Mathematical models in biology, 2021Q1
Miniprojects' proposals
B3. Neuronal networks

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Contents

1 Small conductance-based network

In this project, we aim at simulating a small (two-neuron) network formed by identical conductance-based neuron models, with the following structure:

- Neuron 1 receives a Poisson input at ν Hz through synapses modulated by an α function.
- Neuron 1 excites Neuron 2 through a graded synapsis.
- Neuron 2 inhibits Neuron 1 through a graded synapsis.

In the last part of the project, we will study the effect of plasticity (facilitation and depression).

1. **Simulate an input Poisson train for 1 second with rate $\nu = 50$Hz.** For the homogeneous Poisson process we have

$$P[\text{ 1 spike during } \Delta t] \approx r\Delta t,$$

where r is the input rate. This equation can be used to generate a Poisson spike train $\{t_j\}_{j=1}^{n_{spk}}$ by first subdividing time into short intervals, each of duration Δt. Then, generate a sequence of random numbers $x[i]$, uniformly distributed between 0 and 1. For each Δt-interval, if $x[i] \leq r\Delta t$, generate a spike. Otherwise, no spike is generated. This procedure is appropriate only when Δt is very small, i.e, only when $r\Delta t << 1$. Typically, $\Delta t = 0.1$ msec should suffice.

   For more information, see these notes by David Heeger (NYU).

2. **Study of the post-synaptic potentials induced by the Poisson train.** From the spike train obtained in (1), generate an synaptic input $g_{syn}(t) = \bar{g}\sum_j \alpha(t-t_j)H(t-t_j)$, where $\alpha(t) = 1/\tau_s^2 t\exp(-t/\tau_s)$ and H is the Heaviside function. Inject it into the system (you can try to inject first only one):

$$\begin{aligned} C\dot{V} &= I - g_L(V-E_L) - g_{Na}m_\infty(V)(V-E_{Na}) - g_K n(V-E_K) + \mathbf{g_{syn}(t)}(V-E_{syn}) \\ \tau_n\dot{n} &= n_\infty(V) - n \end{aligned} \tag{1}$$

with

$$m_\infty(V) = 1./(1.+\exp(-(V-V_{max,m})/k_m)),$$

and

$$n_\infty(V) = 1./(1.+\exp(-(V-V_{max,n})/k_n)).$$

Use the following parameters: $I = 0\,\mu\text{A/cm}^2$, $C = 1\,\mu\text{F/cm}^2$, $g_{Na} = 20\,\text{mS/cm}^2$, $E_{Na} = 60\,\text{mV}$, $g_K = 10.\,\text{mS/cm}^2$, $V_K = -90\,\text{mV}$, $g_L = 8\,\text{mS/cm}^2$, $E_L = -80\,\text{mV}$, $V_{max,m} = -20\,\text{mV}$, $k_m = 15\,\text{mV}$, $V_{max,n} = -25\,\text{mV}$, $k_n = 5\,\text{mV}$, $\tau_n = 1\,\text{ms}$. For the α function, we choose $\tau_s = 5\,\text{ms}$.

(a) Show the output voltage together with the marks of the Poisson train.

(b) Compute the average of the synaptic current along time and the spiking frequency of the cell. Do these two results match according to the $f-I$ curve of the neuron model?

3. We want to explore the synapses modeled using the formalism of voltage-gated ionic channels (also called *graded synapses*). Consider two neurons that are modeled according to the system described above:

$$\begin{aligned} C\dot{V}_i &= I_i - g_L(V_i - E_L) - g_{Na}m_\infty(V_i)(V_i - E_{Na}) - g_K n_i(V_i - E_K) \\ \tau_n \dot{n}_i &= n_\infty(V_i) - n_i \end{aligned}$$

for $i = 1, 2$. Consider that Neuron 1 excites and Neuron 2, and Neuron 2 inhibits and Neuron 1. This implies that the equation of V_1 must contain the term $-g_{inh,max}s_2(V_1 - E_{inh})$, whereas the equation for V_2 must contain the term $-g_{exc,max}s_1(V_2 - E_{exc})$. The dynamics of s_1 and s_2 are regulated by the following type of differential equation:

$$\dot{s}_i \;= A_s f_{pre}(v_i)(1 - s_i) - \beta_i s_i, \qquad i = 1, 2,$$

where $f_{pre}(v) = 1/(1 + \exp(-(v - v_t)/v_s))$.

By default, we take the following values: $v_t = 2\,\text{mV}$, $v_s = 5\,\text{mV}$, $A_s = 1\text{s}^{-1}$, $\beta_1 = 0.25\,\text{ms}^{-1}$, $\beta_2 = 0.1\,\text{ms}^{-1}$, $g_{exc,max} = 1\,\text{mS/cm}^2$ and $g_{inh,max} = 0\,\text{mS/cm}^2$.

(a) Explore the spiking activity of the two neurons for different values of the maximal inhibitory synaptic conductance: $g_{inh,max} \in \{0, 1, 2\}\,\text{mS/cm}^2$ and comment on the results (for instance, frequency of both cells, order of spikes, spikes suppressed when increasing inhibition,...).

(b) With the given values, the excitatory synapsis has a time constant of $1/\beta_1$ ms and the inhibitory synapsis, $1/\beta_2$ ms. Explore the impact of increasing the time constants, for instance taking the new β's to change by a factor λ with respect to the original ones, with $\lambda \in \{1, 0.5, 0.1\}$. How can you explain the changes?

4. Tsodyks and Markram (Tsodyks 98) proposed a model for short term synaptic plasticity (STP), read this Scholarpedia article. Let x ($0 \le x \le 1$) be the fraction of available vesicles after neurotransmitter depletion and let u be an utilization variable (release probability). Each time there is a spike, we update both variables u and x as follows (we denote as u^-, x^- the values of the variables just before the arrival of the spike, and u^+, x^+ the values at the moment just after the spike): u is increased (due to spike-induced calcium influx to the presynaptic terminal) by an amount $a_f\,(1-u)$ (that is, $u^+ = u^- + a_f\,(1-u^-)$)

and x is decreased by an amount u^+x (a fraction u of available resources x is consumed to produce the post-synaptic current); that is, $x^+ = x^-(1 - u^+)$. Between spikes, u decays back to 0 with time constant τ_f while x recovers to 1 with time constant τ_f. In summary, the dynamics for STP are:

$$\begin{aligned} \tau_d \dot{x} &= 1 - x \\ \tau_f \dot{u} &= -u \end{aligned}$$

The synapsis is modeled as:

$$\tau_s \dot{s} = -s$$

and $s^+ = s^- + A\,u^+\,x^-$. Choose $\tau_s = 20\,\mathrm{ms}$ and $A = 1$. The interplay between the dynamics of u and x determines whether the joint effect of $u\,x$ is dominated by depression or facilitation.

Consider the network from Exercise 3 with the default parameter values. Show that when $\tau_d >> \tau_f$ (for instance, $\tau_f = 50\,\mathrm{ms}$, $\tau_d = 750\,\mathrm{ms}$, $a_f = 0.45$) then the synapse is STD-dominated. If $\tau_f >> \tau_d$ and small a_f (for instance, $\tau_d = 50\,\mathrm{ms}$, $\tau_f = 750\,\mathrm{ms}$, $a_f = 0.15$) then the synapse is STF-dominated. The outputs can be (a) the plot of the voltages of the two cells and (b) the synaptic current received by Neuron 2 in the three cases (no plasticity, STD-dominated and STF-dominated).

2 LIF as a basis for a synaptic-drive firing rate model

We will derive a synaptic drive formulation for a firing rate model using the LIF model.

1. First, consider the LIF model:

$$\begin{cases} C_m \dot{V} = -(V - V_{rest})/R_m + I \\ \text{if } V(t_f) > V_{th}, \text{ then a spike occurs and } V(t_f^+) = V_{rest} \end{cases}$$

   For this problem we will use the model in dimensionless form. Introduce the dimensionless voltage $v(t) = [V(t) - V_{rest}]/[V_{th} - V_{rest}]$ and replace t by $\tau = t/\tau_v$ to show that the model becomes:

$$\frac{dv}{d\tau} = -v + i \quad \text{with firing/reset: } v(t_f) = 1, \text{then } v(t_f^+) = 0$$

   Define τ_v (the membrane time constant) and i in terms of C_m, R_m and I.

2. Compute the analytical expression of period T vs i when $v(T) = 1$. Plot the frequency $f(= 1/T)$ vs i for $0 < i < 30$, and determine analytically the minimum value of i for which repetitive firing exists.

3. Replace the injected current input i by a steady synaptic conductance input: $i = g_{ex}(v_{ex} - v)$. Plot the frequency f vs g_{ex} over the same range as in 2. If you need a value for v_{ex}, use $v_{ex} = 5$. Find analytically the minimum value of g_{ex} for which repetitive firing exists. Compare and discuss the shapes of the curves (with respect to the result from statement 2). Explain their differences.

4. Suppose that when a LIF neuron fires, it initiates in a target cell a pure exponential decaying post-synaptic conductance time course $s(t)$ proportional to $\exp(-t/\tau_s)$ between spikes, that is:

$$\tau_s \dot{s} = q\delta(t - t_f)(1 - s) - s,$$

   where t_f is a firing time and $q \in [0, 1]$ represents the size of the instantaneous δ-function effect of synaptic transmitter on opening synaptic current channels. In other words, at $t = t_f$, we set $s(t_f^+) = s(t_f^-) + (1 - \exp(-q/\tau_s))(1 - s(t_f^-))$. Use $q = 0.1$ and $\tau_s = 1$ for numerical examples.

5. Suppose that our LIF cell experiences the summed total input from the other LIF neurons in the network as a net steady conductance g_{ex} (i.e. constant g_{ex}). As in statement 3 above, with g_{ex} constant, $v(t)$ is periodic with period $T = T(g_{ex})$ (firing at $t = 0, T, 2T, \ldots$). So our LIF neuron is firing periodically with period $T = T(g_{ex})$. We want to find the associated periodic s-profile, $s(t)$, that our cell activates in the target cells. Suppose $s(0^+) = s_0$ then find s_0 such that $s(t)$ is periodic, that is, such that

$s(T^+) = s_0$. NOTE: At $t = T$, $s(t)$ will have a jump discontinuity. Here, s_0 will be a function of $T(g_{ex})$.

6. Compute the (single-cycle) time average of $s(t)$, that is $\bar{s} = 1/T \int_0^T s(t)dt$, as a function of g_{ex} (can be done analytically). Plot $\bar{s}$ vs g_{ex}.

7. Now we will find the net steady synaptic drive g_{ex} in this network of purely excitatory, all-to-all coupled, asynchronous LIF cells. We want to find the steady states of the firing rate model for this setup. For this we solve the self-consistency equation:

$$g_{ex} = \bar{g}_{ex}\bar{s}(g_{ex}),$$

where $\bar{g}_{ex}$ is the coupling strength in the network (it depends on the strength of synaptic connections and on the number of cells in the network). This is an implicit equation for g_{ex}. Analyze it graphically. Plot $\bar{s}(g_{ex})$ vs g_{ex} and also plot $g_{ex}/\bar{g}_{ex}$ vs g_{ex}. Intersections correspond to steady states of the system. Describe (qualitatively and quantitatively) how the network steady states depend on $\bar{g}_{ex}$, say for $\bar{g}_{ex} = 1, 2, \ldots, 6$.

8. **(Optional)** Build-up a network to test the previous statements computationally. Consider a network with N neurons, (take $N = 100$, for instance), each one modeled as a LIF:

$$\begin{aligned} v_i' &= -v_i + \frac{1}{N}\sum_{j=0}^{N} \bar{g}_{ex} s_j (v_{ex} - v_i) \\ s_i' &= -s_i \end{aligned}$$

with the resetting condition: if $v_i > 1$ the $v_i = 0$ and $s_i = s_i + \exp(-q/\tau_s)(1 - s_i)$. Take the initial voltages distributed between 0 and 1 (e.g. $v_i(0) = i/N$, for $i = 1...N$) and $s_i(0)$ with some value distinct from 0. Consider different values of $\bar{g}_{ex}$ and check that results agree with the predictions.

3 Working memory

1. Design a model for working memory using bump attractors from the following guideline. Consider a ring model of $N = 60$ units/populations, each one coding for a particular angle of the input position ($\alpha_j = 2\pi j/N$) and modeled with a rate equation:

$$\tau \dot{r}_j = -r_j + F(\frac{15}{N}\sum_{k=1}^{N} w_{kj} r_k + I_j(t)),$$

for $j = 1...N$. Here, r_j represents the firing rate of population j and F is the transfer function given by

$$F(x) = \begin{cases} 0 & x \leq \theta, \\ x & \theta \leq x \leq 1, \\ 1 & x \geq 1. \end{cases} \tag{2}$$

Take $\theta = 0.2$ and $\tau = 1$. The terms w_{kj} represent the connectivity between two populations, which depends on $D = |k - j| \pmod{N/2}$; that is, the distance between two areas. When computing the distance, take into account the fact that neurons are arranged on a ring. Assuming that the inhibition is fast with respect to the excitation, then the interactions are of "Mexican hat" type (guess why by plotting $\hat{w}(x)$), $w_{kj} = \hat{w}(D/N) = w_e(D/N) - w_i(D/N)$, where

$$w_e(x) = a \exp(-0.5(x/\sigma_e)^2)$$

and

$$w_i(x) = b \exp(-0.5(x/\sigma_i)^2).$$

Choose $\sigma_e = 0.08$, $\sigma_i = 0.25$, $a > 1$, and $b = 1$.

Suppose that we need to remember the stimulus located at the angle α_n. Then, the input will be $I_j = \hat{I}(D/N)$ where $D = |n - j| \pmod{N/2}$ and $\hat{I}(x)$ is a function of Gaussian type:

$$\hat{I}(x) = 0.5 \exp(-0.5(x/\sigma)^2).$$

Choose $\sigma = 0.05$.

2. Show that if a is strong enough, then the bump can be sustained when the input is removed. What happens if a is small. What is the meaning of a?

3. What happens if there is no inhibition in the system?

4. What happens to this model if you show two different stimuli located at two different angular locations. Can it remember both? What happens if they are close to each other?

4 Binocular rivalry

In binocular rivalry, each eye views a different image but our perception alternates (on a time-scale of seconds) between the images. Several existing models account for the oscillations by incorporating two neuronal populations that compete through mutual inhibition. A slow fatiguing mechanism, such as adaptation, mediates the back and forth switching of dominance. In this project, we want to study a simple firing-rate model. Let $u_j(t)$ be the firing rate of population j ($j = 1, 2$) and let $a_j(t)$ the corresponding (slow) adaptation variables. The firing rates of the populations evolve in time according to the following set of ODEs:

$$\begin{aligned} \dot{u}_j &= -u_j + f(-\beta u_i - \gamma a_j + I_j) \\ \tau_a \dot{a}_j &= u_j - a_j \end{aligned}$$

with $f(x) = 1/(1 + \exp((\theta - x)/k)$ and control parameter values: $\beta = 0.9$, $\gamma = 0.5$, $I_1 = I_2 = 0$, $\tau_a = 10$, $\theta = 0.2$ and $k = 0.1$.

1. Identify and describe the terms and parameters in the model (inhibition, external input, etc.)

2. Show that for $\beta = 0.9$ and $I = 0.8$ ($I = I_1 = I_2$) the model oscillates. Plot the time courses of u_1 and a_1 on the same axes (ordinate: -0.1 to 1.1, abscissa: 0 to 300), and describe the behavior (phases of dominance, suppression, etc). Overlay u_1 and u_2 on another plot and describe the trajectory. The underlying mechanism is bistability in the "fast dynamics". Show it: think of a_j as slow; freeze them, say at 0.5 and look at u_1 and u_2-nullclines.

3. Show that the model oscillates for a range of I-values; compute and plot the period, T vs I; also plot the maximum and the minimum of u_1 vs I. According to Levelt's Proposition 1 (LP1), based on psychophysical experiments, the oscillation period is expected to decrease as I increases. Does the model satisfy LP1?

4. Increase β (to 1.1) and compute the model's behavior for $0 < I < 2.5$; summarize it in a plot of amplitude vs I (bifurcation diagram); also, T vs I. Note and describe the new behavior (Winner-Take-All, WTA) for an intermediate range of I values. Use some phase plane projections to demonstrate bistability in this WTA regime. For what I-range(s) is LP1 (more-or-less) satisfied or not satisfied?

5. Show that decreasing τ_a eliminates oscillations (why?) and leaves only the WTA regime.

6. Complete your response diagrams of amplitude of u_1 vs I by including the special "uniform steady state" (time independent, $u_1 = u_2$, $a_1 = a_2$). Can you show analytically that it is monotonic? Identify the bifurcations that occur as different solution states appear/disappear.

5 Small-world network of excitable integrate-and-fire neurons

Consider an array of N integrate-and-fire (IF) neurons, whose voltage is determined by the equation

$$\tau_m \frac{dV_i}{dt} = -V_i + I_{ext} + g_{syn} \sum_{j,m} w_{ij}\, \delta(t - t_j^{(m)} - \tau_D), \tag{3}$$

assuming that the neuron fires whenever its voltage exceeds 1 and, then, the voltage is reset to 0. Observe that V_i has been normalized, and that these neurons are not oscillatory, but excitable, in the regime $I_{ext} < 1$.

1. Identify and describe the terms and parameters in the model (τ_m, g_{syn}, $t_j^{(m)}$, τ_D).
2. Create a small-world network (SWN) in this way:
   (a) model the local connections as nearest-neighbor couplings ($w_{ij} = 1$ if and only if $|i - j| = 1$) (underlying regular lattice);
   (b) establish the long-range connections from randomly adding a fixed fraction $p\,N$ of unidirectional couplings $w_{ij} = 1$.
   (c) Using the corresponding undirected graph, compute the clustering coefficient and the average shortest path length of the resulting network for $p = 0.1 * k$, $k = 1, \ldots, 10$. HINT: You need to use software that computes these graph-theoretic properties (SAGE, MATLAB,...).
3. Consider $N = 1000$, $I_{ext} = 0.85$, $gsyn = 0.2$, $\tau_m = 10$ and $\tau_D = 1$. Since the synaptic conductance is chosen to satisfy $I_{ext} + g_{syn} > 1$, then a single input suffices to sustain firing activity. Check that the network does not show persistent activity, that is, the activity slows down as time goes by ($t_{max} \approx 2000$ should be enough) for $p = 0$.
4. Now, change $p = 0.1$ and simulate 10 realizations of the network. Repeat the experiment with $p = 0.9$. Which are the differences that you observe in terms of persistent activity? Why do they occur?
5. **(Optional)** Build up an automatic procedure to determine whether there is persistent activity or not.
6. For different p from 0 to 1 (for instance, $p = 0.1 * k$, $k = 1, \ldots, 10$), average over 2000 realizations to calculate the probability of persistent activity. Plot the complementary probability of failure versus p, for $N = 250, 1500, 1000, 2000$ and comment the results. Observe that the probability of failure is an increasing function of p with increasing steepness as the size N of the system increases.

7. Prove that a single input will be able to elicit a spike only if the elapsed time from its preceding firing exceeds

$$T_R^{(1)} = \tau_m \ln \left(\frac{I_{ext}}{I_{ext} + g_{syn} - 1} \right). \tag{4}$$

   Hint: the time elapsed from the preceding firing of this neuron must allow for a recovery to $V \geq 1 - g_{syn}$.

8. Reproduce the same plot with $\tau_D \in \{0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8\}$.

6 Other ideas

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