

## 4 Subthreshold Gain

We consider how dendrites may have gain, and possibly generate spikes, as a means of faithfully communicating dendritic signals. This seems more and more to be the rule as a means to avoid the big (and highly conducting) soma if you expect it to integrate subthreshold potentials. These issues were first addressed in hippocampal neurons by Spenser and Kandel back in 1961, whose data was consistent with dendritic spiking. While it has been known for quite some time that the dendrites of DRG cells produce spikes, a good twenty years went by until dendritic spiking was directly observed in neurons local to the mammalian brain. The best studied of these is the cerebellum, with more recent work focused on hippocampal cells.

### 4.1 Dendritic Gain and Spikes

As we will see shortly, gain results in amplification without a regenerative events, e.g., without a bistable potential like we talked about on the first day, while spiking is such a bistable event. The same channels are often involved in the two processes, except that for gain alone the density may be much lower, i.e., a critical current and thus a critical density must be reached for a regenerative event.

Gain is usually associated with channels that are activated (or inactivated) near the resting potential of a neuron, which is typically in the range -70 to -50 mV. The two iontrophoretic gain mechanism are

- The turning on of a current that has a positive reversal potentials, such as the noninactivating or persistent  $Na^+$ -current ( $V_{th} \approx -50mV$ ) or the low-threshold (T- or transient-type) calcium current ( $V_{th} \approx -40mV$ ).
- The turning off of a current that has a negative reversal current, such as the inward rectifier potassium channel ( $V_{th} \approx -60mV$ )

Without loss of generality, we consider the circuit equations for a cell with a leak current and a voltage activated persistent  $Na^+$  current. The leak current includes all the linear conductances and potentials, i.e.,  $V_{Leak}$  and  $G_{Leak}$ . In EE-speak, this is the Thevnin equivalent circuit for all but the  $Na^+$  current. The  $Na^+$  current is assumed to be of the form  $I_{Na} = G_{Na}P(V)[V - V_{Na}]$ , where  $P(V)$  is a Boltzman activation curve of the form

$$P(V) = \frac{1}{1 + e^{-ze(V-V_{th})/k_B T}} \quad (4.1)$$

The circuit equation for our model is

$$C \frac{dV}{dt} = G_L[V - V_{Leak}] + G_{Na}P(V)[V - V_{Na}] + I_{ext} \quad (4.2)$$

At steady state, such as when the cell is at its resting potential,  $dV/dt = 0$  and the steady state potential, denoted  $V^{ss}$ , is found by solving the transcendental equation

$$0 = G_L[V^{ss} - V_{Leak}] + \frac{G_{Na}[V^{ss} - V_{Na}]}{1 + e^{-ze(V^{ss}-V_{th})/k_B T}} + I_{ext} \quad (4.3)$$

For  $V^{ss} \ll V_{th}$ , clearly  $V^{ss} \simeq V_{Leak}$ . We can linearize the response for voltage changes around  $V^{ss}$  for a given change in current  $\Delta i$ . We denote  $\Delta v \equiv V - V^{ss}$ , so that

$$\Delta i = G_L \frac{d[V - V_{Leak}]}{dV} \Big|_{V=V^{ss}} \Delta v + G_{Na} \frac{d(P(V)[V - V_{Na}])}{dV} \Big|_{V=V^{ss}} \Delta v . \quad (4.4)$$

Noting that

$$\frac{dP(V)}{dV} = \frac{ze/k_B T}{(1 + e^{-ze(V-V_{th})/k_B T})^2} = \frac{ze}{k_B T} P(V)[1 - P(V)] \quad (4.5)$$

the conductance, given by the slope of the I-V curve, is given by

$$\begin{aligned} \frac{\Delta i}{\Delta v} &= G_L + G_{Na} \left( 1 + [1 - P(V^{ss})] \frac{ze(V^{ss} - V_{Na})}{k_B T} \right) P(V^{ss}) \\ &= G_L + G_{Na} \left( 1 - [1 - P(V^{ss})] \frac{ze(V_{Na} - V^{ss})}{k_B T} \right) P(V^{ss}) \end{aligned} \quad (4.6)$$

The key is the term that multiples  $G_{Na}$ . If it is greater than zero, the sodium conductance leads to a larger overall conductance and the cell is less sensitive to its inputs. On the other hand, if the term is less than zero, the overall conductance of the cell has gone down and a given input current will lead to a larger voltage change. This constitutes gain, as the total conductance is reduced to less than  $G_L$ . It occurs when

$$[1 - P(V^{ss})] \frac{ze(V_{Na} - V^{ss})}{k_B T} > 1 \quad (4.7)$$

The minus sign constitutes the competition between attenuation via increased channel conductance and depolarization through the pull to  $V_{Na+}$ .

For the case of  $V^{ss} \ll V_{th}$ , we can expand  $1 - P(V^{ss})$  as

$$1 - P(V^{ss}) = \frac{1}{1 + e^{ze(V^{ss}-V_{th})/k_B T}} \sim 1 - e^{-ze|V^{ss}-V_{th}|/k_B T} \quad (4.8)$$

to form the inequality

$$\left[ 1 - e^{-ze|V^{ss}-V_{th}|/k_B T} \right] \frac{ze(V_{Na} - V^{ss})}{k_B T} > 1 \quad (4.9)$$

The equality can be satisfied for all potentials because  $(V_{Na} - V^{ss}) \sim 100$  mV  $\sim 4k_B T/e$ ,  $z = 4$  (more or less) for  $Na^+$  channels, and the exponential term is very

small. Thus the persistent  $Na^+$  channel leads to always gain at hyperpolarizing potentials. However, the size of the gain is small since  $P(V^{ss})$  is exponentially small.

For the case of  $V^{ss} \sim V_{th}$ , we can expand  $1 - P(V^{ss})$  as

$$1 - P(V^{ss}) \sim \frac{1}{1 + [1 + ze(V^{ss} - V_{th})/k_B T + \dots]} \sim \frac{1}{2} \left[ 1 + \frac{ze(V^{ss} - V_{th})}{2k_B T} \right] \quad (4.10)$$

to form the inequality

$$\left[ 1 + \frac{ze(V^{ss} - V_{th})}{2k_B T} \right] \frac{ze(V_{Na} - V^{ss})}{2k_B T} > 1 \quad (4.11)$$

which is true for a range of useful potentials, at least until  $V^{ss}$  exceeds  $V_{th}$  by about  $k_B T/2e \sim 12$  mV.

Lastly, in the limit of  $V^{ss} \gg V_{th}$ , we can expand  $1 - P(V^{ss})$  to form the inequality

$$e^{\frac{-ze|V^{ss}-V_{th}|}{k_B T}} \frac{ze(V_{Na} - V^{ss})}{k_B T} > 1 \quad (4.12)$$

which is generally not true because of the exponential factor. Thus we see that gain exists only for a range of potentials not too far above  $V_{th}$ , and that they are significant only for  $V^{ss} \sim V_{th}$ .

One may also ask what happens if the negative conductance term with  $G_{Na}$  gets so big that the total conductance goes negative. This, as we shall soon see, leads to an unstable situation and gives rise to the action potential.

#### 4.1.1 Gain by Persistent $Na_+$ Currents

Hirsch performed measurements of the post synaptic potential caused by a distal input as a function of the post-synaptic potential. Such a systematic exploration has the means to reveal an underlying gain mechanism. In particular, in the absence of gain the post synaptic potential will decrease as the cell is depolarized due to a drop in driving force, since the synaptic current is proportional to  $V - V_{Na}^+$ . In practice, Hirsch observed gain that was dependent on a persistent- $Na^+$  current.

#### 4.1.2 Gain by Inward Rectifier $K_+$ Currents

Wessel performed measurements of the post synaptic potential caused by a distal input as a function of the post-synaptic potential. He found that the post synaptic potential increased as the steady-state voltage of the cell increased. Unlike the experiments of Hirsch, in this case the gain was caused by a turning off of a  $K^+$  channel, the inward rectifier, so named since its threshold for activation is close to the reversal potential. The effect of turning off the channel is seen both in the conductance and the time constant of the cell.

One consequence of the gain is that the response to successive EPSP's increases in amplitude.

### 4.1.3 Gain by Low Threshold $Ca^{2+}$ Currents

An independent mechanism for gain is localized spikes in specific dendrites. In particular, Llinas showed that the dendrites actually produce  $Ca^{2+}$ -based, as opposed to  $Na^+$ -based spikes.

The issue of localization of calcium currents was first addressed in the imaging experiments of Ross, using a  $Ca^{2+}$  sensitive dye in slice. He found that selective regions of the distal dendrites could be excited, providing experimental evidence for the idea of localized activation in dendrites.