Appendix B  Time average voltage

Koch et al. (1995) argue that to a surprisingly good approximation the time averaged voltage of a simulated cell above threshold depends logarithmically on the applied current and linearly on the firing frequency. This dependence suggests that the spiking mechanism be modeled by a diode, a circuit element with a logarithmic relationship between voltage and current—the diode model. However, this was only tested this for one particular model of a cell, the model described by Bernander et al. (1991, 1994). Since that compartmental model had only voltage-independent time constants for the conductances, it is possible that the relationship is an artifact of the model and does not apply to real cells.

I attempted to explore the validity of the logarithmic relationship for other systems. I looked at integrate and fire cells and the basic Hodgkin-Huxley equations; I also attempted to test real cells in slice as well.

B.1  Integrate–and–fire

For integrate and fire cells receiving constant input it is possible to compute the time averaged voltage analytically. Suppose we have a leaky integrator with a capacitance $C$, a membrane resistance $R$, and a threshold voltage $V_{th}$. Then the membrane potential between spikes is described by

$$C \frac{dV_m}{dt} = -\frac{V_m}{R} + I$$  \hspace{1cm} (B.1)

where $I$ is the input current. Let $T$ be the interval between spikes not counting the refractory period; then

$$T = \begin{cases} -RC \ln \left(1 - \frac{V_m}{V_{th}}\right) & \text{for a leaky integrator}, \\ \frac{CV_m}{V_{th}} & \text{for a perfect integrator}. \end{cases}$$  \hspace{1cm} (B.2)

The time averaged membrane potential, averaging over the spike itself and the refractory period as well as the intervals between spikes, will be

$$\langle V_m \rangle = ft_r V_{\text{spike}} + (1 - ft_r)V_{ISI},$$  \hspace{1cm} (B.3)

where $f$ is the firing rate and $t_r$ is the length of the spike and the refractory period, $V_{\text{spike}}$ is the average voltage during the whole period $t_r$, including both the spike and the refractory period. This is an arbitrary constant in the integrate-and-fire model, $V_{ISI}$ is the average voltage between spikes (during all the time not counted in the refractory period $t_r$).

$V_{ISI}$ can be computed from

$$V_{ISI} = \frac{1}{T} \int_0^T V_m(t) \, dt,$$  \hspace{1cm} (B.4)

where (as above) $T$ is the length of the period between spikes, not including the refractory period. For a perfect integrator, since the voltage increases linearly, this works out to be $V_{ISI} = V_{th}/2$.  

APPENDIX B.  TIME AVERAGE VOLTAGE
After some rearrangements,

\[ \langle V_m \rangle = \frac{V_{th}}{2} + \frac{t_r}{t_r + \frac{C}{V_m}} \left( V_{spike} - \frac{V_{th}}{2} \right) \]

\[ = \frac{V_{th}}{2} + f_r \left( V_{spike} - \frac{V_{th}}{2} \right). \]  

(B.5)

Thus \( \langle V_m \rangle \) depends linearly on the firing frequency \( f \) and sub-linearly (not exactly logarithmically) on \( I \). If there were no refractory period \( (t_r = 0) \) then \( \langle V_m \rangle = V_{th}/2 \), regardless of the value of \( f \) and \( I \).

For a leaky integrator, the time averaged membrane potential is linear in \( I \) if \( I < I_{th} \), where \( I_{th} = V_{th}/R \) is the current threshold. For \( I > I_{th} \),

\[ \langle V_m \rangle = \left( 1 - \frac{t_r}{t_r - \tau \ln \left( 1 - \frac{I}{I_{th}} \right)} \right) \left( \frac{I}{I_{th}} + \frac{1}{\ln \left( 1 - \frac{I}{I_{th}} \right)} \right) V_{th} + \]

\[ \frac{V_{spike} t_r}{t_r - \tau \ln \left( 1 - \frac{I}{I_{th}} \right)} \]

\[ = (1 - f_r) \left( \frac{1}{1 - e^{-(\frac{I}{I_{th}})/\tau}} + \frac{\tau}{I - I_{th}} \right) V_{th} + f_r V_{spike} \]

(B.6)

where \( \tau = RC \). This function is non-monotonic because for just subthreshold currents, \( \langle V_m \rangle \approx V_{th} \); when spiking begins, the spike reset mechanism reduces the potential back to zero, thus lowering \( \langle V_m \rangle \). For high \( I \) the curve approaches that of the perfect integrator but always remains a distance away; the leak is like subtracting a constant current (chapter 4).

These results for one particular set of numerical parameters are shown in figure B.1. Membrane potential is approximately a logarithmic function of current, but not a linear function of firing frequency except when the interspike interval is comparable to the time constant.
Figure B.2: Time averaged membrane potential for the Hodgkin-Huxley equations in a single compartment. Simulations were for the parameters measured for the squid at 6.3°C. Parameters: cell body was a cylindrical compartment with a diameter of 500 μm and a length of 100 μm, with a capacitance of 1 μF/cm². \( g_{Na} = 0.12 \) S/cm², \( g_{K} = 0.036 \) S/cm², \( g_{leak} = 0.0003 \) S/cm², \( E_{Na} = 50 \) mV, \( E_{K} = -77 \) mV. The logarithmic fit (\( \langle V_{m} \rangle = 4.0 \ln I - 67 \)) was done by eye; the linear fit (\( \langle V_{m} \rangle = 0.14f - 65.3 \)) was done with linear regression on the points above threshold.

### B.2 Hodgkin-Huxley equations

Simulation of the raw Hodgkin-Huxley equations using the defaults in the NEURON program produce similar looking plots (figure B.2). \( \langle V_{m} \rangle \) is not exactly logarithmic (not as impressively logarithmic as the model discussed by Koch et al., 1995) but can be approximated by a logarithm. Above threshold, \( \langle V_{m} \rangle \) is approximately linear in \( f \).

### B.3 Cortical cells in slice

Although conceptually simple, it is sometimes difficult to determine \( \langle V_{m} \rangle \) for cells in response to current injection. If bridge circuitry is used, as in the case of the many recordings I examined from the laboratory of Kevan Martin and Rodney Douglas, often the bridge is not exactly balanced. Also, in some cases electrode polarization causes a slower change in the membrane potential which can be significant for higher currents. Since the shift is dependent on the current (often proportional to it for low currents), this can give seriously misleading results.

I analyzed data collected from cat area 17 slices by Berman (1991). In only one experiment (s98) were the current injections long enough (320 ms) for averaging over time. Most of the 36 cells from this experiment do not appear to have a stable enough membrane potential when current is being injected to be useful in this analysis\(^1\), since we expect that the time averaged membrane potential changes very slowly as a function of current; systematic differences of 1–2 mV may seriously affect the results.

It is difficult to determine with any precision whether there is an artifactual shift in the DC potential since there is no clear reference point. The peak amplitude of a spike does not seem to be a good indicator because the spikes are slightly shorter when the current is higher. Instead, I determined by eye whether the spike thresholds appeared to be constant as a function of current and time. I found that I was able to discriminate differences of about 1 mV by eye.

This means we can only discuss the average membrane voltage relative to threshold. However, it is reasonable to expect from biophysical models that the voltage threshold should not change much

\(^1\)Many of them probably could be compensated by subtracting a linear function of the current from the membrane voltage, but I did not want to introduce any more assumptions.
Figure B.3: Example of procedure for determining variations in baseline. For each trial of the cell at a different current level, 20 ms surrounding each of the last 10 spikes are extracted and aligned on the trace. Different groups of aligned spikes correspond to trials with different current levels. As the current increases (from left to right), the spike thresholds are roughly constant up until about 350 ms on the x axis; this means that the DC level is roughly stable until 1.8 nA (the trace which is around 350 ms).

as a function of current (Koch et al., 1995). The threshold is determined to a large extent by the sodium conductance, and the sodium conductance will not be affected by the amount of current injected unless the firing rate is sufficiently high that the current has not recovered from inactivation during the previous spike. At low firing rates, then, we expect the threshold to be relatively constant, while at very high firing rates it may vary more significantly.

An example of the procedure is shown in figure B.3. The last 10 spikes in each trial are aligned at the point where they cross a threshold (I used −20 mV). Trials are arranged along the x axis in order of increasing current. In this case, the threshold is roughly constant until the trace at roughly 350 ms; this trace corresponds to a current of 1.8 nA. So trials from this cell for which the current is less than 1.8 nA are accepted.

With this analysis, there were 6 cells that had stable enough threshold levels to be useful for determining \( \langle V_m \rangle \). Current was injected for only 320 ms, and adaptation was not complete until about 100 ms into the trace. That leaves only 200 ms to average over, or typically 2–3 spikes. Such a small number of spikes can lead to artifacts. For example, suppose there are only two spikes in the region we average over, but for a very slightly larger current there would be 3 spikes. This means that our average will be artifactually low. To avoid problems like this, the average started 3 ms before a spike and ended 3 ms before the last spike, so there was always an integral number of interspike intervals. When the current was below threshold, the last 100 ms or so (depending on the trace) was used for averaging. Each trace was examined by eye to validate the range of times to compute \( \langle V_m \rangle \).

Results from these cells are shown in figure B.4. In general, the membrane potential above threshold appears to increase slowly, but there is no good way of deciding between a logarithmic fit and a linear fit. A logarithmic fit to the above threshold data does not even come close to the subthreshold data (not shown), unlike the model considered by Koch et al. (1995).

B.4 Conclusions

In addition to the equations simulated by Koch et al. (1995), both the integrate-and-fire and the Hodgkin-Huxley equations for the squid giant axon show an approximately logarithmic relationship
between the time averaged membrane potential and the input current, and a linear relationship between membrane potential and firing frequency. The logarithmic fit of these simpler models is not nearly as impressive as for the detailed pyramidal cell model, but it is nevertheless approximately valid. Thus the diode model is not merely an artifact of one particular set of simulated currents. With the data I have available, it does not seem possible to confirm or deny a logarithmic relationship between \( \langle V_m \rangle \) and input current. Better quality recordings are needed.

Nevertheless, the basic phenomena observed by Koch et al. (1995) is supported: the spiking mechanism acts like a kind of voltage clamp. Over a wide range of input currents and firing rates, the time average voltage at the soma does not vary much (only a few mV). This is a generic property of a spiking mechanism, and not a peculiarity of any particular model. This has strong implications for the effects of conductance changes (chapter 4 on page 49).