{d}V}{b+V^2} = T \\ \implies &\frac{1}{b}\int_{V_{reset}}^{V_{peak}} \frac{\mathrm{d}V}{1+\left(V/\sqrt{b}\right)^2} = T \end{aligned}$$

With the change of variable $y = V/\sqrt{b}$:

$$\begin{aligned} T &= \frac{1}{\sqrt{b}}\int_{\sqrt{b}V_{reset}}^{\sqrt{b}V_{peak}} \frac{\mathrm{d}y}{1+y^2} \\ &= \frac{1}{\sqrt{b}}\left[\arctan\left(V_{peak}\sqrt{b}\right) - \arctan\left(V_{reset}\sqrt{b}\right)\right] \\ &= \frac{1}{\sqrt{b}}\arctan\left[\frac{V_{peak}-V_{reset}}{1/\sqrt{b}+V_{peak}V_{reset}\sqrt{b}}\right] < \frac{\pi}{\sqrt{b}} \end{aligned}$$

The last line results from the identity $\arctan(x) - \arctan(y) = \arctan\left[\frac{x-y}{1+xy}\right]$.

In between, starting from a potential V_0 and reaching a potential $V(t)$ at time t, the last relation can be inverted to get the evolution of the membrane potential:

$$V(t) = \sqrt{b}\cdot\tan\left(\sqrt{b}(t+t_0)\right)$$

with $t_0 = \frac{1}{\sqrt{b}}\arctan\left(V_0/\sqrt{b}\right)$.

2.2 $b < 0$

7. Can you characterize the steady states of the neuron? Plot the graph of these steady states against b.

Canceling the time derivative in (2), when $b < 0$ we have two steady states $V_s^{\pm} = \pm\sqrt{|b|}$. Plotting on a graph against b, they describe a parabola.

To study their stability, we can add a small first-order perturbation to each of these values $V = \pm\sqrt{|b|} + \delta^{\pm}$ (linear stability analysis):

$$\frac{\mathrm{d}\delta^{\pm}}{\mathrm{d}t} \approx \pm 2\sqrt{|b|}\ \delta^{\pm}$$

We see that a small perturbation to the $+\sqrt{|b|}$ solution gets amplified whereas one to the $-\sqrt{|b|}$ solution decays to 0: the primer is unstable, the latter is stable.

A totally equivalent but quicker way to get the stability of the steady states is the following:

- *Get the steady state equation, obtained by canceling the derivative in the model equation: $V^2 + b = 0$*
- *Compute the derivative of the left hand side according to the variable you are looking at, here V: $2V$*
- *Look at its sign evaluated at the steady states; a positive/negative sign respectively correspond to an unstable/stable steady state: $2V_s^{\pm} = \pm 2\sqrt{|b|}$, such that V_s^+ is unstable and V_s^- is stable*

8. Depending on V_{reset} and $b < 0$, what are the different behaviors of the neuron regarding excitation?

   We count 3 possible behaviors, as V_{reset} can either be:

   - *Strictly lower than $\sqrt{|b|}$: after a reset, the neuron is brought to the stable solution. It is however excitable. A short pulse of current, if strong enough, can drive it above the unstable point and make it spike.*
   - *Equal to $\sqrt{|b|}$: after a reset, the neuron in on the unstable point. A tiny current can either drive it to spiking or to stability.*
   - *Above $\sqrt{|b|}$: after a reset, the neuron keeps on spiking. However, it can start and remain on the stable point; a strong enough pulse of current would then bring it to oscillatory spiking. As such, the neuron is said to be bistable.*

2.3 Bifurcation diagram

9. Plot the bifurcation diagram of the system, in the V_{reset} and b space.

   Regardless of the value of V_{reset}, we have a bifurcation at $b = 0$, which gives a straight vertical line. We have another line for $V_{reset} = \sqrt{-b}$ because it corresponds to a change of behavior, as described in the previous question.

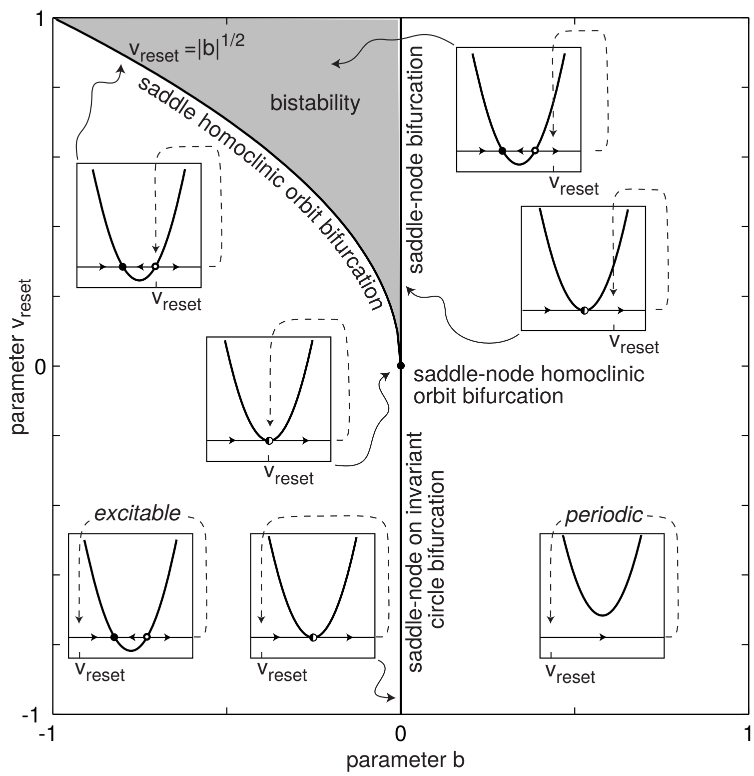

Figure 1: Bifurcation diagram of the QIF model. The insets show the parabola corresponding to the steady-state solutions of (2). V evolves on the horizontal line which moves up and down depending on b. Reproduction from Izhikevich, *Dynamical Systems in Neuroscience.*

10. We consider $V_{reset} > \sqrt{|b|}$. Can you compute the period of the oscillations? We note that the solution

of the differential equation in this case is:

$$V(t) = \sqrt{|b|}\,\frac{1 + \exp\left(2\sqrt{|b|}(t + t_0)\right)}{1 - \exp\left(2\sqrt{|b|}(t + t_0)\right)}$$

with $t_0 = \dfrac{1}{2\sqrt{|b|}} \log\left(\dfrac{V_{reset} - \sqrt{|b|}}{V_{reset} + \sqrt{|b|}}\right)$.

Using the previous formula to get the period T to go from $V = V_{reset}$ to $V = V_{peak}$, we find:

$$T = \frac{1}{2\sqrt{|b|}}\left[\log\left(\frac{V_{peak} - \sqrt{|b|}}{V_{peak} + \sqrt{|b|}}\right) - \log\left(\frac{V_{reset} - \sqrt{|b|}}{V_{reset} + \sqrt{|b|}}\right)\right] \tag{3}$$

2.4 Analogy with "theta neurons"

The theta model is described by the following equation:

$$\frac{\mathrm{d}\theta}{\mathrm{d}t} = 1 - \cos\theta(t) + [1 + \cos\theta(t)] \cdot I(t) \tag{4}$$

We consider that a spike is emitted when θ reaches the value π.

11. Show that for $I < 0$ there are two equilibria for the system, a stable and an unstable one. Show that if θ is not initially equal to the unstable equilibrium, it converges to the stable equilibrium.

    Canceling the derivative in the above equation, we get the steady state equation:

    $$\cos\theta = \frac{1 + I}{1 - I} \tag{5}$$

    If $I < 0$ this equation has two solutions. We obtain the stability by looking at its derivative $-\sin\theta$.

12. In the case $I > 0$, show that there is no equilibrium. Conclude that the trajectories are periodic orbits with regular spiking.

    If $I > 0$, $1 + I(t) > I(t) - 1$, hence the steady state equation has no solution. Because it is positive, we observe periodic orbits.

13. Can you see a link with the quadratic model? What happens when $I = 0$?

    We remark that the change of variable $v = \tan\theta$ transforms the quadratic integrate and fire ODE into the theta neuron equation. At $I = 0$ we have a bifurcation from 2 to 0 equilibrium points.