Chapter 2

The neuron and minimal spiking models.

Neurons stand out from other cells because of their extensive structures, which allow them to target and interact with specific cells located far away, and because of their active electrical properties, which allow them to send rapid signals to those distal cells. In Chapters 2 and 4 we focus on the electrical responses of neurons, while connections between neurons are the subject of Chapter 5.

At the end of this chapter, Table 2.2 contains the meaning and a description of each of the many variables used throughout Chapter 2.

2.1. The Nernst equilibrium potential.

Our brains consume energy—1/4 of the total energy of the body, in spite of being 1/50 of the body's mass in the average human. Much of this energy consumption is in the maintenance of ongoing electrical activity in neurons. The electrical activity arises from the rapid flow of ions back and forth across the cell membrane. The flows of different types of ion conspire to produce spikes in the membrane potential—an electrical potential difference between the inside and outside of the cell—that can travel down axons of neurons. Since ions are electrically charged, their movement across the membrane must be propelled by a driving force that acts like the electromotive force of a battery. It is the continual recharging of tens of billions of such tiny effective batteries that requires so much energy.

Box 2.1. Membrane potential: The potential difference across the cell membrane, which can vary across a range of tens of millivolts in neurons.

Box 2.2. Voltage spike: Also called an action potential, a rapid upswing in the membrane potential that can propagate down the axon of a neuron and enable fast transmission of information throughout the brain and the body.

Box 2.3. Ion channel: A channel allowing entry or exit of a particular type of ion into or out of the cell through the cell membrane. Ion channels can be passive, with fixed conductance, or active, with a conductance that depends on conditions such as the membrane potential.

An effective battery is generated by the differences in the concentration of ions across the membranes of neurons. When an ion channel opens in the membrane, it permits a specific type of ion to flow through it. The ions flow preferentially from high concentration to low concentration, tending to reduce the concentration-difference. However, the concentration-difference is maintained by the ATP-dependent action of ion pumps and exchangers in the neural cell membrane. The pumps are constantly expending energy to move ions "upstream" against the concentration gradient they have produced. By doing this, the pumps are recharging the effective batteries that drive the flow of electrical current into and out of active neurons (see Section 1.3.3).

The flow of ions through a channel can be combatted by an electrical potential difference that drives the ions in the opposite direction of their concentration gradient. The value of such a potential difference at which the electrical force exactly matches the force

due to the concentration gradient across the cell-membrane of a specific type of ion is the Nernst potential for that ion. If the potential difference between the inside and the outside of a cell is equal to the Nernst potential of a particular ion, then there is no net flow of that ion across the membrane through an open channel. Any inward flow is balanced by outward flow, such balance leading to the Nernst potential also being called the Nernst equilibrium.

Box 2.4. Nernst potential: Also called reversal potential, the membrane potential at which the flow of a particular ion is in a dynamic equilibrium, meaning the outflow is precisely matched by the inflow of that ion.

If the concentration of ions within the cell is identical to that outside the cell, then the Nernst potential is zero, since any drift of ions by chemical diffusion into the cell is balanced by chemical diffusion out of the cell and any potential difference would break that balance.

The derivation of the formula for the Nernst potential depends on some physics and is left to the Appendix (Eqs 2.23 to 2.27), but its properties can be understood without the details of the derivation. For an ion, A, of charge z_A, with intracellular concentration $[A_{in}]$ and extracellular concentration $[A_{out}]$, the Nernst potential for that ion, E_A, is given by:

$$E_A = \frac{k_B T}{z_A q_e} \ln\left(\frac{[A_{out}]}{[A_{in}]}\right), \qquad \text{Eq. 2.1}$$

where T is the temperature in absolute units of Kelvin, k_B is the Boltzmann constant ($1.38 \times 10^{-23} JK^{-1}$), which converts units of temperature to units of thermal energy, and q_e is the fundamental electronic charge (*i. e.*, the charge of an electron, $1.60 \times 10^{-19} C$).

Ion	Charge	Internal Concentration	External Concentration	Nernst Potential
Sodium	+1	15mM	120mM	55.5mV
Potassium	+1	150mM	6mM	-86.0mV
Calcium	+2	50nM	2mM	141.5mV
Chloride	-1	10mM	120mM	-66.4mV

Table 2.1. Ions and their properties. The most common species of ions that flow through ion channels in neurons with some typical values of their intracellular and extracellular concentrations alongside the Nernst potentials so-produced at 37°C (310K).

For an ion such as sodium with unit positive charge, a quick calculation of the factor in front of the natural logarithm yields a value of 25.1 mV at a typical lab temperature of 18°C (291K) and a slightly higher value of 26.9 mV at human body temperature (37°C = 310K). This sets the scale of typical changes in neural membrane potentials to be in the tens of millivolts, since even a 100-fold concentration ratio would lead to an additional factor of only 4.6 after taking the natural log in Eq. 2.1.

The temperature-dependence of the Nernst potential is a consequence of the kinetic energy of ions being proportional to absolute temperature: a greater electrical potential difference is needed to counteract diffusion when the ions move more rapidly. It is important to bear this in mind when measuring the membrane potentials of neurons in the laboratory and extrapolating to their operation at body temperatures *in vivo*.

The Nernst potential is inversely proportional to the charge on an ion. Intuitively, this is because the electrical force on an ion is proportional to its electrical charge and to the potential difference, so the electrical force needed to counteract diffusion is achieved at a smaller potential difference if the ion has greater charge.

Since the membrane potential is measured as the internal potential minus the external potential, a positive membrane potential acts to drive positive ions out of the cell. Therefore, a positively charged ion has a positive Nernst potential when the outside of the cell has greater ionic concentration than the inside of the cell. In such a case, at the Nernst potential, the inward diffusive flow is balanced by the outward electrically driven flow of the positive ions.

The logarithmic dependence on the concentration ratio (Eq. 2.1) produces a potential difference of zero when concentrations are equal ($\log(1) = 0$). It results from the exponential reduction in the probability of an ion moving against an electrical potential gradient as that gradient increases. The dependence on the concentration ratio is important in experiments *in vitro*, where the extracellular medium (artificial cerebro-spinal fluid, aCSF) is controlled by the scientist. When different laboratories measure the properties of the same neuron, but with different concoctions for their aCSF, they will arrive at different results. *In vivo*, ionic concentrations are well-regulated. In cases such as epileptic seizures, during which neural activity is so strong that the ion pumps cannot maintain standard operating conditions, the resulting imbalance in ionic concentration and change in Nernst potentials may play an important role in bringing each seizure to an end.

Box 2.5. Equilibrium potential: Also called resting potential, the membrane potential at which the flow of electrical current from all types of ions into and out of the cell is balanced, so there is no net current and the membrane potential is not caused to change.

The potential at which total currents into and out of the cell are balanced is the "equilibrium potential" (also called the resting membrane potential or leak potential). The membrane potential moves toward this balance point when not driven away from it by sources of electrical current. The equilibrium potential is negative for most neurons, from which we can deduce that the dominant channels transmit either positive ions with a high internal concentration or negative ions with a high external concentration. These conditions are satisfied by potassium ions and chloride ions (respectively), which both have negative Nernst potentials (Table 2.1). Sodium ions and calcium ions, both of which can open to produce strong current influx to the neuron, have positive Nernst potentials, but their corresponding channels are almost entirely closed at equilibrium.

2.2. An equivalent circuit model of the neural membrane.

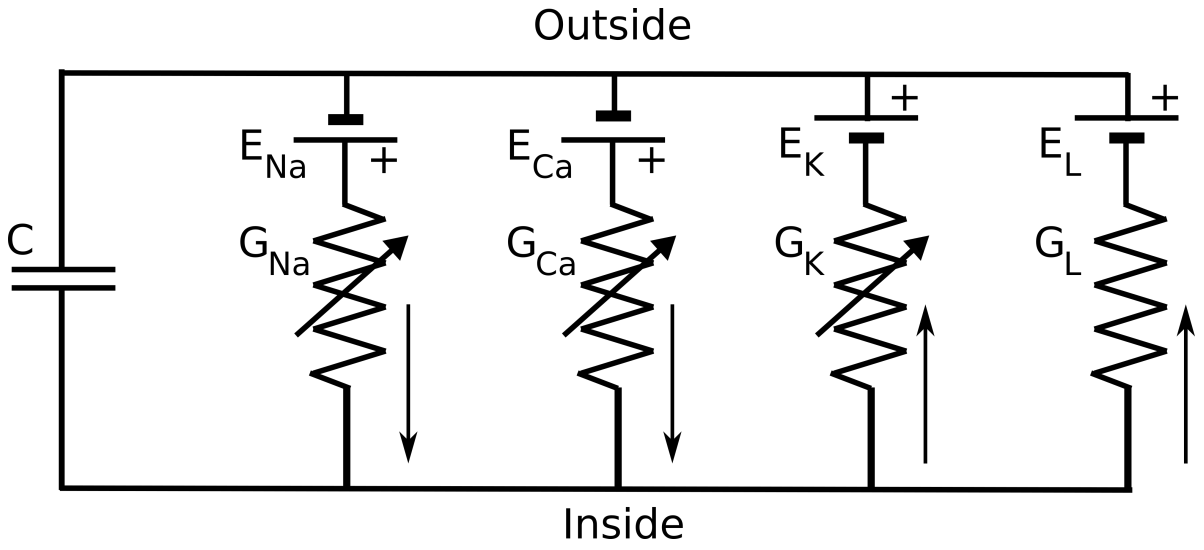

Figure 2.1. The equivalent circuit representation of the neuron's membrane. Various ion channels, each type represented by a resistor in series with a battery, span the cell membrane. All operate in parallel with each other—so their conductances sum—and with a capacitor, which represents the insulating cell membrane. The battery for a type of ion channel is directed to bring the membrane potential (electrical potential on the inside of the membrane minus the potential on the outside) to the Nernst equilibrium potential for that ion. Types of ion channels with a variable total conductance—sodium (G_{Na}), calcium (G_{Ca}), and potassium (G_K)—are represented by the arrow through the resistor, whereas the leak conductance, G_L, is defined as a constant. The vertically directed arrows indicate the direction of current flow when the membrane potential is at zero or another intermediate value. If all channels with variable conductance are closed so that no current flows through the central parallel paths in the above circuit, then current will flow through the leak channels (charging the capacitor) until the inside of the cell membrane is at the leak potential E_L.

Membranes of neurons, like other cells, are formed by a lipid bilayer, which is a hydrophobic electrical insulator that does not permit ions to flow across it. Rather, charge can be stored on its surface, so the membrane acts as a capacitor with a capacitance (capacity to store charge) that is proportional to its area.

Within the lipid bilayer are implanted ion pumps and ion channels. The action of the pumps is to create concentration differences across the membrane for specific ions. The action of pumps produces the separate Nernst potentials for each ion (Table 2.1) and does not have to be explicitly modeled.

Ion channels are selective, often permitting the flow of only one species of ion. When open, they pass electrical current in the direction needed to bring the membrane potential toward the Nernst potential of the specific ions that flow through the channel. That is, if the Nernst potential is more positive than the membrane potential, then positive ions flow into the cell or negative ions flow out of the cell, either of which would make the membrane potential more positive. Conversely, if the Nernst potential is more negative than the membrane potential, then positive ions flow out of the cell or negative ions flow into the

cell, either of which would make the membrane potential more negative. For this reason, the Nernst potential for a channel is also called its *reversal potential*.

Each type of ion channel can be modeled as a battery in series with a resistance (Figure 2.1). The inverse of the resistance—the conductance—is proportional to the number of open channels. In many cases this conductance is both temperature- and voltage-dependent. The capacitance of the membrane—its ability to store charge—is not affected by channels opening and closing because these channels make up only a tiny fraction of the membrane's total surface area. The capacitance is therefore treated as a constant in all standard models.

We can use the equivalent circuit to determine the resting membrane potential, which is the potential at which the electrical charge on the capacitor remains constant, *i. e.*, at which there is no net flow of current into or out of the cell. When the potential difference across the circuit is equal to the resting potential, the currents through each of the resistors must cancel, so that inward currents through sodium and calcium channels are matched by outward currents through the potassium and leak channels. The current through a channel is given by:

$$I_i = G_i(V_m - E_i)$$

where the index, i, represents the type of channel. In this terminology, which is standard, a positive current is one that flows out of the cell. When the cell is at equilibrium the different currents balance each other out and sum to zero:

$$I_m = \sum_i I_i = \sum_i G_i(V_m - E_i) = 0, \qquad \text{Eq. 2.2}$$

where I_m is the total membrane current.

In the specific circuit of Figure 2.1, the equilibrium condition in Eq.1.2 becomes:

$$G_{Na}(V_m - E_{Na}) + G_{Ca}(V_m - E_{Ca}) + G_K(V_m - E_K) + G_L(V_m - E_L) = 0. \qquad \text{Eq. 2.3}$$

Solving Eq. 2.3 for V_m, we find that the resting membrane potential, at which no net current flows, is a weighted average of the individual Nernst potentials:

$$V_m = \frac{G_{Na}E_{Na} + G_{Ca}E_{Ca} + G_K E_K + G_L E_L}{G_{Na} + G_{Ca} + G_K + G_L}. \qquad \text{Eq. 2.4}$$

The derivation of the resting membrane potential is typically more complicated, because the conductance values themselves depend on the membrane potential, However, in general the membrane potential of the cell moves toward the Nernst potential of the ion channel whose conductance is greatest.

We can begin to understand the dynamics of the changing membrane potential by first focusing on the passive properties of the cell, *i. e.,* its properties when all ion channels have fixed conductance. These constant values of conductance can be gathered together and combined as a single leak conductance. The resting potential then acts as the leak potential and the entire circuit reduces to the outer loop of Figure 2.1.

The membrane potential is generated by the charge stored on the membrane. It depends on both the stored charge and the membrane's capacitance, C_m, via the standard equation for a capacitor (Section 1.3.1):

$$Q = C_m V_m. \qquad \text{Eq. 2.5}$$

We use the convention that positive charge on the inner surface produces a positive membrane potential. Recalling that current is defined as positive when it flows out of the

cell, the rate of change of charge on the inside of the cell's membrane is the negative of the total membrane current, which can be written as:

$$\frac{dQ}{dt} = -I_m = -G_L(V_m - E_L). \qquad \text{Eq. 2.6}$$

Since the capacitance is fixed, Eqs 2.5 and 2.6 can be combined to yield the dynamics of the membrane potential as:

$$C_m \frac{dV_m}{dt} = G_L(E_L - V_m). \qquad \text{Eq. 2.7}$$

This is a linear, first-order ordinary differential equation—the one differential equation whose solution all scientists should know (Section 1.4.1)—which tells us that the membrane potential follows an exponential decay from any initial value to its steady state value, E_L. The time constant of the decay is $\tau_m = C_m/G_L$ or $\tau_m = R_m C_m$ where $R_m = 1/G_L$ is the total membrane resistance. The equation for the time-dependence of the membrane potential, $V_m(t)$, when it is initially at a value of $V_m(0)$ is:

$$V_m(t) = E_L + [V_m(0) - E_L]\exp(-t/\tau_m). \qquad \text{Eq. 2.8}$$

We will use the term exponential decay for any such exponential function whose rate of change approaches zero at large times, even if the function increases with time rather than decreases (Figure 2.2).

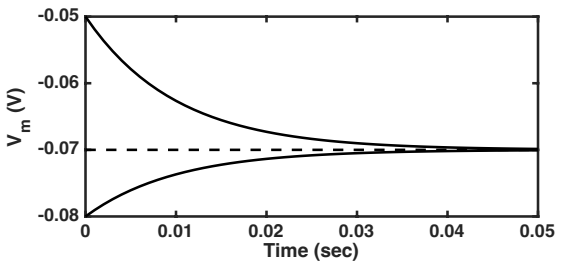

Figure 2.2. Exponential decay of the membrane potential. A leak potential of -70mV (dashed line) is reached by exponential decay with a time constant of 10ms. The solid curves follow the equation above, but differ in their initial conditions, $V_m(0)$, which is -50mV (upper curve) or -80mv (lower curve). This figure is created by the online code `exponential.m`.

2.2.1. Depolarization versus Hyperpolarization

In simple models, the resting potential—the neuron's equilibrium in the absence of inputs—is at the leak potential, E_L, in the range of -60mV to -75mV. The negative resting membrane potential means the interior of the neuron is at a negative potential compared to the exterior, because of a net removal of positive ions from the cell. Since like charges repel each other, the excess internal negative charge builds up on the cell's membrane. The membrane is therefore polarized, with negative charge on the inner surface and positive charge on the outer surface. An inward current (positive charge flowing into the cell) reduces the charge imbalance across the membrane. Since the reduction in charge imbalance reduces the polarization of the membrane, such an inward current is termed a depolarizing current. Conversely, an outward current that removes positive charge from the cell (or injects negative charge) and increases the membrane's polarization is termed a hyperpolarizing current.

Box 2.6. Depolarization: Increase of the membrane potential toward a more positive value through inward electrical current.

Box 2.7. Hyperpolarization: Decrease of the membrane potential toward a more negative value through outward electrical current.

Table 2.1 reveals that when sodium and calcium channels are open they produce a depolarizing, inward current, whereas when potassium channels open they produce a hyperpolarizing outward current. Chloride channels are interesting as the current they produce can be depolarizing or hyperpolarizing depending on the exact reversal potential of chloride ions and the value of the membrane potential. Late in development the current through chloride channels tends to be hyperpolarizing, or at least sufficient to inhibit depolarization. However, early in development, the difference in chloride ion concentrations across the membrane is not quite so stark, so the reversal potential for chloride ions is less negative, making the chloride current depolarizing.

2.3. The leaky integrate-and-fire model.

The leaky integrate-and-fire (LIF) model[1] is a good starting point for simulating neurons, because it reproduces some of the qualitative features of the membrane potential's dynamics, it emits spikes at a rate that increases with injected current, and it introduces a framework upon which we can build more realistic models of neurons.

The LIF model is a differential equation for the membrane potential of a neuron with a capacitance and a leak term (the outer loop of the equivalent circuit in Figure 2.1) combined with an additional caveat: When the membrane potential reaches a particular value—the threshold—a spike is emitted and the membrane potential is returned to a low, reset value. In this manner, spikes are added to the model artificially to make up for the neglect of the voltage-dependent sodium and potassium channels that would otherwise produce a biophysical spike. We hold off our discussion of the mechanisms of biophysical spikes until Chapter 4.

One of the most common electrophysiological measurements of a neuron is its response to injected current. To simulate such externally applied current, we include an additional term, I_{app}, in the dynamical equation for the membrane potential, which follows:

$$C_m \frac{dV_m}{dt} = G_L(E_L - V_m) + I_{app} \;\; ; \;\; \text{if } V_m > V_{th} \text{ then } V_m \mapsto V_{reset}. \qquad \text{Eq. 2.9}$$

The first part of Eq. 2.9 produces leaky integration. In the absence of the leak conductance, the membrane potential would perfectly integrate the applied current as charge is added to the cell's membrane. However, the conductance term causes charge to leak out and the voltage to decay with the time constant of C_m/G_L. The second part is the "fire", which includes a reset. Notice that the spike itself does not appear in the dynamics of the membrane potential—to see a spike of the membrane potential in any simulation of the LIF model it must be put in by hand before the membrane potential is reset. Spike times are recorded at the time when the membrane potential crosses the threshold.

Box 2.8. Threshold current: The amount of inward current needed before a neuron or a model neuron produces spikes.

The behavior of the leaky integrate-and-fire neuron in response to three different levels of applied current is shown in Figure 2.3. It can be seen that if the applied current is insufficient then the membrane potential does not reach threshold and the model neuron does not produce any spikes (Figure 2.3A). The threshold current needed to produce spikes can be determined by calculating the membrane potential reached by the neuron in the presence of a fixed applied current, while ignoring the "fire" and reset mechanism. Setting $\frac{dV_m}{dt} = 0$ in Eq. 2.9 reveals the steady state membrane potential, V_m^{ss}, to be

$$V_m^{ss} = E_L + I_{app}/G_L. \qquad \text{Eq. 2.10}$$

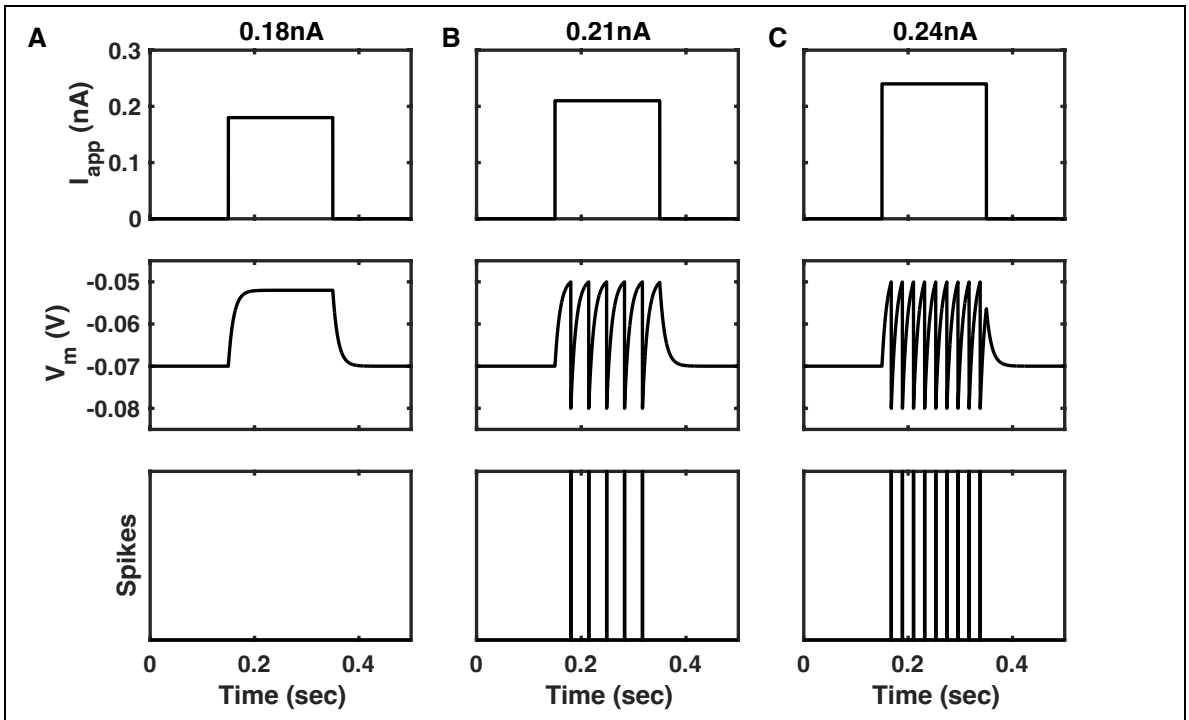

Figure 2.3. Behavior of the leaky integrate-and-fire neuron. Membrane potential of the model neuron (Eq. 2.7) in response to three different 200ms current pulses (top) is depicted in the middle row, with spike times indicated by vertical lines in the bottom row. Parameters of the model are: $C_m = 100pF$, $G_L = 10nS$, $E_L = -70mV$, $V_{th} = -50mV$, and $V_{reset} = -80mV$. Combining these parameters yields a time constant of $\tau_m = 10ms$ and $I_{th} = 200pA$. This figure was created by the online code `LIF_model.m`.

If the steady state is below threshold then the model neuron does not fire. The threshold current, I_{th}, is the applied current needed to ensure steady-state membrane potential reaches the threshold (*i.e.*, $V_m^{ss} = V_{th}$) so that spikes can be produced. This requirement, when combined with Eq. 2.10, leads to

$$I_{th} = G_L(V_{th} - E_L). \qquad \text{Eq. 2.11}$$

Box 2.9. Steady state: The state of a system, as described by the values of all of its variables, which the system approaches and at which it remains without further change.

2.3.1. Specific versus absolute properties of the cell

In the equivalent circuit and the formulae derived from it so far, we have included the cell's properties as parameters that depend on the ability of the total membrane of the cell to either store charge or allow its passage. These properties depend on the cell's surface area. An equivalent formalism is possible using the specific properties of the cell membrane. For example, the resistivity or specific resistance of the cell's membrane is the resistance of a unit area of membrane. Similarly, the specific capacitance is the capacitance per unit area of membrane. We use lower case letters to denote these specific or intrinsic properties of the cell's membrane and upper case letters to denote the total value for the cell. The relationships between specific and absolute properties are:

$$C_m = Ac_m \; ; \; R_m = r_m/A \; ; \; G_L = Ag_L.$$

The equation for the leaky integrate-and-fire neuron is unchanged if specific units are used, so long as in place of total injected current, I_{app}, the current per unit area, $i_{app} = I_{app}/A$, is used. In neural circuits, current enters each cell through ion channels, which are likely to become more numerous as the cell's size increases. Therefore, the total current is likely to increase with the size of the cell, making current per unit area a quantity that could be less variable across cells. The dynamics of the membrane potential then follows:

$$c_m \frac{dV_m}{dt} = g_L(E_L - V_m) + i_{app}, \qquad \text{Eq. 2.12}$$

which is obtained from the previous equation for the LIF model (Eq. 2.9), once the cell's surface area is divided out on both sides.

In the simplest neural models, such as the LIF model, the cell's surface area does not impact the membrane potential's dynamics so long as the applied currents are scaled accordingly. In more sophisticated models in which the spatial structure of the cell is considered, the relative areas of different sections of the cell are important. When charge flows from one part of the cell to another, its effect on the local membrane potential depends on the surface area over which it is distributed—the smaller the region, the bigger the effect for a given amount of charge transfer. In models that incorporate any effect of the concentration of an ion—in particular the concentration of calcium—then it is important to consider that the ions of a particular species spread out over a volume (concentration depends on inverse volume) while the excess charge in a region is stored on the surface, so a factor converting surface area to volume is needed. Such a factor would be size- (and shape-) dependent.

2.3.2. Firing rate as a function of current (f-I curve) of the leaky integrate-and-fire model.

When the applied current is held fixed, the time for the neuron's membrane potential to increase from its reset value to the threshold can be calculated. We use the formula for the passive properties of the cell to obtain the equation for the membrane potential as a function of time while it is below threshold. We set the initial value of the membrane potential to the reset level and use Eq. 2.10 for the steady state of the membrane potential, V_m^{ss}, to obtain the solution of the leaky-integration part of Eq. 2.9 as

$$V_m(t) = V_m^{ss} + [V_{reset} - V_m^{ss}]\exp(-t/\tau_m). \qquad \text{Eq. 2.13}$$

In Eq. 2.13, the time, t, corresponds to the time since the previous spike when the membrane potential was last reset to V_{reset}.

We want to find the time, T, when the next spike is produced. We know then that at time, T, the membrane potential has increased to the threshold, so $V_m(T) = V_{th}$. Therefore, the equation to solve for T is:

$$V_{th} = V_m(T) = V_m^{ss} + [V_{reset} - V_m^{ss}]\exp(-T/\tau_m). \quad \text{Eq. 2.14}$$

Eq. 2.14 can be rearranged as:

$$\exp(-T/\tau_m) = \frac{V_m^{ss} - V_{th}}{V_m^{ss} - V_{reset}}. \quad \text{Eq. 2.15}$$

The term on the right of Eq. 2.15 must be positive and less than 1 for a solution to exist with $T > 0$ (since $0 < e^{-x} < 1$ for all real $x > 0$), which corresponds to a requirement that $V_m^{ss} > V_{th}$. Such a requirement is just the mathematical way to indicate that we can only calculate the time between spikes if the membrane potential increases above threshold so as to produce spikes.

The solution of Eq. 2.15 for the time from one spike until the next—that is the inter-spike interval, ISI—is found as:

$$ISI = T = -\tau_m \ln\left(\frac{V_m^{ss} - V_{th}}{V_m^{ss} - V_{reset}}\right) = \tau_m \ln\left(\frac{V_m^{ss} - V_{reset}}{V_m^{ss} - V_{th}}\right). \quad \text{Eq. 2.16}$$

Therefore, the firing rate of the neuron, the inverse of the inter-spike interval, is:

$$f(I_{app}) = \frac{1}{ISI} = \frac{1}{\tau_m \ln\left(\frac{V_m^{ss} - V_{reset}}{V_m^{ss} - V_{th}}\right)} = \frac{1}{\tau_m \ln\left(\frac{E_L + I_{app}/G_L - V_{reset}}{E_L + I_{app}/G_L - V_{th}}\right)}. \quad \text{Eq. 2.17}$$

While the formula looks complicated, this is a rare case where the firing rate curve can be written in terms of standard mathematical functions, and so can be plotted easily following a calculation rather than requiring a simulation. In Tutorial 2.1, the calculated curve will be compared with the simulated curve.

Box 2.10. Inter-spike interval (ISI): The time between two successive voltage spikes.

2.4. Tutorial 2.1: The f-I curve of the leaky integrate-and-fire neuron.

You should be familiar with the material in Sections 1.3, 1.4.1, 1.5 & 1.6 before completing this tutorial.

Neuroscience goals: understand why firing rate increases with current, why the increase is sharp at threshold in the LIF model, and how noise causes a smoothing of the f-I curve.

Computational goals: gain experience using the forward Euler method, recording data from nested for loops, and using the random number generator to add noise.

1) a) Write a code to simulate a model leaky integrate-and-fire neuron from the equation

$$C_m \frac{dV_m}{dt} = (E_L - V_m)/R_m + I_{app}$$

with the condition if $V_m > V_{th}$ then $V_m \mapsto V_{reset}$, by following the steps below:

(i) Define parameters with your choice of variable names that are understandable, setting the values to be: $E_L = -70\text{mV}$, $R_m = 5\text{M}\Omega$ and $C_m = 2\text{nF}$. Assume the spike threshold for the neuron is at $V_{th} = -50\text{mV}$ and the reset potential is $V_{reset} = -65\text{mV}$.
(ii) Create a time vector with steps of $\Delta t = 0.1\text{ms}$ from $t = 0$ to a maximum time of $t_{max} = 2\text{s}$.
(iii) Create a vector for the membrane potential, V, of identical size to the time vector.
(iv) Set the initial value of the membrane potential (the first value in its array) to the leak potential, E_L.
(v) Create a vector for the applied current, I_{app}, of identical size to the time vector with each entry set to a constant value, I_0, to be determined later.
(vi) Set up a '`for`' loop with an index running from 1 to the number of points in the time vector. This loop will be used to integrate through time.
(vii) Within the '`for`' loop update the membrane potential using the Forward Euler method (Section 1.6.1) or your preferred method of integration.
(viii) Within the '`for`' loop at each time point test if the membrane potential is above threshold (use an '`if`' statement) and if it is so, reset the membrane potential to V_{reset}.

b) What is the minimum applied current needed for the neuron to produce spikes? Calculate this current from Eq. 2.11, then simulate the model with applied currents (i) slightly lower than and (ii) slightly higher than this value to check you are correct. Plot the membrane potential, $V(t)$, over a time interval of 200ms (or a complete inter-spike interval if that is longer).

c) Make another `for ... end` loop to use at least 10 different values of I_{app}, one value for each 2s simulation (a "trial") such that the average firing rate (f) varies in the range from 0 to 100 Hz. Plot the resulting firing rate vs. injected current (called the firing-rate curve or f-I curve).

Hint: You will need to create one vector that stores each value of I_{app} and a vector of the same size to store the corresponding firing rates. In each trial, you need to count spikes and convert to a firing rate. You will plot these two vectors against each other after simulating all trials.

d) Compare, by plotting with different symbols on the same graph produced in 1c, the curve you obtain from the equation below for the firing rate of the neuron as you vary injected current:

$$\frac{1}{f} = \tau_m \ln\left(I_{app}R_m + E_L - V_{reset}\right) - \tau_m \ln\left(I_{app}R_m + E_L - V_{th}\right)$$

Note: You will need to use an `if` *statement or* `max` *function to ensure natural log of negative numbers are not taken if plotting over a wide range of* I_{app}.

2) a) Add a noise term to the simulation of Q.1 by adding to the total membrane potential change at each time step (see Section 1.6.6 for an explanation of the square-root term):

```
np.random.randn()*sigma_V*np.sqrt(dt)
```

or you can use a value taken from an entire vector of noise for each time point, generated as:

```
noise_vec =
np.random.randn(len(t))*sigma_V*np.sqrt(dt)
```

Make sure you use a different set of random numbers for each simulation with a different current.

b) Plot the firing-rate curve (firing-rate as a function of I_{app}) for at least 2 different values of `sigma_V` (increase `sigma_V` until you notice a change from the result with a value of zero, but keep `sigma_V` fixed in each firing-rate curve). Explain the effect of increasing `sigma_V`, which is proportional to the standard deviation of the voltage noise.

c) Test that your code is correct by repeating a simulation with your time-step, `dt`, a factor of ten smaller. Are the results very different?

2.5. Extensions of the leaky integrate-and-fire model.

2.5.1. Refractory period

The LIF model replaces the dynamics of opening and closing of ion channels that produce a spike in the membrane potential with the simple rules, "record the spike time" and "reset the membrane potential". 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, τ_{ref}, is related to the time it takes for ion channels to return to their steady state configurations at the resting membrane potential. While this time-course is cell-type specific, a typical refractory period of $\tau_{ref} = 2$ms, when added to models, limits the maximum firing rate to 500Hz (a rate still much higher than that ever observed in most real neurons). The refractory period can be included in models of neurons in a number of ways.

Box 2.11. Refractory period: The minimum time interval between one spike and another spike from a neuron, during which depolarizing ion channels can no longer open as they return back to their baseline state.

Method (1), Forced voltage clamp. Perhaps the simplest method clamps or fixes the voltage at its reset value following a spike for the duration of the refractory period (Figure 2.4A). One 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 can decrease with increased input in such a model, in contrast to the behavior of real neurons.

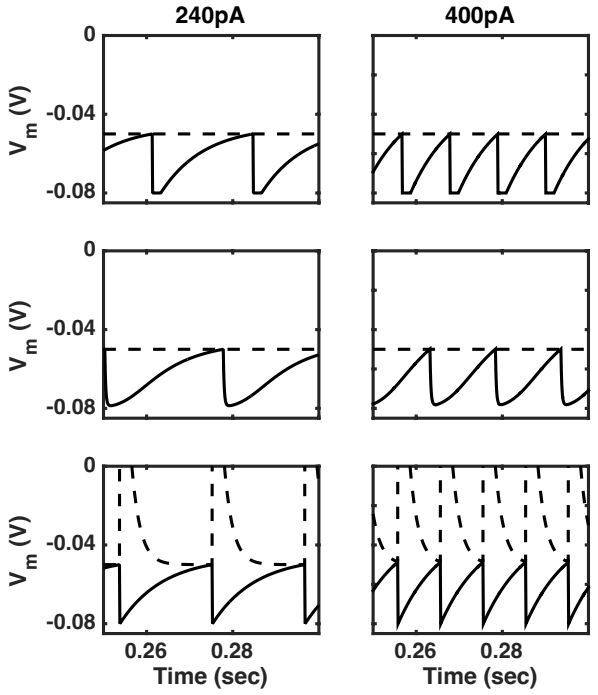

Figure 2.4. Three methods for incorporating a refractory period in an LIF model. Top: Method (1), a hard reset with the membrane potential fixed at the reset value for the refractory period. **Middle:** Method (2), a refractory conductance brings the membrane potential to reset. Its effect lingers as the conductance decays while the membrane potential rises, slowing the rate of spikes. **Bottom:** Method (3), following a hard reset the membrane potential can rise immediately, with the refractory period ensured by a raised threshold (dashed line). Solid line = membrane potential; dashed line = threshold voltage. Left column, input current is 240pA. Right column, input current is 400pA. This figure was created by the online code `LIF_model_3trefs.m`.

Method (2), Refractory conductance. The refractory period can be mimicked by addition of a large conductance that produces an outward (hyperpolarizing) potassium current[2]. Following this method, the refractory conductance increases at the time of each spike and decays between spike times with a short time constant:

$$\frac{dG_{ref}(t)}{dt} = -\frac{G_{ref}(t)}{\tau_{ref}} \text{ and after a spike } G_{ref} \mapsto G_{ref} + \Delta G. \qquad \text{Eq. 2.18}$$

The potassium current produced by this refractory conductance yields an additional term of

$$G_{ref}(t)[E_K - V_m(t)]$$

on the right-hand side of the dynamical equation for the LIF neuron (Eq. 2.9). When $G_{ref}(t)$ is much greater than the leak conductance, this extra term clamps the membrane potential at the Nernst potential for potassium ions, E_K. Therefore, the reset step of the LIF model

can be omitted in simulations using method (2), because the step increase in $G_{ref}(t)$ at the time of a spike causes the desired drop in membrane potential.

Since the refractory conductance persists beyond its time constant while it decays exponentially, it can delay later spikes (Figure 2.4B). Unlike method (1), method (2) has the benefit that, like real neurons, 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.

Method (3), Raised threshold. The voltage threshold for producing a spike can be raised immediately following a spike and allowed to decay back to its baseline level with a short time constant:

$$\frac{dV_{th}(t)}{dt} = \frac{V_{th}^{(0)} - V_{th}(t)}{\tau_{ref}} \text{ and after a spike } V_{th} \mapsto V_{th} + \Delta V. \qquad \text{Eq. 2.19}$$

Method (3) allows the mean membrane potential to increase with firing rate—as is typically observed—while preventing a spike during a refractory period. As with method (2), 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. The raised threshold can be combined either with a hard reset of the membrane potential following a spike (Figure 2.4C), as in the standard LIF model (Eq. 2.9), or with a refractory conductance that produces a temporary drop in the membrane potential, as in method (2).

2.5.2. Spike-rate adaptation (SRA)

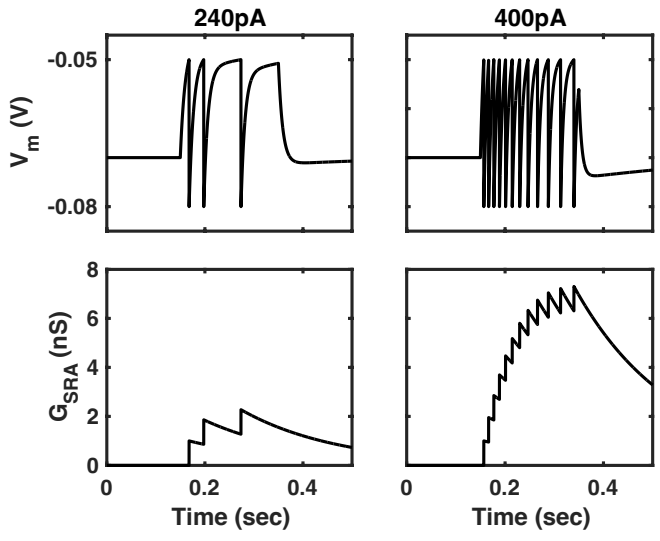

Figure 2.5. Spike-rate adaptation in a model LIF neuron. Top: the membrane potential as a function of time in response to applied current steps of the size indicated. Note the increasing separation between spike times. **Bottom:** the potassium conductance accumulates over successive spikes until its decay between spikes matches its increment following a spike (right), in which case a regular inter-spike interval is reached. This figure is created by the online code, `LIF_model_sra.m`.

Many neurons respond to a pulse of constant current with spikes that appear at a decreasing rate over the course of the current pulse, an effect known as spike-rate (or spike-frequency) adaptation. The time interval between the first and the second spike—the first inter-spike interval—can be substantially shorter than the time interval between later spikes when the response eventually becomes periodic (Figure 2.5). Such adaptation is particularly valuable and noticeable in sensory systems—for example, we have all noticed how a strong smell when we enter a room becomes less noticeable as we adapt to it. The

value of adaptation is that the neuron uses more spikes (and hence more energy) to transmit new information than older information which has already been processed by the brain.

Box 2.12. Spike-rate adaptation: A slowing down of the spike-rate (increase in ISIs) following the first-spike when a neuron responds to depolarizing input.

Spike-rate adaptation can be simulated in the LIF model by incrementing a potassium conductance following each spike in the same manner as method (2) for adding a refractory conductance[2,3]. Also, as with a refractory conductance, the conductance producing spike-rate adaptation should decay between spikes. Therefore, the changes in the LIF equations necessary for adding spike-rate adaptation are *qualitatively* identical to those necessary for adding a refractory conductance.

Yet, since spike-rate adaptation differs from a refractory period, its simulation must also differ. The difference lies in the values of two parameters. First, the increment of the conductance following each spike is much smaller for spike-rate adaptation, which does not prevent spikes, but just slows down their rate. Second, the timescale for the decay of the conductance is much longer—longer than typical intervals between spikes—so that the conductance can accumulate over a spike train (Figure 2.5B).

When we include a refractory conductance or a spike-rate-adaptation conductance in the standard LIF model, we produce a two-variable model. In these two-variable models the time-varying conductance impacts the dynamics of the membrane potential, while in return the value of the membrane potential impacts the dynamics of the conductance. In these initial models, the conductance is only affected by the membrane potential through discrete changes at the discrete times of spikes. In more general models—such as the conductance-based models of Chapter 4—the rate of change of conductance is a continuous function of the membrane potential.

2.6. Tutorial 2.2: Modeling the refractory period.

Neuroscience goals: understand how a biological feature like the refractory period can be implemented in multiple simplified ways in a model, and be aware of the consequences of different simplifications relative to the behavior of real neurons.
Computational goals: Further practice with nested "for loops" and use of conditionals to control the path of execution of the code within each "for loop". Understanding how relevant behaviors can be added into the LIF model using such computational tools. Learning how to affect the output graph to view spikes, without impacting the simulation.

In this tutorial, we will simulate the refractory period via the three different methods shown in Figure 2.4. The refractory period ensures that immediately after a spike the neuron cannot produce a second spike, so the refractory period limits the maximum firing rate of a cell.

Each of the following questions, 1-3, requires you to use just one of the different methods for producing a refractory period. In each question, you will simulate a leaky integrate-and-fire neuron for 2 seconds using a range of input currents, I_{app}, from 100-600 pA. Use the following parameters: $E_L = -70\text{mV}$, $R_m = 100\text{M}\Omega$, $C_m = 0.1\text{nF}$, such that the membrane potential follows

$$C_m \frac{dV_m}{dt} = (E_L - V_m)/R_m + I_{app}.$$

For each of the three questions, calculate and plot on the same graph the mean firing rate as a function of the input current (results for all three questions plotted on the same graph 1). On a separate graph plot the mean membrane potential as a function of the input current for each of the three questions (results for all three questions plotted on the same graph 2). On a third graph plot the mean membrane potential as a function of firing rate for each of the three questions (results for all three questions plotted on the same graph 3). That is, you will produce three graphs in total, each of which will contain three curves, with differences between the curves arising from the different models used in each question. Explain any trends and any non-monotonic behavior, as well as the differences between the curves in each figure.

Also, for each question, plot the membrane potential as a function of time for 100ms when $I_{app} = 220$ pA and on the same trace in a different color, when $I_{app} = 600$ pA. For the membrane potential trace, use a different graph for each question. For each membrane potential trace, make each spike uptick visible by plotting a rise in the membrane potential up to a peak value, $V_{peak} = 50$ mV, for a single time-point. You should only add the peak to each spike, by altering every voltage above threshold to be V_{peak}, after the simulation through time is complete, as otherwise you will disrupt the voltage-update rule.

Q.1) Forced Voltage Clamp.
Assume the spike threshold for the neuron is fixed at $V_{th} = -50$mV and the reset potential is $V_{reset} = -65$mV. If $V_m > V_{th}$ then set $V_m = V_{reset}$ and record the spike time. Following a spike, until the time is greater than the time of the last spike plus the refractory period, $\tau_{ref} = 2.5$ ms, fix $V_m = V_{reset}$ instead of following the differential equation above (you will need to incorporate an `if` statement to check whether sufficient time since the prior spike has elapsed).
Notes: (i) You will need to initialize the time of last spike to a value less than $-\tau_{ref}$ to ensure the simulation does not commence in a refractory period.
(ii) To plot the spikes in the membrane potential you can either plot a single line that increases along the y-axis from V_{th} to V_{peak} at every spike time (using a `for` loop), or, after the simulation change each above-threshold value of the membrane potential to V_{peak}. Finally, via a "dirtier" method, when you reset the membrane potential at the time of a spike to V_{reset}, you can set the value on the previous time-point to V_{peak}. The previous value is never used again in the simulation, so does not affect results. The shift of the time of the spike by the time-step, Δt, will be unnoticeable in any figure.

Q.2) Threshold increase.
Make the voltage threshold dynamic so that it follows

$$\frac{dV_{th}(t)}{dt} = \frac{V_{th}^{(0)} - V_{th}(t)}{\tau_{Vth}},$$

with the baseline, $V_{th}^{(0)} = -50$ mV, an initial condition $V_{th}(0) = V_{th}^{(0)}$ and a refractory time constant, $\tau_{Vth} = 1$ ms.

If $V_m(t) > V_{th}(t)$, a spike occurs. At the time of the spike set $V_m = V_{reset}$ and increase the threshold to the value, $V_{th}^{(\max)} = 200$ mV. Immediately after the spike the dynamical equations are followed for both $V_m(t)$ and $V_{th}(t)$.
Notes: Create a vector for $V_{th}(t)$ of the same size as $V_m(t)$ and update $V_{th}(t)$ in the same `for` *loop as you update $V_m(t)$.*

Q.3) Refractory conductance with threshold increase.
Simulate the leaky integrate-and-fire dynamics with the additional potassium conductance term as follows:

$$C_m \frac{dV_m(t)}{dt} = \big(E_L - V_m(t)\big)/R_m + G_{ref}(t)[E_K - V_m(t)] + I_{app},$$

where $E_K = -80$ mV and the refractory conductance follows:

$$\frac{dG_{ref}(t)}{dt} = -\frac{G_{ref}(t)}{\tau_{Gref}} \text{ and at the time of a spike } G_{ref} \mapsto G_{ref} + \Delta G.$$

Initialize the refractory conductance to zero, $G_{ref}(0) = 0$. Use the parameters $\tau_{Gref} = 0.2$ ms and $\Delta G = 2\ \mu$S. Let the voltage threshold vary in the same manner as Q.2, increasing $V_{th}(t)$ to $V_{th}^{(\max)} = 200$ mV at the time of a spike and decaying back to $V_{th}^{(0)} = -50$ mV between spikes. Do not change $V_m(t)$ at the spike-time—rather you should see a reduction in $V_m(t)$ arise (quickly but not instantaneously) because of the sudden increase in refractory conductance.
Notes: You will need to produce another vector, for $G_{ref}(t)$, of the same size as $V_m(t)$ and update it within the same `for` *loop as you update $V_m(t)$ and $V_{th}(t)$.*

2.7. Further extensions of the leaky integrate-and-fire model.

2.7.1. Exponential leaky integrate-and-fire (ELIF) model.
Perhaps the most obvious failing of the leaky integrate-and-fire model neuron is its lack of a spiking mechanism. Spikes in the membrane potential can be added to the model for aesthetic purposes, simply by setting the membrane potential to a high value such as the Nernst potential for sodium whenever it has crossed threshold, before returning it to reset (as in Tutorial 2.2). However, any electrophysiologist would be disturbed by the manner in which the membrane potential changes more and more slowly as it approaches threshold. In reality, an inflexion point—at which the decreasing gradient begins increasing—is visible in the plot of membrane potential against time for a real cell, as the voltage accelerates up past a threshold.

Moreover, careful experiments indicate there is no fixed threshold of the membrane potential. That is, neurons do not have a point of no return for production of a spike. Rather, there is a threshold range, within which a spike may or may not be produced, depending on prior and subsequent inputs.

The exponential leaky integrate-and-fire (ELIF) model[4] incorporates an additional spike-generating term in the dynamics of the membrane potential to address these failings. The differential equation becomes:

$$C_m \frac{dV_m}{dt} = G_L \left[E_L - V_m + \Delta_{th} \exp\left(\frac{V_m - V_{th}}{\Delta_{th}} \right) \right] + I_{app}, \qquad \text{Eq. 2.20}$$

where V_{th} is the threshold as before, and Δ_{th} denotes the voltage-range over which the spike-generating term becomes important and harder to overcome with inhibition.

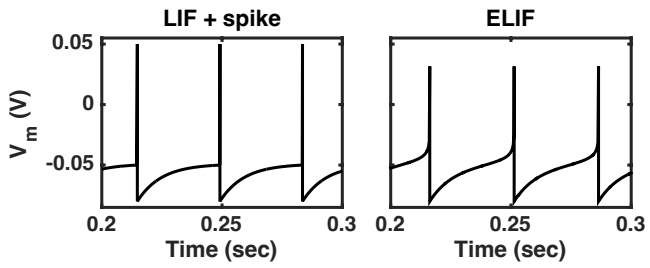

Figure 2.6. Spike generation in the ELIF model. The ELIF model (right) produces the typical inflexion of the voltage trace that is absent in the LIF model (left). Parameters are as in Fig. 2.3 with $I_{app} = 210pA$. For the ELIF model $\Delta_{th} = 5mV$ and $V_{max} = 50mV$. This figure was created by the online code `LIFspike_ELIF.m`.

The additional term produces an inward, depolarizing current that arises when the membrane potential reaches the vicinity of the standard threshold. Thereafter the inward current increases as the membrane potential increases, creating positive feedback: the current causes the membrane potential to rise, which increases the current further. Such positive feedback generates a rapidly accelerating increase in membrane potential (Figure 2.6), producing a spike with an interesting property: the membrane potential becomes infinite in a short, finite time. That may seem bizarre, but mathematically it is fine—for example, the function tan x reaches infinity over a finite range of x.

Box 2.13. Positive feedback: A situation whereby a change in a system causes a process to come into play that produce an enhancement of the change.

Since computers have a problem with infinity and any time-step would need to become infinitesimal to capture the rapid change, in simulations one sets a maximum level of the membrane potential, V_{max} (such as $V_{max} = 50$mV), beyond which it is reset in the standard manner. Therefore, the model includes an additional condition:

$$\text{if } V_m > V_{max} \text{ then } V_m \mapsto V_{reset}.$$

It turns out that the rate of change is so rapid that it makes little difference in simulations whether spikes are clipped to +10mV, +50mV, +200mV, etc., so long as a small enough time-step is used to keep the simulation numerically stable.

2.7.2. Two-variable models: the adaptive exponential leaky integrate-and-fire (AELIF) neuron. The adaptive exponential leaky integrate-and-fire (AELIF) model[5] adds to the ELIF model an outward (hyperpolarizing) spike-rate adaptation current. The adaptation current is similar to that produced in the previous section with an adaptation conductance, but with a twist—the rate of decay of the adaptation current depends on the membrane potential. Therefore, the membrane potential impacts the adaptation current in two ways. First, it produces a step increase in the current at the time of a spike. Second, while the membrane potential is high, even below threshold, the rate of decay of the current is slowed and its steady state is not zero—the current persists in the absence of spikes.

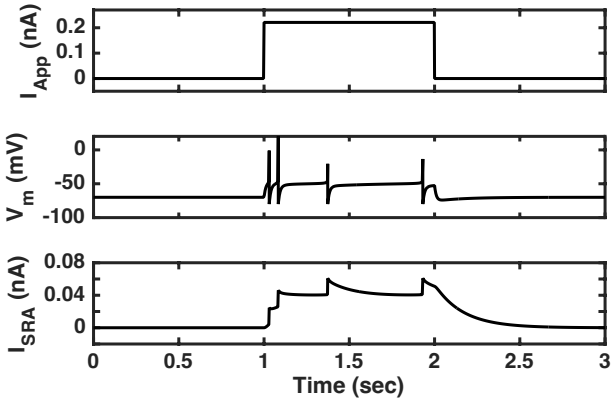

Figure 2.7. Response of the AELIF model to a current step. Top: The applied current. **Center:** The membrane potential. **Bottom:** The adaptation current. Note the very strong lengthening of the inter-spike interval following the first two spikes. Parameters used are: $C_m = 100\text{pF}$, $G_L = 10\text{nS}$, $E_L = -70\text{mV}$, $V_{th} = -50\text{mV}$, $V_{reset} = -80\text{mV}$, $\Delta_{th} = 2\text{mV}$, $V_{max} = 50\text{mV}$, $a = 2\text{nS}$, $b = 20\text{pA}$, $\tau_{SRA} = 200\text{ms}$, and $I_{app} = 0.221\text{nA}$. This figure was created by the online code `AELIF_code.m`.

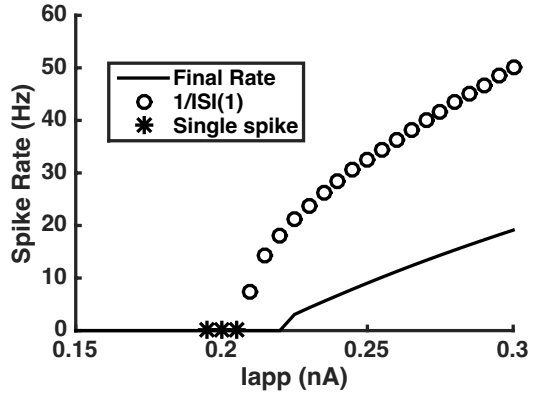

Figure 2.8. Firing rate curve for AELIF model. The solid line is the firing rate after any initial transient when the cell fires periodically. Circles denote the reciprocal of the first inter-spike interval, effectively the initial firing rate, evaluated when a current-step produces two or more spikes. Asterisks correspond to current steps that produce a single spike. Parameters are as in Figure 2.7. This figure was produced by the online code `AELIF_code_loop.m`.

The full model is the pair of coupled differential equations:

$$C_m \frac{dV_m}{dt} = G_L \left[E_L - V_m + \Delta_{th} \exp\left(\frac{V_m - V_{th}}{\Delta_{th}} \right) \right] - I_{SRA} + I_{app} \qquad \text{Eq. 2.21}$$

$$\tau_{SRA} \frac{dI_{SRA}}{dt} = a(V_m - E_L) - I_{SRA}, \qquad \text{Eq. 2.22}$$

combined with the two rules:

$$\text{if } V_m > V_{max} \text{ then } V_m \mapsto V_{reset} \text{ and } I_{SRA} \mapsto I_{SRA} + b.$$

The full model presented above is surprisingly versatile. The equation includes two additional parameters: a, possessing units of conductance, and b, possessing units of current. a and b are both positive if the I_{SRA} term is to represent the magnitude of an adaptation current. In the standard nomenclature, although I_{SRA} is defined to be positive, it is an outward current acting to hyperpolarize (make more negative) the membrane potential (it enters the membrane potential's dynamics with a minus sign). The AELIF model can be simulated with either or both of the terms a and b being negative, in which

case the model can be used to simulate other classes of neurons, although the biophysical meaning of the additional terms is lost.

2.7.3. Limitations of the LIF formalism.

We have seen that the leaky integrate-and-fire model can be extended to incorporate a realistic upswing of the spike, a refractory period without any clamping of the membrane potential, and spike-rate adaptation. In principle, any observed behavior of the membrane potential in response to inputs could be reproduced in a model based on the LIF neuron if appropriate extra terms are added to the set of ordinary differential equations. One might ask then, why simulate more complex models based on active conductances (as we will in Chapter 4)?

First, if we want to understand the effect of any change in the ion channels in a cell—either addition of a new type of channel, or modulation of the properties of any existing channel—models based on the LIF are of little value. For example, it is unclear which parameters in the model AELIF neuron would change and by how much, if the total potassium conductance were to increase.

Second, if we wanted to consider any properties of a neuron that do not just depend on the membrane potential—for example, any changes wrought by an influx of calcium ions—then the corresponding ion channels should be modeled explicitly.

Third, if we need to consider any spatial variation in the membrane potential of a cell then a more realistic depiction of a spike becomes important. For example, suppose we want to know how the membrane potential in the dendrites depends on the membrane potential in the soma. The actual shape of the spike determines how much current flows between soma and dendrite, so just knowing the spike time is insufficient.

In Chapter 4 we consider how to implement these behaviors in more realistic conductance-based models of the neuron. The basis of models such models is the Hodgkin-Huxley formalism, with which we introduce that chapter.

2.8. Tutorial 2.3: Models based on extensions of the LIF neuron.

Neuroscience goal: understand the reciprocal impacts of adaptation currents on spike trains and spike trains on adaptation currents; understand how limitation on firing rate and mean membrane potential depend on the spiking mechanism.

Computational goal: simulate coupled differential equations with two variables; analyze simulation results and plot appropriate features of the simulation, for example depending on the number of spikes produced.

In this tutorial, we will analyze the impact of adaptation currents on the f-I curve of a neuron.

1) Write a code to simulate the LIF model with an adaptation current so that the full model becomes:

$$C_m \frac{dV}{dt} = (E_L - V)/R_m + G_{SRA}(E_K - V) + I_{app}$$

and

$$\frac{dG_{SRA}}{dt} = -G_{SRA}/\tau_{SRA},$$

with the rule that if $V > V_{th}$ then $V \longmapsto V_{reset}$ and $G_{SRA} \longmapsto G_{SRA} + \Delta G_{SRA}$.

Use the parameters: $E_L = -75\text{mV}$, $V_{th} = -50\text{mV}$, $V_{reset} = -80\text{mV}$, $R_m = 100\text{M}\Omega$, $C_m = 100\text{pF}$, $E_K = -80\text{mV}$, $\Delta G_{SRA} = 1\text{nS}$, and $\tau_{SRA} = 200\text{ms}$. Initially set $V = E_L$ and $G_{SRA} = 0$.

a) Simulate the model neuron for 1.5s, with a current pulse of $I_{app} = 500pA$ applied from 0.5s until 1.0s. Plot your results in a graph, using three subplots with the current as a function of time, the membrane potential as a function of time and the adaptation conductance as a function of time stacked on top of each other as in Figure 2.7.

b) Now repeat at least twenty 5-second simulations of the model, each time with a different level of constant applied current (*i. e.* without a step pulse) such that the steady state firing rate of the cell varies from zero to 50Hz. For each applied current calculate the first inter-spike interval and the steady-state inter-spike interval. On a graph plot the inverse of the steady-state interspike interval against applied current to produce an f-I curve. On the same graph plot as individual points (e. g. as crosses or squares) the inverse of the initial inter-spike interval as in Figure 2.8. Give reasons for your observed results.

2) Write a code to simulate the AELIF model:

$$C_m \frac{dV_m}{dt} = G_L \left[E_L - V_m + \Delta_{th} \exp\left(\frac{V_m - V_{th}}{\Delta_{th}} \right) \right] - I_{SRA} + I_{app}$$

$$\tau_{SRA} \frac{dI_{SRA}}{dt} = a(V_m - E_L) - I_{SRA},$$

while if $V_m > V_{max}$ then $V_m \mapsto V_{reset}$ and $I_{SRA} \mapsto I_{SRA} + b$.
Use the parameters: $E_L = -75$ mV, $V_{th} = -50$ mV, $V_{max} = 100$ mV, $V_{reset} = -80$ mV, $\Delta_{th} = 2\text{mV}$, $G_L = 10\text{nS}$, $C_m = 100\text{pF}$, $a = 2\text{nS}$, $b = 0.02\text{nA}$ and $\tau_{SRA} = 200\text{ms}$. Initially set $V = E_L$ and $I_{SRA} = 0$.

a) Simulate the model neuron for 1.5s, with a current pulse of $I_{app} = 500pA$ applied from 0.5s until 1.0s. Plot your results in a graph, using two subplots with the current as a function of time above the membrane potential as a function of time.

b) Now repeat at least twenty 5-second simulations of the model, each time with a different level of constant applied current (*i. e.* without a step pulse) such that the steady state firing rate of the cell varies from zero to 50Hz. For each applied current calculate the first inter-spike interval and the steady-state inter-spike interval. On a graph plot the inverse of the steady-state interspike interval against applied current to produce an f-I curve. On the same graph plot as individual points (e. g. as crosses or squares) the inverse of the initial inter-spike interval. Give reasons for your observed results.

3) **CHALLENGE QUESTION.**

Alter the AELIF model to produce a refractory period using a combination of the methods of Tutorial 2.2—in particular, change the spike-rate-adaptation **current** into a refractory **conductance** and make the neuron's spiking threshold dynamic. The goal is to produce a cell whose average membrane potential increases monotonically with input and firing rate, while producing reasonable spikes at a firing rate that never exceeds 500Hz, even with excessively large input currents. Do not change the basic cell properties (*i. e.,* R_m, C_m, E_L, E_K are the same as in Q.2). However, parameters producing the spiking mechanism can be altered and V_m can be reset to any desired value following each spike. Also, the steady-state of the refractory conductance can be made into any nonlinear function of the membrane potential (*i. e.* the term $a(V_m - E_L)$ can be altered in the dynamics of I_{SRA}). Produce a figure with four different subplots: A) an example of the membrane potential dynamics; B) Firing rate as a function of input current; C) Mean membrane potential as a function of input current; and D) Mean membrane potential as a function of firing rate.

Figure 2.9 provides an example of a solution to this question.

Note: in Chapter 4 we will see that in more realistic models of neurons, as the injected current to a cell is increased, a point is reached where the spiking mechanism breaks down, so the neuron's firing rate is fundamentally limited.

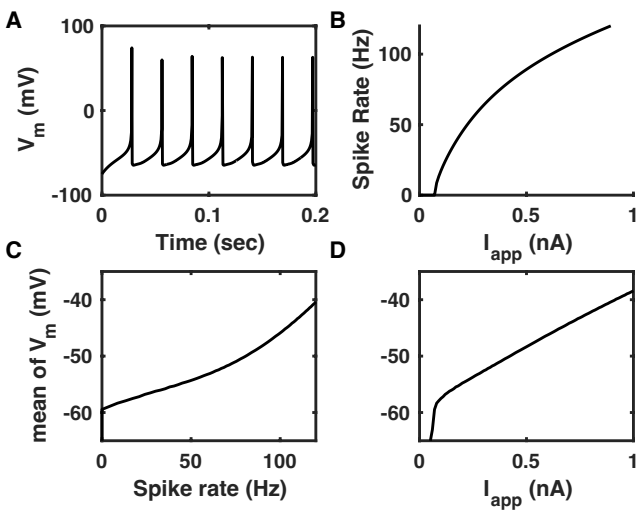

Figure 2.9. Response of an altered AELIF model to produce a refractory period. Possible solution of Tutorial 2.3, Q3. **A)** Response of membrane potential to applied current of 160pA. **B)** Firing rate as a function of applied current (currents in the tens of nA produce failure rather than high rates in this model). **C)-D)** Mean membrane potential increases monotonically with firing rate (C) and with applied current (D). This figure is produced by the online code `Tutorial_1_3_Q3.m`.

Table 2.2. List of symbols used in Chapter 2.		
Symbol	**Meaning**	**Description**
E_A	Reversal potential of ion-channel "A"	Membrane potential at which the ionic current through a particular channel is zero
k_B	Boltzmann constant	Converts temperature to thermal energy
T	Temperature	In units of Kelvin (degrees Celsius + 273)
q_e	Charge of an electron.	
z_A	Valence of an ion "A"	Total charge of ion in units of q_e
C_m	Total membrane capacitance	Cell's capacity to store charge on its surface
c_m	Specific membrane capacitance	Capacitance per unit area of membrane
G_A	Total conductance of ion-channel "A"	Ability of ions to flow in or out of the cell through channels of type "A"
g_A	Specific conductance of "A"	Conductance per unit area of membrane
I_m	Total membrane current	Rate of flow of charge through the membrane
i_m	Specific membrane current	Current per unit area of membrane
V_m	Membrane potential	Interior potential minus exterior potential
τ_m	Membrane time constant	Timescale for changes in V_m
t	Time	Time is essential for change and dynamics!
Q	Electrical charge	Used for amount stored on total membrane
G_L	Leak conductance	Fixed value not ascribed to a particular ion
R_m	Total membrane resistance	The fixed component at rest with $R_m = 1/G_L$
E_L	Leak reversal potential	Value of V_m where leak current is zero
V_{th}	Threshold potential	Value of V_m at which a spike is produced
V_{reset}	Reset potential	Value to which V_m is set after a spike
I_{th}	Threshold current	Value of applied current required for spiking
I_{app}	Applied current	Current supplied by experimental apparatus
V_m^{ss}	Steady state of V_m	Asymptotic value of V_m with fixed conductance
$f(I)$	Firing rate at a given current	Defines the response of a neuron to input
ISI	Inter-spike interval	Time between spikes, $ISI = 1/f$

τ_{ref}	Refractory period	Time following a spike during which generation of a new spike is impossible
V_{peak}	Peak membrane potential	Used to plot a spike of membrane potential up to a particular value, V_{peak}, if the spike itself is not generated within the code
$V_{th}^{(0)}$	Baseline of threshold potential	If V_{th} increases following a spike, $V_{th}^{(0)}$ is the value it returns toward between spikes
τ_{Vth}	Time constant of threshold potential	Less than a few ms to describe the rate of change of V_{th} back to baseline over the refractory period
G_{ref}	Refractory conductance	Temporary conductance of a hyperpolarizing channel that opens after a spike
ΔG_{ref}	Change in refractory conductance	Sufficiently large increment in G_{ref} following a spike to temporarily prevent another spike
τ_{Gref}	Time constant of refractory conductance	Fast time constant (up to a few ms) for decay of G_{ref} soon after a spike before the next spike is possible
Δ_{th}	Voltage-range for spike uptick	Used in the ELIF model to simulate a spike that accelerates over this range of membrane potential as it approaches threshold
V_{max}	Maximum membrane potential	Used to limit the membrane potential's rapid rise to infinity in the ELIF model by simulating only until V_m reaches V_{max}
I_{SRA}	Spike-rate adaptation current in the AELIF model	Typically defined as a positive quantity representing a hyperpolarizing outward current that grows with increasing spike rate
a	I_{SRA} control term	Determines the voltage-dependent decay rate and steady-state of I_{SRA} in the AELIF model
b	I_{SRA} current step	Step change in I_{SRA} following each spike in the AELIF model
G_{SRA}	Spike-rate adaptation conductance	Time-varying conductance of hyperpolarizing potassium channels
ΔG_{SRA}	Step change in G_{SRA}	Increment in G_{SRA} following each spike

τ_{SRA}	Time-constant for G_{SRA}	Slow (a few hundred ms) time constant for decay of the G_{SRA} between spikes

Questions for Chapter 2.

1) If the extracellular concentration of potassium gets reduced, what do you expect to happen to the resting membrane potential of a neuron, and why?

2) Consider an LIF neuron (Eq. 2.9) with parameters: $E_L = -75\text{mV}$, $G_L = 400\text{nS}$, $C_m = 2\text{nF}$, $V_{th} = -50\text{mV}$ and $V_{reset} = -70\text{mV}$.

a) If it receives an applied current of 6nA, what is its steady state membrane potential?

b) If it receives an applied current of 15nA, what is its firing rate?

3) Explain two similarities and two differences between how you incorporate a refractory period and how you incorporate an adaptation conductance into a simulation of an LIF neuron.

4) In the models of spike-rate adaptation which we have produced, is there any possibility that the model neuron can respond to a prolonged current step with a small number of spikes followed by complete quiescence (an absence of spiking) while the applied current remains, because of the adaptation current? Explain your reasoning.

2.9. Appendix: Calculation of the Nernst Potential.

In this Appendix, we will calculate the value of the membrane potential, *i. e.*, the potential difference across the cell membrane, such that any flux of ions due to a concentration difference across the membrane is exactly matched by a flux due to the potential difference.

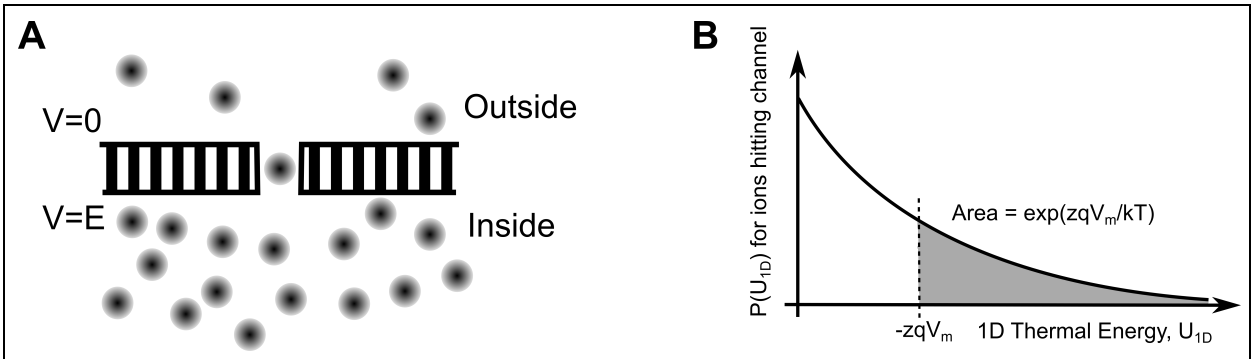

Figure 2.10. Calculation of Nernst Equilibrium Potential. A. When a species of ion, such as potassium, has a greater concentration inside than outside the neuron, there would be a net outward flow of ions through any open channel (*i. e.*, upward in the diagram) unless countered by a flow in the opposite direction due to a potential difference (in this case the outside of the cell should be at a higher electrical potential than the inside, in order to drive positive ions back into the cell). **B.** In a simplified model, when the outside of the cell is at a higher potential than the inside, external ions that reach the channel opening will pass through it, but internal ions that reach the channel opening will only pass through if they have enough velocity, v_{1D}, in the direction perpendicular to the channel opening. The speed criterion for exiting the cell is that the component of their kinetic energy perpendicular to the channel opening, $mv_{1D}^2/2 = U_{1D}$, is greater than the potential energy the ion would acquire when passing through the channel, $-zq_eV_m$, where zq is the total charge on the ion and V_m is the membrane

potential. The distribution of U_{1D} is exponential, such that the probability any ion has $U_{1D} > -zqV_m$ is $\exp(zq_eV_m/kT)$, for $V_m < 0$.

To make progress, we consider potassium ions, which have greater concentration inside than outside the cell, a positive charge, and a negative reversal potential (Figure 2.10).

For the net flow through a channel to be zero for a particular ion, the rate of ions reaching the channel opening multiplied by their probability of passing through the channel once they reach the opening, must be the same in both directions, *i. e.*,

$$(Outside\ arrival\ rate) \cdot P(entry) = (Inside\ arrival\ rate) \cdot P(exit). \quad \text{Eq. 2.23}$$

The rate of ions reaching the channel opening is simply proportional to the concentration of ions—one can consider a small ion-size volume adjacent to the channel opening and the probability of an ion occupying that volume in any small time-interval is simply the concentration of ions multiplied by the volume. Therefore, the ratio of arrival rates is the ratio of concentrations:

$$\frac{(Outside\ arrival\ rate)}{(Inside\ arrival\ rate)} = \frac{[K_{out}]}{[K_{in}]}, \quad \text{Eq. 2.24}$$

where $[K_{out}]$ and $[K_{in}]$ are respectively the external and internal concentrations of the ion under consideration, in this case potassium.

For the equilibrium of Eq. 2.23 to hold, then Eq. 2.24 can be combined with Eq. 2.23 to give:

$$\frac{P(exit)}{P(entry)} = \frac{(Outside\ arrival\ rate)}{(Inside\ arrival\ rate)} = \frac{[K_{out}]}{[K_{in}]}. \quad \text{Eq. 2.25}$$

We can calculate the ratio of probabilities of exit to entry from the total change in energy of an ion when it crosses the channel. If biological details are included, this should be evaluated as a multi-step process with forward and backward transition rates. However, the resulting probability ratio only depends on the total change of energy, so can be evaluated by ignoring any complexities of the channel and simply thinking of it as a "tunnel" through the membrane, as we do in the next paragraph.

Equation 2.25 tells us that at equilibrium, the electrical potential difference between the ends of the channel must reduce the probability of ions exiting the cell when the internal ion concentration exceeds the external concentration. Therefore, for potassium ions, the reversal potential must be negative, so that when ions from inside the cell reach the channel entrance they have a lower propensity to exit the channel. By way of analogy, the potassium channel is then equivalent to a vertical chimney through the roof of a house. A high density of rapidly moving balls (*c. f.* ions) inside the house generates a net upward flow through the chimney that is considerably reduced by the requirement that a ball entering the chimney has sufficient vertical velocity to exit. Such upward movement could be matched by a much lower density of balls outside the chimney, where they more rarely reach the chimney opening, but then always flow through it.

A result from statistical mechanics and thermodynamics, shows that the component of kinetic energy in a particular direction—which, for ions is dependent on their thermal energy—is an exponential function that depends on temperature. The proportion of ions with sufficient energy to escape an energy barrier in the manner suggested is $\exp(-\Delta U/k_BT)$ where ΔU is the energy barrier, k_B is Boltzmann's constant and T is

temperature. For ions of charge, zq_e, moving across an electrical potential difference of $-V_m$, the energy barrier is $-zq_eV_m$. Combining these results and setting $V_m = E_K$ at the Nernst equilibrium (the reversal potential) for potassium ions, where Eq. 2.23 and Eq. 2.25 are satisfied, we find:

$$\frac{P(exit)}{P(entry)} = \exp(zq_eE_K/kT) = \frac{[K_{out}]}{[K_{in}]}. \qquad \text{Eq. 2.26}$$

Rearrangement of Eq. 2.26 to solve for E_K leads to the Nernst Equation (see also Eq. 2.1):

$$E_K = \frac{kT}{zq_e}\ln\left(\frac{[K_{out}]}{[K_{in}]}\right). \qquad \text{Eq. 2.27}$$

References for Chapter 2

1. Tuckwell HC. *Introduction to Theoretical Neurobiology.* Cambridge Univ. Press, Cambridge, U.K.; 1988.
2. Dayan P, Abbott LF. *Theoretical Neuroscience.* MIT Press; 2001.
3. Bond CT, Maylie J, Adelman JP. Small-conductance calcium-activated potassium channels. *Ann N Y Acad Sci.* 1999;868:370-378.
4. Fourcaud-Trocme N, Hansel D, van Vreeswijk C, Brunel N. How spike generation mechanisms determine the neuronal response to fluctuating inputs. *J Neurosci.* 2003;23(37):11628-11640.
5. Brette R, Gerstner W. Adaptive exponential integrate-and-fire model as an effective description of neuronal activity. *J Neurophysiol.* 2005;94(5):3637-3642.