# Chapter 4 The Variety of Channels

We have discussed several types of active (voltage-gated) channels for specific neuron models. The Hodgkin–Huxley model for the squid axon consisted of three different ion channels: a passive leak, a transient sodium channel, and the delayed rectifier potassium channel. Similarly, the Morris–Lecar model has a delayed rectifier and a simple calcium channel (with no dynamics). Hodgkin and Huxley were smart and supremely lucky that they used the squid axon as a model to analyze the action potential, as it turns out that most neurons have dozens of different ion channels. In this chapter, we briefly describe a number of them, provide some instances of their formulas, and describe how they influence a cell's firing properties. The reader who is interested in finding out about other channels and other models for the channels described here should consult http://senselab.med.yale.edu/modeldb/default.asp, which is a database for neural models.

#### 4.1 Overview

We briefly describe various ion channels in this section. Most of the voltage-gated channels follow the usual formulation of the delayed rectifier, the calcium model, and the transient sodium current we have already discussed. However, there are several important channels which are gated by the internal calcium concentration, so we will describe some simple models for intracellular calcium handling.

All of the channels that we describe below follow the classic Hodgkin–Huxley formulation. The total current due to the channel is

$$I_{\text{channel}} = m^p h^q I_{\text{drive}}(V),$$

where m and h are dynamic variables lying between 0 and 1, p and q are nonnegative integers, and V is the membrane potential. Thus, the channel current is maximal when m and h are both 1. By convention, h will generally inactivate (get smaller) with higher potentials of the cell and m will activate. Not all channels have both activation and inactivation. For example, the Hodgkin–Huxley potassium channel and both the Morris–Lecar calcium and potassium channels have no inactivation. The Hodgkin–Huxley sodium channel has both activation and inactivation.

The drive current generally takes two possible forms corresponding to the linear model or the constant field model, respectively:

$$I_{\rm lin} = g_{\rm max}(V - V_{\rm rev}) \tag{4.1}$$

and

$$I_{\rm cfe} = P_{\rm max} \frac{z^2 F^2}{RT} V\left(\frac{[C]_{\rm in} - [C]_{\rm out} e^{\frac{-zVF}{RT}}}{1 - e^{\frac{-zVF}{RT}}}\right).$$
(4.2)

The constant  $g_{\text{max}}$  has units of siemens per square centimeter and the constant  $P_{\text{max}}$  has units of centimeters per second, so the driving current has dimensions of amperes per square centimeter.

The gates *m* and *h* generally satisfy equations of the form

$$\frac{\mathrm{d}x}{\mathrm{d}t} = a_x(1-x) - b_x x$$

or

where the quantities 
$$a_x$$
,  $b_x$ ,  $x_{\infty}$ , and  $\tau_x$  depend on voltage or some other quantities.  
The functional forms of these equations often take one of the following three forms:

 $\frac{\mathrm{d}x}{\mathrm{d}t} = (x_{\infty} - x)/\tau_x,$ 

$$F_e(V, A, B, C) = A e^{(V-B)/C},$$
  

$$F_l(V, A, B, C) = A \frac{(V-B)}{1 - e^{(V-B)/C}},$$
  

$$F_h(V, A, B, C) = A/(1 + e^{-(V-B)/C})$$

Generally speaking, most of the voltage-gated ion channels can be fit with functions of the form

$$x_{\infty}(V) = \frac{1}{1 + e^{(V - V_{\rm T})/k}}$$
(4.3)

and

$$\tau_x(V) = \tau_{\min} + \tau_{amp} / \cosh \frac{V - V_{\max}}{\sigma}.$$
(4.4)

# 4.2 Sodium Channels

Roughly speaking, there are two types of sodium currents: the transient or fast sodium current and the persistent or slow sodium current. We have already described the former when we discussed the Hodgkin–Huxley model. The fast sodium current is found in the soma and axon hillocks of many neurons. The persistent (slow) sodium current (which activates rapidly; the "slow" in its name refers to inactivation) has been implicated as underlying both subthreshold and suprathreshold firing in many neurons by adding a small depolarizing current which keeps them active. The fast sodium current used in the Hodgkin–Huxley equations is not suitable for neurons in the brains of mammal; instead, modelers often use a model that is due to Roger Traub [269]. The equations for this channel and all others in this chapter can be found online.

As an example of the utility of the persistent sodium channel we will introduce a simple model of the pre-Bötzinger complex, a group of neurons responsible for generating the respiratory pacemaker oscillations in the brainstem. (That is, these are the cells that make us breathe.) Here, the persistent sodium channel and its inactivation play a crucial role in generating the pacemaker potential for the oscillation [55]. The model has the form

$$C_{\rm m} \frac{\mathrm{d}V}{\mathrm{d}t} = -g_{\rm L}(V - E_{\rm L}) - g_{\rm K}n^4(V - E_{\rm K}) - g_{\rm Na}m_{\infty}(V)^3(1 - n)(V - E_{\rm Na})$$
$$-g_{\rm Nap}w_{\infty}(V)h(V - E_{\rm Na}),$$
$$\frac{\mathrm{d}n}{\mathrm{d}t} = (n_{\infty}(V) - n)/\tau_n(V),$$
$$\frac{\mathrm{d}h}{\mathrm{d}t} = (h_{\infty}(V) - h)/\tau_h(V).$$

Note that for the fast sodium channel, the inactivation has been replaced by 1 - n as in the Rinzel reduction of the Hodgkin–Huxley equations (see Sect. 3.6). The variable *h* now corresponds to inactivation of the persistent sodium channel. The key feature in this model is that the inactivation of the persistent sodium current has a time constant of 10 s. Figure 4.1a shows a simulation of this model for 40 s. The voltage oscillates at a period of about 6 s, which is commensurate with the 10-s time constant for inactivation of the persistent sodium channel. In Chap. 5, we will explore the role of the persistent sodium channel in producing the bursts. Here, we restrict our discussion to the pacemaker duties of the persistent sodium channel.

Butera et al. [30,31] showed that one of the key parameters in inducing the bursting is the leak potential  $E_{\rm L}$ . If  $E_{\rm L} = -65$  mV, then the system exhibits stable resting behavior. By shifting this parameter from -65 to -60 mV, they obtained the pattern shown in Fig. 4.1a. If we block the transient sodium channel by setting  $g_{Na} = 0$ , then we can look at the bifurcation diagram of the "spikeless" model as a function of  $E_{\rm L}$ . Figure 4.1b shows the voltage as a function of the leak current. There are two Hopf bifurcations: a subcritical bifurcation at about -60 mV and a supercritical bifurcation at about  $-54 \,\mathrm{mV}$ . Thus, for a range of leak potentials there is a slow pacemaker potential. We can further understand this by noting that the variable h is much slower than (V, n). If we set  $n = n_{\infty}(V)$ , then this leads to a two-dimensional system in (V, h), the phase plane of which we show in Fig. 4.1c. At  $E_{\rm L} = -62 \,\mathrm{mV}$ , there is a single stable fixed point. As  $E_{\rm L}$  increases, the V-nullcline moves down and intersects the h-nullcline in the middle branch. Since h is very slow, this leads to a relaxation oscillation shown in the phase plane and in Fig. 4.1d. The period of the pacemaker potential is about twice that of the full model (in Fig. 4.1a). This is because the spikes produced by the full model cause more inactivation of the persistent sodium channel.



Fig. 4.1 The persistent sodium channel provides the pacemaker current for the model pre-Botzinger cell. (a) Potential with  $E_{\rm L} = -60 \,\mathrm{mV}$  for the full bursting model. (b) Bifurcation diagram with the fast sodium channel blocked showing the onset of pacemaker oscillations at the Hopf bifurcation. (c) Phase plane with  $n = n_{\infty}(V)$  showing relaxation oscillation. (d) Potential of the simple relaxation model

#### 4.3 Calcium Channels

Calcium channels are quite similar to sodium channels in their form, function, and dynamics. However, because the concentration of calcium in the cell is very low (e.g., of the order of  $10^{-8}$ M), the small amount of calcium coming into the cell from the channel opening can drastically alter the driving potential. Thus, many modelers (but no theoreticians!) use the constant-field equation (CFE) (4.2) rather than the simple ohmic drive (4.1). Using the CFE model requires an extra equation for the intracellular calcium concentration, but this is often ignored. The CFE just adds a nonlinearity to the current with little effect on the dynamics.

We can divide calcium channels into roughly two classes (although experimentalists describe many more): (1) T-type calcium currents  $I_{Ca,T}$ , which are low-threshold but inactivate, and (2) L-type calcium currents,  $I_{Ca,L}$  which have a high threshold and do not inactivate.  $I_{Ca,T}$  is fast and both the activation and the inactivation are voltage-dependent. This current is responsible for bursting in many neurons, particularly in the thalamus, where it plays the dominant role in producing oscillatory activity during sleep [58,59].  $I_{Ca,L}$  is responsible for spikes in some cells (such as the Morris–Lecar model). It does, in fact, inactivate, but the inactivation is calcium- rather than voltage-dependent.

The T-current has some interesting properties, such as the ability to produce rebound bursts and subthreshold oscillations. Let us see some of these features. We will look at a simple model in which the spiking currents (sodium and potassium) are blocked so that all that is left is the T-current and the leak:

$$C \frac{dV}{dt} = I_0 - g_L(V - E_L) - I_T, \qquad (4.5)$$

$$\frac{dh}{dt} = (h_\infty(V) - h)/\tau_h(V),$$

$$I_T = m_\infty(V)^2 h I_{cfe}(V, [Ca]_o, [Ca]_i),$$

$$m_\infty(V) = 1/(1 + \exp(-(V + 59)/6.2)),$$

$$h_\infty(V) = 1/(1 + \exp((V + 83)/4)),$$

$$\tau_h(V) = 22.7 + 0.27/(\exp((V + 48)/4) + \exp(-(V + 407)/50)).$$

To simplify the analysis of this model, we have set the activation variable *m* to its steady state  $m_{\infty}(V)$ . Full parameters for the model are given online. What sets the behavior for this model is the resting potential. Various neural modulators (chemicals which alter the behavior of neurons in a quasiconstant manner) set the resting potential from either relatively depolarized at, say, -60 mV to relatively hyperpolarized at -80 mV. The inactivation *h* has a half-activation at -83 mV in the present model, so if the resting potential is -60 mV, then  $h \approx 0$ . This means no amount of depolarizing current can activate the current. In the sensory literature, when the thalamic neurons are depolarized like this, the network is said to be in "relay" mode. Inputs to the thalamus are transmitted as if the cell were just a nonlinear spiker like we have already encountered. However, if the network is hyperpolarized, then inactivation of the T-current, *h*, will be much larger and a subsequent stimulus will lead to an explosive discharge of the neuron.

Suppose the leak is set so that the resting potential is around -60 mV. Figure 4.2a shows the response of the model to brief depolarizing and hyperpolarizing pulses. At -60 mV, the T-current is completely inactivated, so the response to depolarizing pulses is the same as it would be if the current were not there. In this simplified model, the result is a passive rise in voltage followed by a passive decay. However, if the same membrane is provided with a brief and strong hyperpolarizing stimulus, it responds with a calcium action potential when released from the stimulus. This is called *rebound* and is a classic property of cells with a T-type calcium current. Figure 4.2b provides a geometric explanation for rebound. At rest, the membrane sits at the lower-right fixed point. At this point  $h \approx 0$ . A hyperpolarizing input moves the V-nullcline upward; if the hyperpolarization is maintained, the trajectory will move toward the new fixed point (upper-left circle.) If, instead, the hyperpolarization is transient, then when the stimulus is removed, the V-nullcline moves to its original position. Since h is slow compared with V, the potential will rapidly move horizontally to reach the right branch of the V-nullcline, leading to the calcium spike.



Fig. 4.2 Properties of the T-type calcium current

In contrast, consider the system when the leak is -80 mV. Then, the resting state is about -78 mV and the T-current inactivation, h, is no longer negligible. Figure 4.2c shows that a small depolarizing input is now sufficient to elicit a calcium action potential. Similarly, a small hyperpolarizing input will also result in the firing of an action potential. Figure 4.2d provides an explanation for why depolarization will work in this case. Depolarizing lowers the V-nullcline, allowing the trajectory to jump to the right branch of the nullcline and produce a spike.

The T-current also provides a mechanism for subthreshold calcium oscillations which can be pacemakers for bursting like the persistent sodium current. In Exercise 2, you are asked to find these oscillations and give a geometric explanation for them.

# 4.4 Voltage-Gated Potassium Channels

There is no doubt that the greatest variety of channels is found among those which involve potassium. We have already seen the workhorse for spiking, the delayed rectifier, in the Hodgkin–Huxley model, the Butera model of the pre-Botzinger complex, and the Morris–Lecar model. The delayed rectifier is rather fast and has only an activation gate. Potassium channels provide the main repolarizing force for nerve cells. If they are fast, then the cells are allowed to rapidly repolarize, so very fast spike rates are possible. If they are slow, they cause the spike rate to slow down with sustained depolarization, an important form of adaptation. In addition to the voltage-gated potassium channels which we describe here, there are also calciumgated potassium channels which perform similar roles.

## 4.4.1 A-Current

The Hodgkin–Huxley model was based on a quantitative analysis of the squid axon. In 1971, Connor and Stevens [45] introduced an alternative model for action potentials in the axons of crab legs. The transient sodium current and the delayed rectifier were similar to those in the Hodgkin–Huxley model although they were faster. In addition, Connor and Stevens introduced a transient potassium current, the *A-current*. Like the transient sodium current, this current has both an activation and an inactivation gate:

$$I_{\rm A} = g_{\rm A} a^3 b (V - E_{\rm A}).$$

The reversal potential  $E_A$  is close to that of the delayed rectifier. The activation variable *a* increases with voltage, whereas the inactivation variable *b* decreases;  $b_{\infty}(V)$  has a half-activation at about -78 mV. (The full Connor–Stevens model is given online.) One consequence of having this current is that it induces a delay to spiking when the cell is relatively hyperpolarized. Intuitively, the reason for this is that when the cell is somewhat hyperpolarized, *b* will be large. Depolarization engages *a* and thus there will be a large potassium current. However, when the membrane is depolarized,  $b_{\infty}(V)$  will be small, so *b* will decrease, leading to a gradual loss of the A-current. The neuron will spike only when this current is sufficiently small. Thus, the A-current causes a delay to spiking. Figure 4.3a shows an example of the delay to spiking due to the A-current.

One of the most interesting dynamic consequences of the A-current in the Conner–Stevens model is that it converts the transition to repetitive firing from class II (like the Hodgkin–Huxley model) to class I. Recall that for a class II neuron, the transition from resting behavior to oscillations is via a Hopf bifurcation; moreover, the steady-state voltage–current (I-V) relationship is monotonic. For a class I neuron, the transition to oscillations is via a saddle–node on an invariant circle (SNIC) bifurcation and the I-V relationship is nonmonotonic.

The A-current provides a means to make the I-V relationship nonmonotonic since the steady-state current,

$$I_{\mathrm{A},\mathrm{ss}} = g_{\mathrm{A}} a_{\infty}(V)^3 b_{\infty}(V)(V - E_{\mathrm{A}}),$$



**Fig. 4.3** Connor–Stevens model. (a) Delay to spiking depends on the A-current. The *dashed curve* shows  $g_{\rm K} = 27.7$  and  $g_{\rm A} = 40$ , and the *solid curve* shows  $g_{\rm K} = 17.7$  and  $g_{\rm A} = 50$ . (b) Steady-state I-V curve with two different amounts of A-current. (c) Full bifurcation diagram for the Connor–Stevens model with default parameters. (d) Frequency–current curve for the Connor–Stevens model showing class I behavior

is nearly zero. Thus, if the majority of the potassium current is A-type rather than the delayed rectifier current, then the steady-state I-V curve will be dominated by the sodium current.

To explore this idea in more detail, we consider the Connor–Stevens model keeping the maximal total potassium conductance constant:  $g_A + g_K = g_{total} = 67.7$ . The choice of 67.7 for the total is so that the Connor–Stevens model is our default,  $g_K = 20$  and  $g_A = 47.7$ . Figure 4.3b shows the steady-state I-V curve for the standard Connor–Stevens parameters and also for when the A-current is reduced to 40 while the delayed rectifier is increased to 27.7. It is clear that the I-V curve is monotonic with the reduced A-current, so class I (SNIC) dynamics is impossible. Figure 4.3c shows the bifurcation diagram for the standard Connor–Stevens model as current is injected. A branch of periodic orbits emerges at high applied currents at a supercritical Hopf bifurcation (not shown). This branch terminates via a SNIC on the steady-state I-V curve. The frequency is shown in Fig. 4.3d and as predicted by the general theory has a square-root shape and vanishes at the critical current. We point out that the steady-state I-V curve in the standard parameter regime is not a simple "cubic" as in the Morris–Lecar model. Rather, there are values of the applied current where there are five fixed points. Rush and Rinzel [239] were the first to notice this. The phenomenon occurs over a very narrow range of values of  $g_A$ . In Exercise 5, you are asked to explore the behavior of the system with slightly different values of  $g_A$ .

# 4.4.2 M-Current

There are several slow potassium currents which are responsible for a phenomenon known as spike-frequency adaptation. That is, this slow low-threshold outward current gradually reduces the firing rate of a neuron which has been depolarized sufficiently to cause repetitive firing. The M-current and related slow potassium currents are able to stop neurons from firing if they are strong enough and thus can provide an effective brake to runaway excitation in networks.

Figure 4.4 shows an example of spike-frequency adaptation in a simple cortical neuron model due to Destexhe and Paré [57]. The left-hand graphic shows the voltage as a function of time when the current is instantaneously increased to  $6 \,\mu A/cm^2$ . The initial interspike interval is short but over time this lengthens. Figure 4.4b shows the instantaneous frequency (reciprocal of the initial interspike interval) as a function of the spike number. The frequency drops from 130 to 65 Hz over about 1 s.

The M-current does far more than just slow down the spike rate. Because it is active at rest (the threshold is -30 mV), the M-current can have profound effects on the steady-state behavior. Figure 4.5a shows the bifurcation diagram of steady states as the conductance of the M-current ( $g_m$ ) is increased. With no M-current, the model has a SNIC bifurcation to a limit cycle, so it is a class I membrane. For



**Fig. 4.4** Spike-frequency adaptation from the M-type potassium current. The model is from Destexhe and Paré [57] and represents a cortical pyramidal neuron. The applied current is  $6 \,\mu\text{A/cm}^2$  and  $g_M = 2 \,\text{mS/cm}^2$ . (a) Voltage and (b) instantaneous frequency versus spike number



**Fig. 4.5** Effects of M-current on equilibria. (a) Steady state as a function of current at three values of  $g_m$ . With no M-current, the neuron is class I and oscillations are borne via a saddle-node on an invariant circle along the fold curve F. With large enough M-current ( $g_m = 2$ ), oscillations are borne via a Hopf (H) bifurcation and the fold points no longer exist since there is a unique equilibrium point. For intermediate values, the folds still exist, but the Hopf bifurcation occurs on the lower branch of fixed points. (b) Two-parameter diagram. The twofold curves (F) meet at a cusp point (c) near I = 4.8 and  $g_m = 1.8$ . There is a curve of Hopf points (H) which terminates at a Takens–Bogdanov (TB) point when the Hopf curve meets a fold curve. The *dashed line* corresponds to  $g_m = 1$ ; as I increases, there is first a Hopf point and then the fold. At  $g_m = 0$ , no Hopf point is encountered and when  $g_m = 2$ , there are no folds

larger values of  $g_m$  (Destexhe and Paré used  $2 < g_m < 5$ ) the resting state loses stability at a Hopf bifurcation, so the membrane is class II. The transition from class I to class II occurs for  $g_m = 1$  where the fold points (saddle–nodes) remain but the lower branch of fixed points loses stability at a Hopf bifurcation. Figure 4.5b shows a two-parameter bifurcation diagram of this system where the applied current and  $g_m$  vary. As  $g_m$  increases, the two fold points merge at a cusp point (labeled C) and for  $g_m$  larger, there is only a single fixed point. Additionally, there is a curve of Hopf points which terminates on the rightmost fold point at a Takens–Bogdanov point. In some sense, the Takens–Bogdanov point marks the transition from class I to class II excitability. The global picture is complex. For example, when  $g_m = 0$ , there is a single branch of periodic solutions terminating at the fold point via a SNIC. However, when  $g_m = 1$ , a branch of periodic solutions must bifurcate from the Hopf point. This branch must somehow either merge with the SNIC branch or disappear. The interested reader could attempt to put together a plausible global picture as a project. (The reader could also consult [136], p 197.)

## 4.4.3 The Inward Rectifier

The inward rectifier is hyperpolarization-activated. That is, if the neuron is hyperpolarized enough, the current is activated, further hyperpolarizing the model. This implies the possibility for bistability in the hyperpolarizing direction. The current has the form

$$I_{\rm Kir} = g_{\rm Kir} h(V) (V - E_{\rm K}),$$

where

$$h(V) = 1/(1 + \exp((V - V_{\text{th}})/k)).$$

Typical values for the parameters are  $V_{\text{th}} = -85 \text{ mV}$  and k = 5 mV. With a leak current the steady-state current satisfies

$$I = g_{\rm L}(V - E_{\rm L}) + g_{\rm Kir}h(V)(V - E_{\rm K}).$$

Differentiating this equation, we obtain

$$\frac{\mathrm{d}I}{\mathrm{d}V} = g_{\mathrm{L}} + g_{\mathrm{Kir}}h(V) + g_{\mathrm{Kir}}h'(V)(V - E_{\mathrm{K}}).$$

The first two terms are positive. However, if  $V > E_K$ , then since h'(V) < 0, it is possible that this last term can be large and negative enough so that the I-V curve is cubic-like. Necessary conditions are that  $E_K < V_{th}$  and k must be small enough. Once there is bistability, it is possible to generate oscillations. Izhikevich [136] points out that if you add a delayed rectifier potassium current, then it is possible to generate oscillations with two potassium currents! Given the fact that this current can induce bistability, this is not surprising. In Exercise 8, you can give this a try. Another way to induce oscillations in this model is to assume there is extracellular potassium accumulation. This will result in the reversal potential for potassium becoming more positive, inactivating the channel. Thus, there will be negative feedback to a bistable system and possibly oscillations; see Exercise 9.

#### 4.5 Sag

We end our discussion of voltage-gated channels with a description of the socalled sag current,  $I_h$ . This is a slow inward current with a reversal potential of between -43 and 0 mV, but which requires hyperpolarization to become active; that is, the activation curve decreases monotonically. The ions involved are a mixture of sodium and potassium ions, so the reversal potential lies between that of sodium and that of potassium. The sag current is implicated as a pacemaker in many different systems [158, 186]. It also plays an important role in dendritic computations [203, 277]. There are several models for this current; some have a single component and others have multiple components. The simplest model is due to Huguenard and McCormick [131]:

$$I_h = g_h y (V + 43), (4.6)$$



where

$$\frac{\mathrm{d}y}{\mathrm{d}t} = (y_{\infty}(V) - y)/\tau_{y}(V),$$
  

$$y_{\infty}(V) = 1/(1 + \exp((V - V_{\mathrm{th}})/k)),$$
  

$$\tau_{y}(V) = \tau_{0}\mathrm{sech}((V - V_{m})/b).$$

The time constant  $\tau_0$  varies from 50 ms to over 1,000 ms. (Note that the function  $\tau_y(V)$  used by McCormick et al. is more complicated than the present version, but they are almost identical in shape.) Figure 4.6 shows how the sag gets its name. Hyperpolarizing the membrane causes the potential to drop and thus activates the sag current, which then repolarizes the membrane. In Exercise 10, you combine this current with  $I_{\text{Kir}}$  from Sect. 4.4.3 to obtain a slow pacemaker oscillation.

# 4.6 Currents and Ionic Concentrations

So far, we have assumed the ionic concentrations both inside and outside the cell are held constant. This is usually a good assumption except for the calcium ion. Because the internal free calcium levels are very low in a cell  $(10^{-4} \text{ mM})$ , the entry of calcium through voltage-gated channels can substantially contribute to the intracellular calcium. Indeed, calcium is a very important signaling molecule and it often sets up complex reaction cascades within the cell. These reactions have both long-term and short-term effects on the cell. Thus, it is useful to understand how to model the flow of calcium due to voltage-gated channels. In certain pathological cases, the buildup of extracellular medium has quite a low level of potassium, if many neurons are firing simultaneously, they are releasing large amounts of potassium into the medium. The surrounding nonneural cells (glia) buffer the potassium concentration, but this process can be slow.

Consider a current due to some ionic species  $I_X$ . Suppose this is a positive ion. The current is typically measured in units of microamperes per square centimeter. Recall that an ampere is a coulomb of charge per second. We need to convert this current to a concentration flux which has dimensions of millimolar. Recall that 1 M is 1 mol/L, or 1 mol per 1,000 cm<sup>3</sup>. Faraday's constant, 96,485 C/mol, is just what we need. Suppose the valance of the ion is z. Then,  $I_X/(zF)$  gives us the transmembrane flux in units of micromolar per centimeter per second. To convert this into a concentration flux, we suppose the ions collect in a thin layer of depth d (in microns) near the surface of the cell. Thus, the change in concentration is  $I_X/(zdF)$ . Finally, we want our units of concentration to be in millimoles per liter per millisecond. Noting that 1 L is 1,000 cm<sup>3</sup>, we find that the total in(out)flux of an ion is

$$f_X = 10I_X/(zFd),$$
 (4.7)

where F = 96,485, d is the depth in microns, and  $I_X$  is the current in microamperes per square centimeter.

Having defined the flux of ions moving through the cell, we need to write equations for the total concentration of the ion, X:

$$\frac{\mathrm{d}X}{\mathrm{d}t} = \pm f_X - \delta(X),$$

where  $\delta(X)$  is the decay of ion X through uptake or buffering. Which sign should we take for the flux? If we are interested in the intracellular concentration, then we take the negative sign and if we are interested in extracellular concentrations, we take the positive sign. The simplest form for the decay is

$$\delta_P(X) = (X - X_0)/\tau,$$

which means in absence of the ionic current, X tends to  $X_0$ . Another common form is

$$\delta_M(X) = \frac{K_1 X}{K_h + X},$$

which is a passive buffering model due to the reaction

$$X + B \rightleftharpoons XB \longrightarrow B + Y,$$

where Y is the inactivated form of X. We finally note that the flux term  $f_X$  can have a factor multiplying it to account for buffering [84]. Thus, for intracellular ion accumulation, we can write

$$\frac{\mathrm{d}X}{\mathrm{d}t} = -\gamma I_X - \delta(X),\tag{4.8}$$

where the parameter  $\gamma$  takes into account the buffering and depth of the membrane pool.

The main ion of interest is calcium. Wang [282] used  $\gamma = 0.002 \ \mu M$   $(ms \ \mu A)^{-1} cm^2$  to produce a 200 nM influx of calcium per spike. This amount is based on careful measurements reported in [120] in cortical pyramidal neurons. Wang also used a simple decay for calcium,  $\delta(X) = X/\tau$ , where for the dendrite,  $\tau = 80 \text{ ms.}$ 

#### 4.7 Calcium-Dependent Channels

The main reason to track calcium is that there are several important channels whose behavior depends on the amount of intracellular calcium. The two most important such channels are  $I_{K,Ca}$ , the calcium-dependent potassium current, and  $I_{can}$ , the calcium-dependent inward current. The former current appears in many neurons and is responsible for slow afterhyperpolarizations (AHPs) and spike-frequency adaptation. It is often referred to as the AHP current. The calcium-activated nonspecific cation (CAN) current can last for many seconds and causes sustained depolarization. It has been implicated in graded persistent firing [64] and in the maintenance of discharges by olfactory bulb granule cells [116]. To model these currents, we need to keep track of the calcium. Thus, (1) there must be a source of calcium and (2) we need to track it via (4.8).

# 4.7.1 Calcium Dependent Potassium: The Afterhyperpolarization

A typical model for  $I_{K,Ca}$  is due to Destexhe et al. [61]:

$$I_{\rm K,Ca} = g_{\rm K,Ca} m^2 (V - E_{\rm K}),$$
 (4.9)

$$\frac{\mathrm{d}m}{\mathrm{d}t} = (m_{\infty}(c) - m)/\tau_m(c), \qquad (4.10)$$

$$m_{\infty}(c) = \frac{c^2}{K^2 + c^2},\tag{4.11}$$

$$\tau_m(c) = \max(\tau_{\min}, \tau_0/(1 + (c/K)^2)). \tag{4.12}$$

Typically, K = 0.025 mM,  $\tau_{min} = 0.1$  ms, and  $\tau_0$  varies. In [61]  $\tau_0$  was around 40 ms, but values as high as 400 ms can be found in the literature. A simple way to incorporate this model into one which has a calcium channel is to assume it depends instantly on the calcium concentration,

$$m = m_{\infty}(c),$$

so to incorporate this current into a spiking model one need only add an instantaneous calcium channel (if one is not present), the calcium dynamics, and the



Fig. 4.7 Calcium-dependent potassium channel. (a) Spike-frequency adaptation showing decrease in frequency over time. (b) Steady-state firing rate with and without adaptation

instantaneous AHP current. As with all the models, the equations for this are found online. Figure 4.7a shows the behavior of the firing rate over time when this current is added to the Morris–Lecar model. The onset of spiking is unaffected by the presence of this current because it turns on only when the cell is spiking (and calcium enters the cell). Thus, unlike the M-current, the AHP current cannot alter the stability of the resting state.

One very interesting effect of the AHP is shown in Fig. 4.7b. It is not surprising that the AHP current lowers the frequency–current curve. However, it also tends to make the curve more linear. This point was first described in [282] for a model similar to that depicted above. We now attempt to explain the origin of this linearization effect [68]. We will first formulate this problem rather abstractly and then consider a full biophysical model.

Suppose the unadapted neuron is able to fire at arbitrarily low rates and that the derivative of the firing rate function tends to infinity as the threshold for firing is approached. Let z be the degree of adaptation in the model and suppose  $z = \alpha f$ , where f is the firing rate. The adaptation acts negatively on the total current injected into the neuron; thus,

$$f(I) = F(I - gz),$$

where F(I) is the unadapted firing rate function and g is some constant. Since  $z = \alpha f$ , this leads us to

$$f(I) = F(I - g\alpha f). \tag{4.13}$$

Differentiating this with respect to I and rearranging, we obtain

$$\frac{\mathrm{d}f}{\mathrm{d}I} = \frac{F'(I - \alpha gf)}{1 + \alpha gF'(I - \alpha gf)}$$

For large F', we see that

$$\frac{\mathrm{d}f}{\mathrm{d}I}\approx\frac{1}{\alpha g},$$

showing that it is approximately linear. If we suppose  $F(I) = A\sqrt{I}$  so that the neuron has a class I firing rate curve, we can exactly solve for f:

$$f(I) = -\kappa + \sqrt{\kappa^2 + A^2 I},$$
 (4.14)

where  $\kappa = A^2 \alpha g/2$ . For small *I*, the prominent nonlinearity in the firing rate curve disappears and the slope at the origin of the firing rate curve is finite. Thus, for currents near threshold, the firing rate is nearly linear.

What does this simple calculation have to do with the full biophysical model? We can exploit the slow dynamics of adaptation to justify (4.13). For simplicity, we assume the conductance of the adaptation is linear rather than the nonlinear model we used as an illustration. Consider

$$C\frac{\mathrm{d}V}{\mathrm{d}t} = I - I_{\mathrm{fast}} - gz(V - E_{\mathrm{K}}), \qquad (4.15)$$

$$\frac{\mathrm{d}z}{\mathrm{d}t} = \epsilon[q(V)(1-z) - z]. \tag{4.16}$$

Here,  $I_{\text{fast}}$  represents all the "fast" currents which are responsible for spiking. There are three keys to the analysis: (1)  $\epsilon$  is very small; (2) the fast system has class I dynamics; (3) the width of the spikes does not change very much as a function of the firing rate. Figure 4.7b shows that the present model is class I. The interested reader can verify that the spike width is nearly independent of the frequency. Finally, we have chosen the calcium time constant to be 300 ms, which is at least an order of magnitude slower than any of the other dynamics. (We remark that the calculations that follow will be often used to justify the simplified firing rate dynamics of biophysical models in Chap. 11.)

#### 4.7.1.1 Slow–Fast Analysis

Since  $\epsilon$  is small, we can treat z as a constant as far as the dynamics of the fast variables is concerned. Thus, we can examine (4.15) using I and z as parameters. Since  $gz(V - E_K)$  is essentially a constant hyperpolarizing current (when z is fixed), we expect that if we inject enough current into the cell, it will fire. We also expect that the onset of firing will be a SNIC at some critical current,  $I_{SN}(z)$ , depending on z. A numerical analysis of the model illustrated in Fig. 4.7 shows that

$$I_{\rm SN}(z) \approx I_0 + g I_1 z.$$

Recall that the firing rate of class I neurons is (at least near the bifurcation) a squareroot function of the distance from the saddle–node:

$$f(I,z) = A\sqrt{I - I_{\rm SN}(z)} \approx A\sqrt{I - I_0 - gI_1 z}.$$
 (4.17)

Thus, if  $I < I_{SN}$ , then the neuron does not fire and if  $I > I_{SN}$ , the neuron fires at a rate dependent on the distance from the saddle–node. Note that the function fneed not be exactly a square root. However, we do assume it depends only on the distance from the saddle–node and that the saddle–node value is a linear function of the degree of adaptation. Now we turn to the slow equation (4.16). We assume the function q(V) is such that if the neuron does not fire an action potential, then q(V) = 0. Thus, at rest, q = 0 and z = 0. Since the adaptation in this section is *high-threshold*, the subthreshold membrane behavior will have no effect on the degree of adaptation. Now, suppose the neuron is firing with period T. Then (4.16) is a scalar periodically driven equation:

$$\frac{\mathrm{d}z}{\mathrm{d}t} = \epsilon [q(V(t))(1-z) - z].$$

Since  $\epsilon$  is small, we can use the method of averaging [111] and replace z by its average Z:

$$\frac{\mathrm{d}Z}{\mathrm{d}t} = \epsilon < q > (1 - Z) - Z,$$

where

$$\langle q \rangle = \frac{1}{T} \int_0^T q(V(t)) \,\mathrm{d}t.$$

Now, we invoke the hypothesis that the spike width is independent of the frequency. Since q(V) is zero except during a spike and the spike width is independent of the frequency, the above integral simplifies to

$$\langle q \rangle = \frac{c}{T}.$$

Here, *c* is the integral of q(V(t)), a frequency-independent constant. But 1/T is just the frequency and this is given by (4.17). Thus, we obtain a closed equation for the degree of adaptation:

$$\frac{\mathrm{d}Z}{\mathrm{d}t} = \epsilon \left[ cA\sqrt{I - I_0 - I_1Z}(1 - Z) - Z \right]. \tag{4.18}$$

The steady states for this equation will yield the steady-state F-I curve. However, one has to solve a cubic equation to get the steady states, so it is not analytically tractable (but see Exercise 11).

#### 4.7.2 Calcium-Activated Nonspecific Cation Current

The CAN channel is similar in many ways to the AHP except that it produces an inward (depolarizing) current which can make the neuron fire quite actively. The

CAN current can be modeled very much like the AHP, so we model the CAN current simply as

$$I_{\rm CAN} = g_{\rm CAN} m_{\rm CAN}^p (V - E_{\rm CAN}).$$

The gate  $m_{\text{CAN}}$  obeys dynamics much like that of the AHP:

$$\frac{\mathrm{d}m_{\mathrm{CAN}}}{\mathrm{d}t} = (q(c)(1 - m_{\mathrm{CAN}}) - m_{\mathrm{CAN}})/\tau_{\mathrm{CAN}},$$

where q(c) is some monotonic function of the calcium. The reversal potential,  $E_{\text{CAN}}$ , ranges from -20 mV to near the calcium reversal potential. Typically,  $q(c) = \alpha (c/c_0)^2$ . The CAN current has been implicated in sustained firing of many neurons, notably those in the entorhinal cortex [64]. A simple illustration of sustained firing due to the CAN current is shown in Fig. 4.8. We use the Destexhe–Paré spiking model for the generation of action potentials and add a small amount of the CAN current:

$$I_{\rm Can} = g_{\rm can} m_c (V + 20),$$

where

$$\frac{\mathrm{d}m_c}{\mathrm{d}t} = 0.005 [Ca]^2 (1 - m_c) - m_c/3000.$$

Since the spiking model does not have any calcium channels, we suppose the synaptic stimulation of the model produces a square pulse of calcium of width 50 ms and magnitude 1 mM (see Chap. 6). The results of three pulses at t = 200, 700, 1200shows the long-lasting graded persistent activity. (This model is quite naive and cannot maintain the firing rate since the CAN current eventually decays. One way to rectify this is to have calcium channels in the model for spiking which will then provide positive feedback. Problems related to this are explored below in one of the exercises/projects.)



Fig. 4.8 The calcium-activated nonspecific cation (CAN) current can explain long-lasting persistent activity. (a) The voltage of a spiking model with three calcium stimuli. (b) The gate for the CAN current

# 4.8 Bibliography

There are thousands of papers in the neurophysiology literature that describe specific computational models for the channels here as well as dozens of other channels. A good place to start is the book by Huguenard and McCormick [131]. Biophysical intuition on what many of these channels do to the firing of the neuron is provided in [140]. The ModelDB Web page (http://senselab.med.yale.edu/senselab/ModelDB/ default.asp) can be searched by specific current and contains hundreds of models. Most of the models are in the scripting language NEURON [33]. Equations for all of rechannels in this chapter and all of reexercises can be found online.

#### 4.9 Exercises

1. On the basis of what you have seen in the Morris–Lecar system, one might guess that there is the possibility of getting oscillations in the Butera model when the fast sodium channel is blocked and the inactivation of the persistent sodium channel is held constant (that is, dh/dt = 0). Thus, the model could be reduced to a planar system in *V*, *n*:

$$C_{\rm m} \frac{\mathrm{d}V}{\mathrm{d}t} = -g_{\rm L}(V - E_{\rm L}) - g_{\rm K} n^4 (V - E_{\rm K}) - g_{\rm NaP} w_{\infty}(V) h(V - E_{\rm Na}),$$
  
$$\frac{\mathrm{d}n}{\mathrm{d}t} = (n_{\infty}(V) - n) / \tau_n(V).$$

Compute the bifurcation diagram of this using h as a parameter at a variety of different values of  $E_{\rm L}$ . Conclude that there can be no oscillations for this. How would you change the shape of  $n_{\infty}(V)$  to generate oscillations in this model?

- 2. Compute the bifurcation diagram of the T-current model using  $E_{\rm L}$  as a parameter starting it at  $-60 \,\mathrm{mV}$  and decreasing it to  $-85 \,\mathrm{mV}$ . Simulate the model when there are calcium oscillations.
- 3. Add sodium and potassium currents to the T-current model using the equations online for cat-spike.ode. Show that when the resting potential is depolarized ( $E_{\rm L} = -65$ ), the application of sufficient depolarizing current leads to a train of action potentials. Show the analogues of Fig. 4.2a and c for the spiking model.
- 4. The T-type calcium current was shown to be capable of oscillations and rebound depending on the leak current. Explore the L-type calcium current, which has calcium-dependent inactivation. The model equations for this are given online. The activation is set to its steady state so that the resulting model is planar. Explore the bifurcation to periodic solutions as a function of the applied current. Compute the bifurcation diagram as  $I_0$ , the applied current, is increased.
- 5. The Connor–Stevens model has its parameters balanced at a nearly critical value in that there are many complicated bifurcations which can occur nearby.

This has not been systematically explored, although Rush and Rinzel mentioned the unusual behavior. Use the Connor–Stevens model in which the A-current and delayed rectifier current are balanced so that their total maximal conductance is fixed. (That is, let  $g_{\rm K} = 67.7 - g_{\rm A}$  in the Connor–Stevens model.) The standard values are  $g_{\rm A} = 47.7$  and  $g_{\rm K} = 20$ . (a) Change the model so that  $g_{\rm A} = 48.7$  and  $g_{\rm K} = 19$ . Compute the bifurcation diagram and show that there are at most three fixed points. (b) Change  $g_{\rm A} = 47.4$  and  $g_{\rm K} = 20.3$ . Compute the bifurcation diagram as a function of the current. Show that there is a small range of currents where there are two stable fixed points. Now, use the parameters  $g_{\rm A}$  and  $I_0$  to create a two-parameter diagram of fold points and Hopf points. You should find something that looks like the left figure below. There are three cusp points corresponding to the coalescence of fold points. There is also a curve of Hopf points which terminates on one to the folds at a Takens–Bogdanov point. An expanded view is shown on the right. Thus, the standard parameters for the Connor–Stevens model are quite weird!



- 6. Compute the *F*-*I* curve for the Destexhe–Paré model with  $g_m = 0$  and with  $g_m = 5$  and compare the two.
- 7. Create a figure like Fig. 4.4b for the Destexhe–Paré model ( $I = 6, g_m = 2$ ) and try to fit the data to a function of the form

$$F = F_{\rm ss} + (F_{\rm inst} - F_{\rm ss})\lambda^{n-1},$$

where  $F_{ss}$  is the steady-state firing rate,  $F_{inst}$  is the instantaneous rate,  $\lambda$  is a parameter, and *n* is the initial interspike interval number. The parameters  $F_{ss}$  and  $F_{inst}$  characterize the degree of adaptation and the parameter  $\lambda$  characterizes the timescale of adaptation.

8. Make a neural oscillator using the inward rectifier and a delayed rectifier model of the form

$$I_{\rm K} = g_{\rm K} n^4 (V - E_{\rm K}),$$

where

$$\frac{dn}{dt} = (1/(1 + \exp(-(V - a)/b)) - n)/\tau.$$

You should try to pick a, b, and  $\tau$  so that the model oscillates. Do not worry if the choices of a are quite low values. Use  $g_{\text{Kir}} = 0.5$ ,  $E_{\text{K}} = -90$ ,  $E_{\text{L}} = 60$ ,  $g_{\text{L}} = 0.05$ , and  $V_{\text{th}}$ , k as in the text.

9. Inward rectifier and potassium accumulation. Let

$$I_{\rm K} = g_{\rm K} m_{\infty}(V) (V - E_{\rm K}),$$

where

$$m_{\infty}(V) = 1/[1 + \exp((V + 71)/0.8)]$$

and

$$E_{\rm K} = 85 \log_{10} K_{\rm out}.$$

Consider the model with external potassium accumulation with passive uptake:

$$C \frac{\mathrm{d}V}{\mathrm{d}t} = I - g_{\mathrm{L}}(V - E_{\mathrm{L}}) - I_{\mathrm{K}},$$
  
$$\tau \frac{\mathrm{d}K_{\mathrm{out}}}{\mathrm{d}t} = \alpha I_{\mathrm{K}} + K_{0} - K_{\mathrm{out}},$$

where  $K_0 = 0.1$ ,  $\alpha = 0.2$ ,  $g_L = 0.1$ , and  $g_K = 0.1$  Sketch the phase plane for various hyperpolarizing currents. Show that if you choose *I* in some small range and  $\tau$  to be sufficiently large, you will obtain oscillations in the potential. (Hint: Show that the *V*-nullcline can be cubic and that it can intersect the  $K_{\text{out}}$ -nullcline in the middle branch. Then, increase  $\tau$  until this fixed point is unstable.)

- 10. Consider a combination of the sag current and the inward rectifier. Parameters should be taken from the model online. Draw the phase plane and integrate the equations. Change the sag model from the McCormick parameters to the Migliore parameters. Does the model still generate subthreshold oscillations? Compute the bifurcation diagram for the model using *I* as a parameter. How is the oscillation born and how does it die?
- 11. Suppose Z is small in (4.18) so that the equation is well approximated by

$$\frac{\mathrm{d}Z}{\mathrm{d}t} = \epsilon [cA\sqrt{I - I_0 - gI_1Z} - Z].$$

Find the steady states of Z and obtain the F-I curve from this.

12. Repeat the calculations for the slow-adaptation model by explicitly computing the averaged quantities for the theta model:

$$\frac{\mathrm{d}\theta}{\mathrm{d}t} = 1 - \cos\theta + (1 + \cos\theta)[I - gz],$$
$$\frac{\mathrm{d}z}{\mathrm{d}t} = \epsilon[\delta(\theta - \pi) - z].$$

The right-hand side of z says that each time  $\theta$  crosses  $\pi$ , z is increased by an amount  $\epsilon$ . Numerically compute the F-I curve for this model with different

values of g (say, 0, 1, 5). Since the firing rate of the unadapted theta model is known exactly (see Exercise 8, Chap. 3.), you should try to fit the numerically computed F-I curves to (4.14).

13. A model related to that in the previous exercise adds spike adaptation to the quadratic integrate-and-fire model. The simplest form of this model is

$$V' = I + V^{2} - u,$$

$$u' = a(bV - u),$$
(4.19)

along with reset conditions such that when  $V = V_{\text{spike}}$ , V is reset to c and u is increased by d. By rescaling V, you can set  $V_{\text{spike}} = 1$  with no loss in generality. (Do this.) The variable u plays several roles in this model. If a = 0, then it can have no effect on the local behavior of the rest point. However, if  $a \neq 0$ , the adaptation can change the stability of rest. Touboul [268] provided a complete analysis of this model as well as generalizations to other nonlinearities.

- (a) Suppose there is a resting state, (V, u). Linearize about the resting state and find the parameters (a, b, I) where there is a saddle-node bifurcation, a Hopf bifurcation, and where the two bifurcations merge at a Takens-Bogdanov point. This is not surprising as the next part of this exercise will show.
- (b) The Takens–Bogdanov bifurcation occurs when there is a double-zero eigenvalue which has geometric multiplicity 1. The Takens normal form for this bifurcation takes the form

$$\frac{\mathrm{d}w}{\mathrm{d}t} = z + \beta w + w^2, \qquad \frac{\mathrm{d}z}{\mathrm{d}t} = \alpha + w^2.$$

Let r = w - z and write equations for the new (r, w) system. Next, let

$$x = w + \frac{\beta + 1}{2},$$
  
$$z = \frac{r}{\beta + 1} + \frac{\alpha + (\beta + 1)^2/2}{\beta + 1},$$

yielding

$$\frac{\mathrm{d}x}{\mathrm{d}t} = -(\beta+1)z + x^2 + k, \qquad \frac{\mathrm{d}y}{\mathrm{d}t} = x - y,$$

where

$$k = \alpha + (\beta + 1)^2/4.$$

Thus, the local dynamics of the quadratic integrate-and-fire model with spike adaptation is the same as that of the normal form. Note that we can get rid of the parameter a by rescaling time and V, z in (4.19). You should attempt this.

(c) The F-I curve of this model cannot be analytically derived even when a = 0, nor can we use AUTO or other bifurcation tools to obtain the F-I curve

since the reset condition makes the equations discontinuous. However, we can pose this as a boundary value problem which *is* smooth and so can be computed with AUTO. We suppose there is a repetitively firing solution with period *P*. This means V(0) = c and V(P) = 1. Thus, the boundary conditions for *V* are specified. We also require that u(0) = u(P)+d since *u* is increased whenever *V* crosses 1. Since the period is unknown, we rescale time, t = Ps, and thus have the following equations:

$$V' = P(V^{2} + I - u),$$
  

$$u' = Pa(bV - u),$$
  

$$V(0) = c,$$
  

$$V(1) = 1,$$
  

$$u(0) = u(1) + d.$$

There are *three* boundary conditions, but only two differential equations. However, there is a free parameter P which can allow us to solve the equations. For example, take (a, b, c, d) = (0.1, 1, -0.25, 0.5) and I = 1 and you will find a repetitive spiking solution with u(0) = 1.211 and period P = 5.6488. Try this, and then use AUTO or some other method to compute the F-I curve. The analysis of the resting state that you did above should tell you the lowest possible current for repetitive firing.

14. Izhikevich [134] adapted the quadratic integrate-and-fire model with linear adaptation (4.19) to look more like a biophysical model. The model has four free parameters as well as the current. The equations are

$$\frac{dV}{dt} = 0.04V^2 + 5V + 140 + I - u, \qquad (4.20)$$
$$\frac{du}{dt} = a(bV - u)$$

along with the reset conditions if V = 30 then V = c and u = u + d. Find a change of variables which converts (4.20) to (4.19). Izhikevich suggested the following sets of parameters (a, b, c, d, I) for various types of neurons. Try these and classify the behavior: (0.02,0.2,-65,6,14), (0.02,0.2,-50,2,15), (0.01,0.2,-65,8,30), (0.2,0.26,-65,0), and let *I* vary in this example. For each of these, start with I = 0 and then increase *I* to the suggested value. Can you derive a method for numerically following a bursting solution as a function of some parameter? (It is likely you will have to fix the number of spikes in a burst.)

15. Sakaguchi and Tobiishi [240] devised a simple model for a one-variable bursting neuron. The equation is as follows:

$$C \frac{\mathrm{d}V}{\mathrm{d}t} = \alpha (V_0 - V + DH(V - V_{\mathrm{T}})),$$
 (4.21)

where H(X) is the step function. There are two reset conditions. If V crosses  $V_{\rm T}$  from below, then V is boosted to  $V_1$ . If V crosses  $V_{T2}$  from above, V is reset to  $V_2$ . Sakaguchi used  $\alpha = 0.035$ , C = 2,  $V_0 = 30$ , D = 5,  $V_{\rm T} = -35$ ,  $V_1 = 50$ ,  $V_2 = -50$ , and  $V_{T2} = 40$ . Compute the period of the Sakaguchi burster for these parameters. What are the conditions on the various resets and thresholds for this model to have sustained periodic behavior?

# 4.10 Projects

In this section, we lay out some projects that could be used in a classroom setting.

- 1. *Artificial respiration*. The Hering–Breuer reflex is a phenomenon through which it has been shown that mechanical deformation of the lungs can entrain the respiratory pattern generator. Use the full Butera model as your simple pacemaker. This pacemaker provides the motor output for the inspiratory phase of breathing. The ventilator provides both inflation and deflation. Inflation is known to inhibit the motoneuron pools for inspiration, so assume the ventilator provides periodic inhibitory input. Explore the range of frequencies and patterns of entrainment and the conditions under which there is 1:1 locking.
- 2. Calcium feedback and bistability. Consider a spiking model

$$C\frac{\mathrm{d}V}{\mathrm{d}t} = -I_{\mathrm{L}} - I_{\mathrm{Na}} - I_{\mathrm{Kdr}} - I_{\mathrm{Ca}} - I_{\mathrm{Can}} + I(t),$$

where you can use the Destexhe–Paré model of the leak, sodium, and potassium currents. Choose a very small instantaneous high-threshold calcium current as was done for the calcium-dependent potassium current. Add calcium dynamics and a CAN current. Try to adjust the parameters so that a sufficient stimulus generates sustained firing. If you give a very strong stimulus, you should be able to get more calcium into the system and thus increase the CAN current. This may lead you to believe that you can get graded persistent firing. But simulations should convince you that the best you can get is bistability. Can you design a model (even an abstract one) which has many fixed points and thus admits a variety of steady-state firing rates? (Hint: See [93, 184, 260].)

3. *Bifurcation analysis of the adaptive exponential integrate-and-fire model (aEIF).* Brette and Gerstner [22] proposed the following simple two-variable integrateand-fire model

$$C \frac{\mathrm{d}V}{\mathrm{d}t} = I - g_{\mathrm{L}}(V - E_{\mathrm{L}}) + g_{\mathrm{L}}\Delta_{\mathrm{T}} \mathrm{e}^{(V - V_{\mathrm{T}})/\Delta_{\mathrm{T}}} - w,$$
  
$$\tau_{w} \frac{\mathrm{d}w}{\mathrm{d}t} = a(V - E_{\mathrm{L}}) - w$$

with the provision that when V(t) = 20, it is reset to  $V_r$  and w is increased by an amount b. A lengthy project would be to study the local behavior of this model using combined analytical and computational methods. For example, find the saddle-node and Hopf bifurcations. Brette and Gerstner fit this model to a detailed biophysical model with parameters C = 281 pF,  $g_L = 20 \text{ nS}$ ,  $E_L =$ -70.6 mV,  $V_T = -50.4 \text{ mV}$ ,  $\Delta_T = 2 \text{ mV}$ ,  $\tau_w = 144 \text{ ms}$ , a = 4 nS, and b =0.0805 nA. Note the units, w is a current and V is a voltage. The time constant of the cell at rest is roughly 9 ms.