Assignment 2

This assignment concerns the effects of calcium-dependent currents, which were the subject of week 4 and bursting, treated in weeks 5 and 6. The hand-in date for this assignment is the 11th of April at 23:00.

Part 1. A minimal model for L-type currents

L-type currents are calcium currents. They are responsible for spikes in some cells, such as the Morris-Lecar models. The "L" in "L-type current" stands for "Long-lasting": these channels have a high activation threshold depending on voltage and a high inactivation threshold that depends on calcium concentration.

We examine a dynamical system for a cell with an L-type current and show that, even when this current is the sole nonlinearity in the model, it can produce self-sustained oscillations. The system is expressed in terms of the time-dependent variables $(V(t), C(t))$ modelling the membrane voltage and the calcium concentration in the cell, respectively.

An L-type current can be modelled as

$$I_{Ca,L}(V,C) = m(V)h(C)I_{drive}(V,C).$$

Each of the quantities above depends on state variables $(V(t), C(t))$. In particular

- m is a gating variable for activation; in an L-type channel m depends directly on the voltage V; hence we write $m(V(t))$ with

$$m(V) = m_\infty(V) = \frac{\alpha_m(V)}{\alpha_m(V)+\beta_m(V)}, \qquad \alpha_m(V) = 0.055\frac{-27.01-V}{\exp(-27.01-V)/3.8)-1},$$
$$\beta_m(V) = 0.94\exp((-63.01-V)/17)$$

  Recall from Week 1 and Section 1.8 in the book that choosing the functions $\alpha_m(V)$ and $\beta_m(V)$ is just another way of expressing $m_\infty(V)$ and $\tau_m(V)$.
- h is a gating variable for inactivation, which depends directly on the calcium concentration $C(t)$, hence $h(C(t))$; we use the following function for modelling this variable

$$h(C) = \frac{k_i}{k_i + C}$$

- As seen in the lecture in Week 4, I_{drive} depends on V and C; here, we model it using the so-called Constant Field Model (for a biological justification of the expression below, see Equation 4.2 and Section 1.3 in the book)

$$I_{drive}(V,C) = P_{max}zF\xi(V)\left(\frac{C - C_{out}\exp(-\xi(V))}{1-\exp(-\xi(V))}\right), \qquad \xi(V) = \frac{zFV}{RT}$$

  The expression above is admittedly complicated. If it makes your head spin, then consider the following: for an ion channel, one typically takes $I_{drive}(V) = g(V-E)$, with E being the reversal potential and g the maximal conductance, that is, the drive depends linearly on the state variable V; in the constant field model, one takes $I_{drive}(V,C)$, that is, the current depends on both state variables V, C in a nonlinear fashion; the expression above is complicated, but it is useful to focus on the nonlinear dependence on V and C: the rest are mostly physical constants, whose value will be given below.

We are now ready to write a model of a cell under the effect of a leak current, an applied current, and an L-type current

$$\dot{V} = I_{app} - g_L(V-E_L) - I_{Ca,L}(V,C), \tag{1}$$
$$\dot{C} = -\beta I_{Ca,L}(V,C) - \frac{C-C_\infty}{\tau_C}. \tag{2}$$

In the model, time is measured in ms (milliseconds), V in mV (milliVolts) and C in M (Molars), and we shall use the following default parameter values, given without units for simplicity:

$P_{max} = 0.002,$
$k_i = 0.001,$
$z = 2,$
$F = 96520,$
$C_{out} = 2,$
$R = 8313.4,$
$T = 273.15 + 25,$
$g_L = 0.05,$
$E_L = -70,$
$C_\infty = 10^{-4},$
$\tau_C = 200,$
$\beta = 0.01.$

Assignment questions

Q1.1: The text above gives details of all terms in equation (1) of the model, which regulates the dynamics of the voltage variable V. We have omitted a description of equation (2) for the calcium dynamics. Write your interpretation of equation (2). A good starting point for your description may be: Explain the meaning of the two terms in the equation's right-hand side; Are these two terms competing?; Is there a time-scale separation between V and C? This question is deliberately open: we want to read how you connect mathematical equations and cellular phenomena, but there is no definitive answer to this question. Give a concise explanation, and keep the discussion focused on equation (2): we don't need to read, for instance, how you interpret $I_{drive}(V,C)$, which we discussed already.

Q1.2: What can you conclude if $P_{max} = 0$, that is, when the L-type current is switched off? Again, this question is open: we want to read your own reasoning. We believe that, in this regime, a lot about the dynamics of $V(t)$ and $C(t)$ can be said without doing any simulation. However, you are welcome to use numerical simulation to support your analytical claims, or even to explore the dynamics **before making any claims**. In questions like this one, it is sometimes hard to know when to stop: how much detail should we write? Is there anything "hidden" I have missed? If you have such questions, we invite you not to stress over them and post them on Zulip instead, where we'll be happy to address them.

Henceforth, we switch back on the L-type current, returning to the case $P_{max} \neq 0$.

Q1.3: Would you say that the activation of the L-type channel is slow, fast, or instantaneous? Justify your claim.

Q1.4: As stated in the model description, L-type channels have a high activation threshold depending on voltage and a high inactivation threshold that depends on calcium concentration. Stated otherwise: they activate when the potential is "high" and inactivate when the calcium is "high". In this question, we ask you to make this statement more precise: plot the gating variables for activation and inactivation, as functions of V and C, respectively. Complete the following statements by providing estimates for the values x and y:

S1: When $V = x$ mV (x milliVolts), approximately 90% of the L-type Calcium channels in the cell are activated
S2: When $C = y$ M (y Molars), approximately 90% of the L-type Calcium channels in the cell are inactivated

Q1.5: Using numerical methods, plot the nullclines of the model for $I_{app}(t) \equiv 1$, that is, applied current equal to 1 for all t. Before addressing this question (and irrespective of whether you use Matlab or not), it may be useful to read the documentation of Matlab's inline function **fimplicit**, which plots an implicit function, or of Matlab's inline function **fsolve** which solves systems of nonlinear equations. You can click on the blue links above to access the documentation.

Q1.6: Let us now perform computations of the model using the parameter values specified in the model description. This question can be addressed using time simulations, phase plots, and bifurcation diagrams. Assume that $I_{app}(t)$ is an **instantaneous switch**, for instance

$$I_{app}(t) = \begin{cases} 0 & \text{if } t < a, \\ I & \text{if } t \geq a. \end{cases}$$

Provide numerical evidence and dynamical-system interpretation for the following statement:

S3: upon switching on an instantaneous stimulus, the model may transition from a rest state to: i) a new steady state, attained without emitting a spike; ii) a new steady state, attained after emitting a spike; iii) a periodic orbit. Take into account the middle and right branches of the V-nullcline in deciding whether a spike is emitted.

Provide numerical evidence and explanations that support or refute the following statement:

S4: Let $I_{app}(t) = I$ for all t. There is an interval $\mathcal{I} \subset [0,3]$ in which the model supports bistability between a periodic orbit and a stationary state.

Part 2. Morris-Lecar Burster

In this exercise, we guide you through conditions A1-A4 in constructing the square-wave burster as outlined in Lecture 6. Specifically, we will consider the role of A4. The model is given by Eq 5.2 in the book, i.e.,

$$\begin{aligned} C_m\frac{dV}{dt} &= I_{app} - g_L(V-E_L) - g_K n(V-E_K) - g_{Ca}m_\infty(V)(V-E_{Ca}) - I_{KCa}, \\ \frac{dn}{dt} &= \phi(n_\infty(V)-n)/\tau_n(V), \\ \frac{d[Ca]}{dt} &= \epsilon(-muI_{Ca} - k_{Ca}[Ca]), \end{aligned} \tag{MLM}$$

where

$$m_\infty(V) = \frac{1}{2}\left[1+\tanh\left(\frac{V-V_1}{V_2}\right)\right],$$
$$n_\infty(V) = \frac{1}{2}\left[1+\tanh\left(\frac{V-V_3}{V_4}\right)\right], \qquad \tau_n(V) = \left[\cosh\left(\frac{V-V_3}{2V_4}\right)\right]^{-1}$$

and

$$I_{KCa} = g_{KCa}\left(\frac{[Ca]}{[Ca]+1}\right)(V-E_K).$$

Here, we consider the parameter values to be $V_1 = -1.2$, $V_2 = 18$, $V_3 = 12$, $V_4 = 17.4$, $g_K = 8$, $g_L = 2$, $g_{Ca} = 4$, $g_{KCa} = 0.25$, $E_{Ca} = 120$, $E_K = -84$, $E_L = -60$, $\phi = 0.23$, $C_m = 20$, $I_{app} = 45$. Note these values differ slightly from those in table 5.1, p109! We initially set $\epsilon = 0.001$ and $\mu = 0.02$, though we vary these below as well. The code for week 6 on ELO can be used here. You may assume there is a value $[Ca]^*$ such that the fast subsystem has a homoclinic bifurcation satisfying condition A3 as in the proof.

Q2.1 Create a 3D plot showing the state variables V, n, Ca combining the parametric branch of equilibria of the fast subsystem (Ca, n^*, V^*) and the 2D manifold defined by $d[Ca]/dt = 0$. Argue that intersection points are equilibria of the full system. As a convention, put V on the z-axis.

Q2.2 Show a simulation of the full system with parameters as specified in two ways. First, show the time series and comment on its similarity to the square-wave burster shown in Figure 5.2 of the book. Second, show the orbit in the three-dimensional plot for the previous exercise.

Q2.3 We define the effective change of the Calcium concentration along one periodic orbit as the average $H = \frac{1}{T}\int_0^T d[Ca]/dt$, where T is the period of the cycle of the fast subsystem. Compute H numerically as a function of the slow variable Ca. The following steps guide you through setting up code to compute H.

- Define a separate ODE for the fast subsytem, with $[Ca]$ as a fixed parameter.
- Perform a simulation so that the orbit has converged to the limit cycle, i.e., transients have faded.
- Find the time of the last two maxima of the potential, i.e., the spiketimes, yielding three arrays $times, V, n$.
- Evaluate $d[Ca]/dt$ along the computed orbit, i.e. substitute (V, n).
- Approximate the integral H using the trapezoidal rule $\int_a^b f(t)dt = \frac{h-a}{2}(f(a)+f(b))$. The array $times$ yields the dt-steps.
- Repeat this for the next value of Ca.
- You may have a look at the code shown in the video recording of Lecture 6.

Q2.4 Demonstrate that H is a monotonously decreasing function of Ca and show that there is a critical value $[Ca]^* < [Ca]^8$ such that $H = 0$.

Q2.5 Explain how lower values of ϵ result in tonic firing, while higher values lead to square-wave bursting. Relate this to the position of the manifold G and the effective change H.

Hint: (A) You may assume the result of Q2.4, even if you could not show that, and (B) perform simulations to convince yourself. The same effect can be achieved by lowering μ, which you do not have to investigate but feel free to explain that too as a bonus.

Q2.6 Increase the homeostasis rate μ. What happens to the manifold G and the points where G intersects the equilibrium branch? Provide a simulation showing this effect, where the initial condition is chosen to be above G, i.e., start along the spiking manifold P. Is the model still bursting? Again, explain this in relation to condition A4.

BONUS We conclude that the Morris-Lecar model for these parameter values serves as a poor example of a square-wave burster. Provide parameter values such that this model satisfies all conditions A1-A4.