6 Compartments and Subthreshold Gain

In the presence of active currents it is usually untenable to model the dynamics of a cell analytically. Thus one breaks the cell into a number of compartments, each of which is a fraction of λ from the previous compartment. We choose to largely avoid the pain of this exercise. While this exercise may ne necessary, at least at the level of a few compartments, when active currents are involves, it is usually an absurd exercise then the dendrites are totally passive. Simply put, electrically long passive dendrites are a nice way to heat up the brain without transmitting much information.

As a means to garner intuition as to the effect of injecting current in the soma versus out in a process, we consider a circuit for a four compartment model of a neuron. The cell consists of a soma, an "apical" dendrite and two distal dendrites. We take each compartment to be on space constant from the other (typically $\lambda \sim 200$ to $500\mu m$), which we "fake" by having cytoplasmic (serial) and parallel (membrane) conductances, denoted G, to be of equal value. We add a touch of realism by taking the somatic conductance, denoted G_s, to be different (generally smaller!) .

FIGURE - chapt-6-compartment-model.eps

$$\begin{aligned} G_s V_s + G(V_s - V_o) &= 0 \\ GV_o + G(V_o - V_s) + G(V_o - V_1) + G(V_o - V_2) &= 0 \\ GV_1 + G(V_1 - V_o) &= -I \\ GV_2 + G(V_2 - V_o) &= 0 \end{aligned} \tag{6.1}$$

so that, with $\Gamma \equiv \frac{G_s}{G}$,

$$V_1 = -\frac{5+7\Gamma}{8+12\Gamma} IG = \begin{cases} -\frac{7}{12} IG & \text{if } \Gamma >> 1 \\ -\frac{6}{10} IG & \text{if } \Gamma = 1 \end{cases}$$

$$V_2 = -\frac{1+\Gamma}{8+12\Gamma} IG = \begin{cases} -\frac{1}{12} IG & \text{if } \Gamma >> 1 \\ -\frac{1}{10} IG & \text{if } \Gamma = 1 \end{cases}$$

$$V_s = -\frac{1}{(4+6\Gamma)} IG = \begin{cases} -\frac{1}{6\Gamma} IG \to 0 & \text{if } \Gamma >> 1 \\ -\frac{1}{10} IG & \text{if } \Gamma = 1 \end{cases}$$

The lesson is pretty clear. Dendrites can be used to segregate synaptic inputs. The cost is not too high, e.g., in this example about half the signal is lost as the

price of segregation. However, we pay a high price for this in terms of the signal at the soma, particularly if the conductance of the soma is relatively high. To overcome the loss, one might 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.

FIGURE - chapt-6-sackmann.eps

6.1 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

$$P(V) = \frac{1}{1 + e^{-ze(V-V_{th})/k_BT}} \tag{6.2}$$

The circuit equation for our model is

$$C\frac{dV}{dt} = G_L[V - V_{Leak}] + G_{Na}P(V)[V - V_{Na}] \tag{6.3}$$

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 transendental equation

$$0 = G_L[V^{ss} - V_{Leak}] + \frac{G_{Na}[V^{ss} - V_{Na}]}{1 + e^{-ze(V^{ss}-V_{th})/k_BT}} \tag{6.4}$$

For $V^{ss} << V_{th}$, clearly $V^{ss} \simeq V_{Leak}$. We can linearize the response for voltage changes around V^{ss}. We denote $v \equiv V - V^{ss}$, so that

$$C\frac{dv}{dt} = G_L\frac{d[V - V_{Leak}]}{dV}|_{V=V^{ss}}v + G_{Na}\frac{d\left(P(V)[V - V_{Na}]\right)}{dV}|_{V=V^{ss}}v \quad . \tag{6.5}$$

Noting that

$$\frac{dP(V)}{dV} = \frac{ze/k_BT}{(1 + e^{-ze(V-V_{th})/k_BT})^2} = \frac{ze}{k_BT}P(V)[1 - P(V)] \tag{6.6}$$

we have

$$\begin{aligned} C\frac{dv}{dt} &= \left[G_L + G_{Na}\left(1 + [1 - P(V^{ss})]\frac{ze(V^{ss} - V_{Na})}{k_BT}\right)P(V^{ss})\right]v \qquad (6.7)\\ &= \left[G_L + G_{Na}\left(1 - [1 - P(V^{ss})]\frac{ze(V_{Na} - V^{ss})}{k_BT}\right)P(V^{ss})\right]v \end{aligned}$$

The key is the term that multiples G_{Na}. If it is greater than 1 the sodium conductance leads to a large overall conductance and the cell is less sensitive to its inputs. On the other hand, if the term is less than one, the overall conductance of the cell has gone down and a given input current will lead to a larger voltage change. This constitutes gain. It occurs when

$$[1 - P(V^{ss})]\frac{ze(V_{Na} - V^{ss})}{k_BT} > 1 \tag{6.8}$$

FIGURE - chapt-6-famous-model.eps

For $V^{ss} << V_{th}$, we can expand $P(V)$ to form the inequality

$$\left[1 + \frac{ze(V_{th} - V^{ss})}{2k_BT}\right]\frac{ze(V_{Na} - V^{ss})}{2k_BT} > 1 \tag{6.9}$$

which is generally true if only because $(V_{Na} - V^{ss}) \sim 100mV \sim 4\frac{e}{k_BT}$ and $z = 4$ (more or less) for Na^+ channels. Thus the persistent Na^+ channel leads to gain at low potential.

For the case of $V^{ss} \sim V_{th}$, we have

$$\frac{ze(V_{Na} - V^{ss})}{2k_BT} > 1 \tag{6.10}$$

which, again, is generally true. Lastly, in the limit of $V^{ss} >> V_{th}$, we can expand $P(V)$ to form the inequality

$$e^{\frac{-ze(V_{ss}-V^{th})}{k_B T}} \frac{ze(V_{Na} - V^{ss})}{k_B T} > 1 \tag{6.11}$$

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}. 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, this leads to an unstable situation and gives rise to the action potential.

6.1.1 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 decreases as the cell is depolarized due to a drop in driving force, since the synaptic current is proportional to $V - V_N a^+$. In practice, Hirsch observed gain that was dependent on a persistent-Na^+ current.

FIGURE - chapt-6-hirsch-gilbert-1.eps

FIGURE - chapt-6-hirsch-gilbert-2.eps

6.1.2 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 it's 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.

FIGURE - chapt-6-wessel-1.eps

FIGURE - chapt-6-wessel-2.eps

One consequcne of the gain is that the respone to successive EPSP's increases in amplitude.

FIGURE - chapt-6-wessel-3.eps

6.1.3 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.

FIGURE - chapt-6-llinas.eps

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.

FIGURE - chapt-6-ca-imaging.eps

FIGURE - chapt-6-ross.eps