Lab 3

January 5, 2010

Frequency Adaptation and Bursting

In the last lab, we explored spiking due to sodium channels. In this lab, we explore adaptation and bursting due to potassium and calcium channels. To realize adaptation the model uses a population of slow potassium channels (M current). During the spike, the neuron's depolarized potential activates the potassium channels. These channels hyperpolarize the membrane, which delays subsequent spikes, adapting the neuron's spike rate.

To realize bursting, the neuron uses a population of calcium channels. During the spike, these calcium channels activate, and remain active for a short time. While they are active they strongly excite the neuron, causing a high frequency train of spikes. Each spike also increases the potassium channels' conductance, which overcomes the calcium current after several spikes, terminating the burst. Potassium activation then decreases until it is low enough to allow another burst of spikes.

We will analyze and experiment with the adapting–bursting neuron, observing the role of the potassium and calcium channels in spiking behavior, focusing on:

- The adapted spike rate
- The interaction between spike frequency and potassium conductance in bursting

3.1 Reading

Adaptation and bursting come in several varieties and can be realized by many combinations of ion channels. The book below introduces adaptation and explains the requirements for the type of bursting neuron in this lab (Section 7.3). It also reviews bursting in general, emphasizing its utility and the relevant mathematics (Section 9.2).

- E. M. Izhikevich. *Dynamical systems in neuroscience: The geometry of excitability and bursting.* MIT Press, 2007, Section 7.3, pp. 252-63, and Section 9.2, pp. 335-47.

3.2 Prelab

This prelab analyzes the frequency behavior of the adapting–bursting neuron.

1. M Current
   (a) We model potassium channels (K) as a conductance (G_k) in parallel with the leak conductance, G_{lk} (to zero potential) (Figure 3.1). A spike causes a change in K

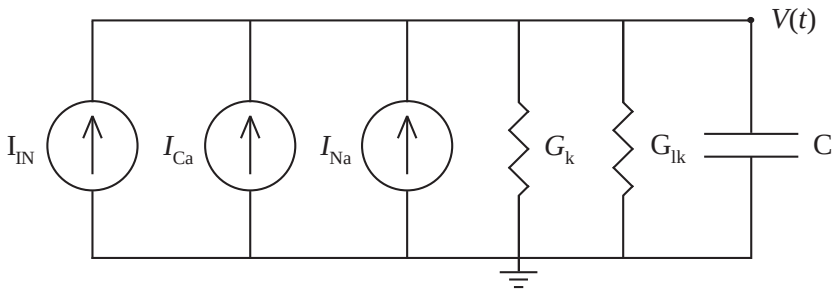

Figure 3.1: A potassium conductance, G_{K}, in parallel with a leak conductance, $\mathrm{G_{lk}}$, produces adaptation. Adding a Ca current (I_{Ca}) results in bursting.

conductance similar to our synapse model, a brief rise followed by an exponential decay. Here we approximate the rise as instantaneous, thus, if $g_{\mathrm{K}}(t_{\mathrm{n}}) \equiv G_{\mathrm{k}}/\mathrm{G_{lk}}$ is the value of the conductance immediately before the nth spike, which occurs at t_{n}, we have:

$$g_{\mathrm{K}}(t) = (g_{\mathrm{K}}(t_{\mathrm{n}}) + \Delta g_{\mathrm{K}})e^{-(t-t_{\mathrm{n}})/\tau_{\mathrm{K}}} \tag{3.1}$$

where τ_{K} is the time constant and $g_{\mathrm{K}}(t)$ increases by Δg_{K} immediately after the nth spike. A neuron spikes regularly with period T in steady-state. Solve for the conductance, $g_{\mathrm{K}\infty}$, by obtaining $g_{\mathrm{K}}(t_{\mathrm{n}}+T)$ from Equation 3.1 and setting it equal to $g_{\mathrm{K}}(t_{\mathrm{n}})$.

(b) We can obtain the steady-state spike frequency using our result from Prelab Question 1a. In steady state, the potassium conductance goes to $g_{\mathrm{K}\infty}$. Rearrange the expression from the previous question to find $g_{\mathrm{K}\infty}$ in terms of f. Simplify this function by using the approximation $\frac{1}{\log(1+x)} \approx \frac{1}{x} + \frac{1}{2}$.

We can approximate potassium's influence on frequency as:

$$f = \frac{3^{7/6}}{2\pi\tau_{\mathrm{m}}}\left(r^{2/3} - \frac{1+g_{\mathrm{K}}}{2}\right) \tag{3.2}$$

which is valid for $g_{\mathrm{K}} \ll r^{2/3}$. Substitute your result into Equation 3.2 to show that the steady-state frequency is given by:

$$f \approx \frac{1}{\tau_{\mathrm{K}}}\left(\frac{2r^{2/3}}{\Delta g_{\mathrm{K}}} + \frac{1}{2}\right) \tag{3.3}$$

Assume $r \gg 1$ and $\tau_{\mathrm{K}} \gg \tau_{\mathrm{m}}$ to simplify the expression.

2. Phase Plot

We model calcium channels (Ca) as an inward current (I_{Ca}) in parallel with the sodium current (Figure 3.1). A spike causes a brief rise in I_{Ca} followed by an exponential decay (described by τ_{Ca}), similar to the potassium conductance but faster. I_{Ca} adds to the neuron's input current, causing an increase in spike rate, until the potassium overcomes it, ending the burst. To visualize this interaction, we use a phase portrait (Figure 3.2). We consider two distinct behaviors, adaptation and bursting. For adaptation, ΔI_{Ca} is small; for bursting, ΔI_{Ca} is large; the other parameters remain unchanged ($r = 10$, $\Delta g_{\mathrm{K}} = 0.25$, $\tau_{\mathrm{K}} = 180$ms, $\tau_{\mathrm{Ca}} = 10$ms, and $\tau_{\mathrm{m}} = 10$ms). Sketch the neuron's trajectory starting from the initial conditions $f = 400$ and $g_{\mathrm{K}} = 4$ in these two cases:

(a) *f responds instantaneously to changes in g_{K}.* In this case, the trajectory follows the f-nullcline (thick light-red or light-blue lines, with $\Delta r_{\mathrm{Ca}} = 1$ or 6, respectively), moving along it to approach the g_{k}-nullcline (thick gray line). Sketch

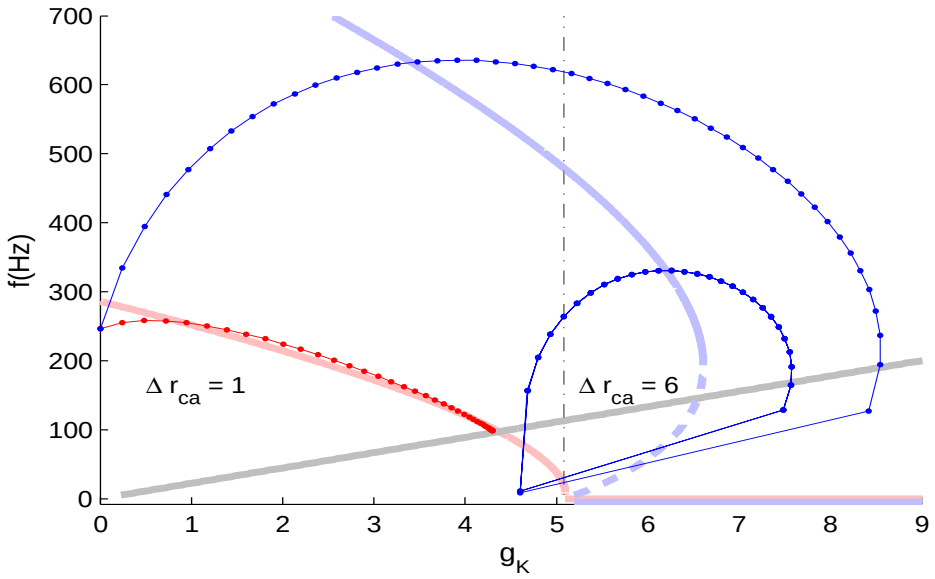

Figure 3.2: A neuron's behavior is set by the strength of its calcium current (Δr_{Ca}). When the calcium current is weak ($\Delta r_{\mathrm{Ca}} = 1$) the neuron adapts, settling at a stable spike frequency. When the calcium current is strong ($\Delta r_{\mathrm{Ca}} = 6$) the neuron bursts, alternating between high frequency spiking and quiescence.

the adapting and bursting trajectories in this case, starting from the given initial conditions. In practice, f does not respond instantaneously because I_{Ca}, which is responsible for boosting the spike rate, takes time to build up, or to decay, which leads to the second part of this question.

(b) *f does not respond instantaneously to changes in g_{K}.* In this case, the trajectory deviates from the f-nullcline (dotted deep-red and deep-blue lines, with $\Delta r_{\mathrm{Ca}} = 1$ or 6, respectively). Before you sketch the adapting and bursting trajectories, starting from the same initial conditions, explain why the trajectories in Figure 3.2 are horizontal when they cross the f-nullcline and vertical when they cross the g_{K}-nullcline.

(c) After a burst terminates, it is followed by a silent period during which g_{K} decays. For a given input, r, the smallest value of g_{K} capable of preventing spiking is called g_{Kmin} (dashed–dotted line). This value makes $\dot{x}$'s minimum value zero:

$$\tau_{\mathrm{m}}\dot{x} = r - x\,(1 + g_{\mathrm{Kmin}}) + \frac{x^3}{3} \tag{3.4}$$

Show that:

$$g_{\mathrm{Kmin}} = \left(\frac{3r}{2}\right)^{2/3} - 1 \tag{3.5}$$

3.3 Setup

As with previous labs, there will be a folder on the Desktop named **AdaptBurstLab**. This folder contains the instrument control program to acquire and view the neuron membrane potential and spikes in real-time. The TA will instruct you on the use of the software.

In this lab, the contents of *parameters.txt* of interest are:

- Input current (I_{IN})
- Leak conductance (G_{lk})
- Potassium conductance amplitude (ΔG_{K})
- Calcium current amplitude (I_{Ca})

As you increase the input current and the leak conductance biases, I_{IN} and G_{lk} increase exponentially. As you decrease the potassium conductance amplitude and calcium current biases, ΔG_{K} and I_{Ca} increase exponentially. The potassium (τ_{K}) and calcium (τ_{Ca}) decay-constants are set to reasonable values such that τ_{K} is about four times τ_{Ca}.

3.4 Experiments

In the first experiment, we will characterize the neuron's adapted spike rate in response to K-channel activity. In the second, we will turn on the model's calcium channels and observe the neuron's various behaviors—bursting, bursting followed by adapting, and adapting.

Experiment 1: Spike-Frequency Adaptation

In this experiment, we will

- Measure the neuron's adapted spike rate for various (constant) input currents.

Turn on the K channels by decreasing the potassium amplitude bias (to about 1.85V). Turn on the Ca channels by decreasing the calcium amplitude bias (to about 1.45V). Increase the input current bias until bursting is observed (to about 0.5V). Adjust the potassium and calcium biases until the burst trajectory fills the available plotting window. Record the K bias at this point: this should remain fixed at this level for the remainder of the experiments.

Now turn off the Ca current by setting the bias to 2.4V. Calculate the spike frequency for several values of input current (10-20), which we normalize and approximate as:

$$r = r_{\mathrm{th}}\, e^{(V_{\mathrm{IN}} - V_{\mathrm{IN0}})\,\kappa/0.0256} \tag{3.6}$$

where as before (Lab 2) $r_{\mathrm{th}} = 2/3$, κ is a transistor fit parameter (0.7 generally works), V_{IN} is the input current bias in volts, and V_{IN0} is the smallest input current bias (smallest input current) that causes the neuron to spike. Plot steady-state f versus r, fitting the plot with the appropriate equation from the prelab. The value of κ may need to be adjusted to create a decent fit. What are τ_{K} and Δg_{K}?

For the next experiment measure the K waveforms and calculate the value of ΔG_{K} (the increase in potassium conductance due to a single spike). Do you expect this value to be the same for all input currents used? Does it make more sense to measure this value using the data from high or low frequencies?

Experiment 2: Bursting Phase Portrait

In this experiment, we will

- Collect phase portraits from a neuron in different regimes.

Set the input current to obtain a frequency around 50Hz with adaptation. Turn on the Ca channels by decreasing the calcium amplitude bias (to about 1.45V). Observe the spike frequency versus potassium trajectory for several values (10-20) of calcium amplitude. Ensure that the calcium current amplitude range is sufficient to realize both adapting (small calcium amplitude) and bursting (large calcium amplitude). Use the measured ΔG_{K} value to calculate $\mathrm{G_{lk}}$ using the value of $\Delta g_{\mathrm{K}} = \Delta G_{\mathrm{K}}/\mathrm{G_{lk}}$ determined in Experiment 1. Normalize G_{K} by $\mathrm{G_{lk}}$ to calculate g_{K}.

On a single graph, plot a phase-portrait curve for each calcium current amplitude: Plot the inverse of each interspike interval (instantaneous spike frequency) versus the average normalized potassium amplitude during that interval. Be sure to include both adpating and bursting waveforms. What is the Ca current at the transition point? Label each phase-portrait curve with its corresponding calcium amplitude bias. From the bursting phase portraits estimate g_{Kmin}. Does this g_{Kmin} yield a reasonable value for r, compared to one calculated from Equation 3.6?

From the adapting phase portraits fit $g_{\mathrm{K}\infty}$ as a function of frequency to an approximation of the expression derived in Prelab Question 1a, given by:

$$g_{\mathrm{K}\infty} \approx \Delta g_{\mathrm{K}} \tau_{\mathrm{K}} f \tag{3.7}$$

Use the slope of this curve and the value of Δg_{K} from Experiment 1 to find τ_{K}. How similar is this to your previous estimate of τ_{K}. Comment on any deviation.

3.5 Postlab

In this Postlab you will design an experiment similar to Experiment 2. In Experiment 2, you varied Δr_{Ca}, which enabled you trace the g_{K}-nullcline, $g_{\mathrm{K}\infty}$. How would you trace the f-nullcline (for fixed Δr_{Ca} and τ_{Ca} values)? What parameter(s) would you vary? Can you trace the unstable regions as well? How would you calibrate your measurements? For instance, if you varied r, how would you determine the actual value that was applied? Sketch phase plots similar to Figure 3.2 to illustrate your plan.