

Appendix E

Of spikes and synapses

This lecture introduces a model for a network of interacting neurons. The model runs the risk of making everyone unhappy. The mathematician may complain that it is too complex, making analysis too difficult, and precluding general and powerful theorems. The biologist will complain that the model is a dismally poor caricature of the real neural networks of the brain, and reject it as a figment of some deluded theorist's imagination.

Nevertheless, the model is a useful starting point, because it captures some essential features of biological neural networks. We can always make the model more complex later if it turns out that something important was missing. On the other hand, it may also be possible to simplify the model if some of its features turn out to be irrelevant.

The model has two types of variables, synaptic conductances and neural membrane voltages. Synaptic conductances modulate neural voltages continuously throughout time. However, neural voltages affect synaptic conductances only sporadically, through discrete events called action potentials or spikes. The dynamics of the network is driven by this interplay between voltages and conductances.

The influence of synaptic conductance on voltage will be described using the classic model of a leaky integrate-and-fire neuron. The influence of spikes on synaptic conductance will also be described using a leaky integrator model. As you learn about these models, you will also absorb the bare essentials of the biophysics of neurons.

E.1 Neural voltages are measured with intracellular electrodes

There is an electrical potential difference between the inside and outside of a neuron's membrane. This difference is called the "transmembrane voltage" or simply the "voltage" of the cell. To measure it, one uses a (micro)electrode created by heating and

Figure E.1: Microelectrode recording

Figure E.2: Passive response of a neuron to small steps of applied current.

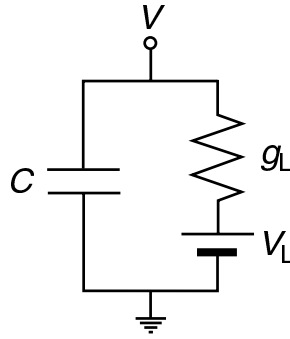


Figure E.3: Equivalent circuit for the membrane of a neuron, valid for small deviations from the resting potential. The membrane is modeled with a capacitor, a resistor, and a battery.

pulling a piece of capillary glass to create a very fine tip. The electrode is filled with electrolyte, and a wire leading to an amplifier is inserted into its barrel.

Two techniques are used to establish electrical continuity between the inside of a neuron and the inside of an electrode. In the “sharp electrode” technique, the cell is impaled on the tip of the electrode. In the whole-cell patch technique, a blunt tip is sealed to the outside of the cell membrane, and a small rupture is made in the membrane by suction. Either method establishes electrical access to the cell, so that current can flow back and forth between it and the electrode. A wire leads from the electrolyte to an amplifier, and is compared with another wire that is connected to a reference electrode in the solution bathing the neuron. These two wires allow the amplifier to sense the voltage difference between the inside and outside of the cell (Figure E.1). With the usual convention of an outside voltage that is zero, the inside voltage is typically -70 mV. This is called the *resting potential* of the neuron.

E.2 Neurons respond passively to small inputs

If current is passed between the two wires, it also passes through the membrane of the neuron that stands between them. The electrical properties of the membrane can be characterized by measuring the resulting changes in its voltage.

Figure E.2 shows the response of a neuron to small steps of applied current. The voltage starts at the resting potential V_L , initially changes linearly, but then approaches a limiting value V_∞ . The difference $V_\infty - V_L$ is proportional to the applied current I_{app} ,

$$V_\infty - V_L = I_{app}R_L = \frac{I_{app}}{g_L}$$

Figure E.4: Spiking of biological neuron in response to applied current. (a) Spike train. (b) f - I curve.

This linear relationship between voltage and current means that the cell membrane behaves like a resistor governed by Ohm's Law. The proportionality constant is R_L , the resistance of the membrane. The inverse of the resistance is $g_L = 1/R_L$, which is called the *leak conductance*.

The approach to V_∞ is not instantaneous, but roughly exponential with some time constant τ_m . This behavior can be modeled as

$$C \frac{dV}{dt} = -g_L(V - V_L) + I_{app} \quad (\text{E.1})$$

Here we've introduced a new parameter $C = \tau_m g_L$, which is the product of the time constant and the leak conductance. This parameter is the *membrane capacitance*.

The electrical circuit equivalent to Eq. (E.1) is shown in Figure E.3. The membrane can be approximated as a resistor, a capacitor, and a battery. Such an electrical circuit is called "passive," because of its linear behavior. It is a good approximation to a neuron for small perturbations about the resting potential.

ion channels

E.3 Neurons are excitable by large inputs

The passive model described above is only valid for small applied currents. If the current exceeds some threshold value, the behavior becomes very nonlinear. A positive pulse in the voltage is generated, with an amplitude of up to 100 mV and a duration of about 1 msec. This behavior is called an action potential, or spike. Once the action potential is initiated, it will continue even if the applied current is removed. This phenomenon is known as excitability. If the current is maintained at a large enough value, the neuron will fire action potentials repetitively (Fig. E.4a).

The relationship between frequency and applied current is called the current-discharge relationship, or the f - I curve. An example is shown in Fig. E.4b. If the current is below a threshold value, known as the rheobase, there is no spiking at all. The frequency rises from zero at threshold, and increases with increasing current. The shape of the curve shown in Fig. E.4 is typical of neurons in the central nervous system of vertebrates. However, other shapes are possible.

The data shown was taken using intracellular recording. However, because spikes have such large amplitude, they can also be measured in brain tissue by an extracellular electrode, which is less demanding to use than an intracellular electrode. A spike sets up current flow in the extracellular space, which leads to sub-millivolt changes in potential that can be detected with an extracellular electrode.

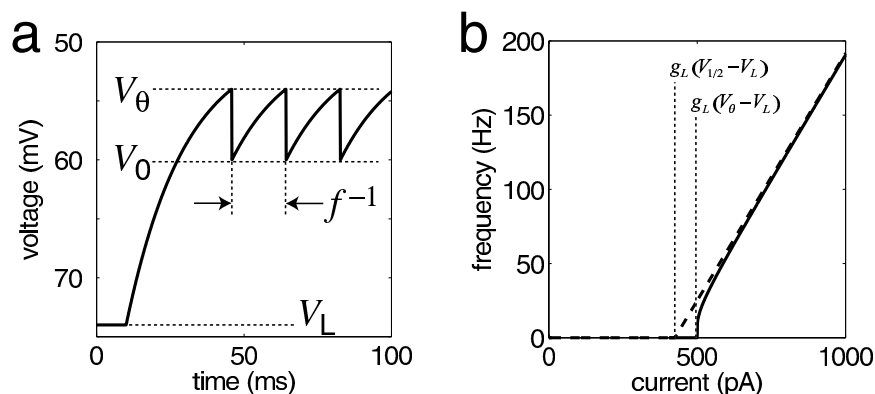


Figure E.5: The leaky integrate-and-fire neuron. (a) Repetitive spiking. The initial voltage is V_L . After application of a constant current, the voltage rises to V_θ . There a spike is said to have occurred, and the voltage is reset to V_0 . This cycle of leaky integration and firing occurs repeatedly. $V_L = -74$ mV, $g_L = 25$ nS, $V_\theta = -54$ mV, $V_0 = -60$ mV and $C = 500$ pF. (b) $f-I$ curve. The dashed line is a linear approximation that is exact in the limit of infinite current.

E.4 A neuron is a leaky integrator with a threshold

Models of neural excitability are much more complex than the passive model given above, because they involve nonlinearity. Such models are outside the scope of this lecture. Instead we'll discuss the minimal modification of the passive model necessary to capture some of the basic features of spiking neurons.

The modification is simple: supplement the linear equation with a threshold crossing condition. Whenever the voltage reaches a threshold value V_θ , a spike is said to happen, and the voltage is reset to the value V_0 .

$$\text{If } V = V_\theta, \text{ then } V := V_0 \quad (\text{E.2})$$

The values of the parameters V_0 and V_θ vary depending on the type of neuron that is being modeled. The combination of Eqs. (E.2) and (E.1) is known as the “leaky integrate-and-fire neuron,” or just “integrate-and-fire neuron” for short. Below threshold, it behaves like a leaky integrator. When the threshold is crossed, it fires an action potential.

A numerical simulation of the model is shown in Fig. E.5a. A constant suprathreshold current is applied, causing repetitive firing. Every time the voltage reaches threshold, it is reset immediately. The actual time course of the voltage during a spike is not modeled. For visualization purposes, it is common to “paste” spikes on top of graphs of voltage of integrate-and-fire neurons. However, these are just to make the graph look more biological, but are not really part of the model.

E.5 The model f - I curve

When the applied current I_{app} is larger than a threshold value, the neuron spikes repetitively. This threshold value will be denoted $I_\theta = g_L(V_\theta - V_L)$. An example f - I curve is plotted in Figure E.5b. For large currents, the rate is approximately linear, with a slope approaching

$$\frac{df}{dI_{app}} \rightarrow \frac{1}{C(V_\theta - V_0)} \quad (\text{E.3})$$

as $I_{app} \rightarrow \infty$. This is the gain of the f - I curve. The exact form of $f(I_{app})$ is given in the exercises. While it is a bit complex, it has the simple approximation shown in Figure E.5b,

$$f \approx \frac{[I_{app} - g_L(V_{1/2} - V_L)]^+}{C(V_\theta - V_0)} \quad (\text{E.4})$$

where we've defined the rectification nonlinearity

$$[u]^+ = \max\{u, 0\} = \begin{cases} u, & u \geq 0 \\ 0, & u < 0 \end{cases}$$

This is exact in the limit $I_{app} \rightarrow \infty$, but has error at small rates (dashed line).

The simple linear behavior at high applied currents is due to the fact that the leakiness of the integrate-and-fire neuron becomes negligible at high firing rates. Therefore the voltage increases approximately linearly with time from V_0 to V_θ during interspike intervals. Making the neuron spike requires injecting an amount of charge given by $C(V_\theta - V_0)$. The time taken for this is the ratio of the charge to the current I , which yields the expression for firing rate.

Exercise E.1. Show that the frequency of spiking is

$$f = \frac{g_L}{C} \left[\log \left(1 + \frac{g_L(V_\theta - V_0)}{I_{app} - g_L(V_\theta - V_L)} \right) \right]^{-1} \quad (\text{E.5})$$

when I_{app} is larger than $g_L(V_\theta - V_L)$.

Exercise E.2. Derive the approximation (E.4), which has vanishing error as $I_{app} \rightarrow \infty$. The voltage $V_{1/2} = (V_\theta + V_0)/2$ is the time average of V during repetitive firing, as V increases linearly from V_0 and V_θ . Therefore $-g_L(V_{1/2} - V_L)$ is the average current dissipated by the leak conductance. Hint: Use the Taylor series expansion $[\log(1+z)]^{-1} \approx 1/z + 1/2 + \mathcal{O}(1/z^2)$.

Exercise E.3. Suppose that V is measured with respect to V_L in units of $V_\theta - V_0$, and applied current is measured in units of the threshold current $g_L(V_\theta - V_0)$,

$$v = \frac{V - V_L}{V_\theta - V_0} \quad i_{app} = \frac{I_{app}}{g_L(V_\theta - V_0)}$$

Show that the leaky integrate-and-fire model can be written in terms of these dimensionless quantities as

$$\tau \frac{dv}{dt} = -v + i_{app}$$

Figure E.6: Synaptic transmission. (a) Response to a single spike. (b) Response to a spike train.

with $\tau = C/g_L$. In the new variables, the threshold voltage and the threshold current are equal to each other, $i_\theta = v_\theta = (V_\theta - V_L)/(V_\theta - V_0)$. The reset voltage is $v_0 = (V_0 - V_L)/(V_\theta - V_0)$.

Exercise E.4. Show that the rate of repetitive firing is

$$f = \frac{1}{\tau} \left[\log \left(1 + \frac{1}{i_{app} - i_\theta} \right) \right]^{-1}$$

when $i_{app} > i_\theta$.

E.6 A synapse is a leaky integrator

Communication at a synapse from neuron j to neuron i can be studied by stimulating j with one electrode, and recording the response of i with another. Current is applied to neuron j to make it generate a spike. The membrane conductance of neuron i is measured while holding its voltage constant. As shown in Figure E.6, a single j spike causes the i conductance to increase suddenly, and then decay exponentially. If the spikes are part of a train, their effects summate.

A simple model for this is to increment the synaptic conductance g_{ij} by

$$g_{ij} := g_{ij} + \frac{\alpha_{ij}}{\tau_{ij}} \quad (\text{E.6})$$

whenever j spikes, and otherwise let it decay exponentially according to

$$\frac{dg_{ij}}{dt} = -\frac{g_{ij}}{\tau_{ij}} \quad (\text{E.7})$$

So the $i \leftarrow j$ synapse is a leaky integrator, counting spikes but forgetting them over time periods longer than τ_{ij} . The response to a single spike is a decaying exponential. The area under this exponential is given by the parameter α_{ij} . When neuron j spikes, the update (E.6) is made for all i .

The conductance g_{ij} is due to proteins called ion channels embedded in the membrane of the postsynaptic neuron. When the presynaptic neuron spikes, it secretes a packet of neurotransmitter. When the neurotransmitter molecules bind to the ion channels, they cause the channels to become permeable to ionic currents. In effect, the neurotransmitter opens very tiny holes in the membrane of the postsynaptic neuron. Eventually the ion channels close again. This can happen for a number of reasons, such as the neurotransmitter unbinding. To model this closing process, we say that g_{ij} decays as a simple exponential with time constant τ_{ij} .

chemical signaling, not electrical

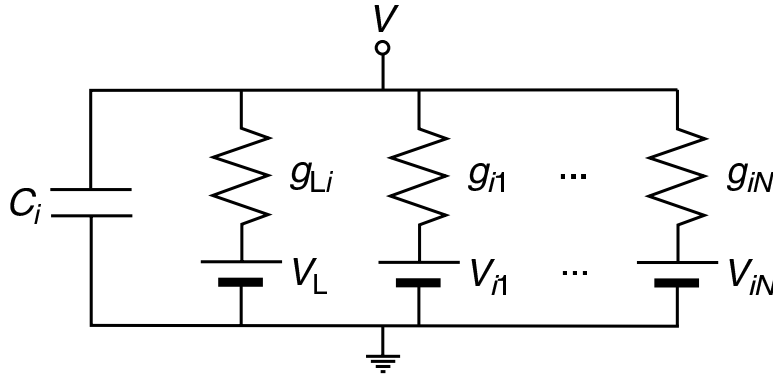


Figure E.7: Equivalent circuit for a neuron, including its synaptic inputs

E.7 Synaptic conductances modulate membrane voltage

We've seen how voltages influence synaptic conductances through discrete events called spikes. Now we'll discuss how synaptic conductances modulate voltages, thereby closing the loop and completing our model.

The equivalent circuit of Fig. (E.3) is modified by adding extra branches, one for each synapse coming into the neuron. In Fig. (E.7), the $i \leftarrow j$ synapse is represented by a battery with voltage V_{ij} in series with a conductance g_{ij} . The synapses are all connected in parallel with the membrane capacitance. In parallel there is also a battery with voltage V_{Li} and conductance g_{Li} .

The current through synapse $i \leftarrow j$ is given by the product of g_{ij} and the *driving force* $V_i - V_{ij}$. This implies that the current reverses sign when the transmembrane voltage crosses V_{ij} , which is why V_{ij} is called the *reversal potential* of the synapse.

So I_{app} in Eq. (E.1) is replaced by $-\sum_j g_{ij}(V_i - V_{ij})$ to obtain

$$C_i \frac{dV_i}{dt} = -g_{Li}(V_i - V_L) - \sum_j g_{ij}(V_i - V_{ij}) \quad (\text{E.8})$$

This equation, the reset condition (E.2), and Eqs. (E.6) and (E.7) for the synaptic conductances define a complete model for a network of integrate-and-fire neurons. The model is summarized in the box.

Network of leaky integrate-and-fire model neurons The dynamical variables are N membrane voltages V_i , and up to N^2 synaptic conductances g_{ij} . During the intervals between spikes, the dynamical variables obey the equations

$$C_i \frac{dV_i}{dt} = -g_{Li}(V_i - V_L) - \sum_j g_{ij}(V_i - V_{ij}) \quad (\text{E.9})$$

$$\frac{dg_{ij}}{dt} = -\frac{g_{ij}}{\tau_{ij}} \quad (\text{E.10})$$

Whenever the membrane potential V_j reaches a threshold value V_θ , it is reset to V_0 , and the conductances of all synapses emanating from neuron j are incremented,

$$\text{If } V_j = V_\theta, \text{ then } V_j := V_0 \text{ and} \quad (\text{E.11})$$

$$g_{ij} := g_{ij} + \frac{\alpha_{ij}}{\tau_{ij}} \quad \forall i \quad (\text{E.12})$$

E.8 Excitatory versus inhibitory synapses

Let's take a more careful look at how synaptic conductances affect the membrane voltage. You can think about the dynamics of the equivalent circuit in Fig. (E.7) as a tug of war between batteries. Each battery wants to pull the membrane voltage to its own reversal potential. The strength of each battery in this tug of war is set by its corresponding conductance. Let's see how this works mathematically.

If all conductances were constant in time, the voltage V_i would exponentially approach the value

$$V_\infty = \frac{g_{Li}V_L + \sum_j g_{ij}V_{ij}}{G_i}$$

where the total conductance G_i is defined by

$$G_i = g_{Li} + \sum_j g_{ij}$$

This result can be obtained by setting $dV_i/dt = 0$ and solving Eq. (E.9) for V_i . In other words, the voltage approaches a value given by the weighted average of the reversal potentials, where the weightings are given by the corresponding conductances. If one conductance is much larger than the others, it will dominate the average, so that the voltage will approach its reversal potential.

A synaptic conductance is defined as excitatory if its reversal potential is greater than the threshold voltage, and inhibitory if its reversal potential is less than the threshold voltage. You might have expected that an excitatory synapse would be defined as one with a reversal potential that is greater than the resting potential. But this is not a good definition. If the reversal potential is between the resting potential and the threshold, then the synapse will not be able to drive the neuron to fire. In fact, when the neuron is near threshold, the synapse will be dragging the voltage downward.

E.9 Limitations of the model

cable theory

- active dendrites

- synaptic dynamics

- voltage dependence of NMDA receptor

E.10 References

Detailed accounts of the biophysics of neurons can be found in Koch, Dayan and Abbott, Johnston and Wu, and Hille.

Troyer and Miller discuss the modeling of cortical neurons as leaky integrate-and-fire neurons.