Ions, Membranes, Noise Levels, and Scales of Voltage

Biology, if we may anthropomorphize, has gleamed a number of essential features from the physical world. These act to form systems that replicate, extract energy out of the environment, and communicate chiefly with each other. We focus here on the computational and communicative aspects of cellular function.

1 Ions and Voltages

A good place to start is with an overview of how sensitive and robust nervous systems are. We consider a fundamental issue, the scale of the potentials across cell membranes relative to the thermal noise floor. We further discuss how these potentials are used to form pulses, or action potentials, that allow one cell to communicate with another. We shall see that the Boltzman energy serves to define a band of voltages that can be used to integrate and process nervous activity, and that the same energy acts as a barrier to isolate integration of inputs from output and communication.

1.1 The Nernst Potential

Bags comprised of lipid walls provide a means to separate high concentrations from low concentrations of ions. Why is this useful? If we recall a little bit of thermodynamics, we realize that a difference in ion concentration leads to a potential, and thus work can be done. Thus, one could conceivably build a device that is capable of communicating to all agents along the surface of a bag, or some topological equivalent, that a disturbance has occurred at a point. Let's run through this.

Consider a world that consists of two compartments, labeled "in" and "out". The compartments are separated by a thin wall. To make this situation somewhat real, we will fill both compartments with water and consider the diffusion of ions in the water. We take these ions to be Na^+ and Cl^-, the ions that result from dissolving ordinary table salt. On the inside of the box, the concentration of ions is denoted $[Na^+]_{in}$ and $[Cl^-]_{in}$ and on the outside they are denoted $[Na^+]_{out}$ and $[Cl^-]_{out}$, where concentration is in units of $molecules/cm^3$ or, in chemistry, in units of moles per liter or $Molar(M)$.

FIGURE - chapt-1-bratenberg.eps

FIGURE - chapt-1-shapeology.eps

FIGURE - chapt-1-dendrites.eps

To get a feel for the scale of $moles/liter$, lets put it into terms relevant for the size of a cell, i.e., ions per cubic micrometer. In a biological cell, the ion concentration is about 0.15 M, so we have about $10^8 ions/\mu m^3$ in a cell.

Suppose we set the box up so that, initially, $[Na^+]_{in} = [Cl^-]_{in}$ and $[Na^+]_{out} = [Cl^-]_{out}$. This insures that individual compartments are electrically neutral. Further, we impose $[Na^+]_{out} > [Na^+]_{out}$, so that the ion concentrations are initially greater on the outside than the inside. Since there is a wall between the two sides, there is clearly no interaction between the two compartments.

Suppose we now remove the wall in entirety. What happens? The Na^+ ions will flow down their concentration difference, so that ultimately $[Na^+]$ is the same on both sides of the membrane. Similarly, the Cl^- ions will flow down their gradient. Thus after some time the concentration of ions is the same on both sides, so that no energy is extracted from the concentration difference. A side remark is that there is a transient potential difference if the mobility of Na^+ and Cl^- are different.

What is the trick necessary to get the concentration difference across the two sides of the wall to turn into a sustained electrical potential? The idea is to make a hole that allows only one kind of ion to pass. This is called an ion selective pore. To be concrete, we open up a hole that allows $[Na^+]$ ions, but not $[Cl^-]$ ions, to pass. This is a Na^+ selective pore, or Na^+ selective channel. Recall that $[Na^+]$ is higher outside than inside.

The process works as follows:

- Initially, the $[Na^+]$ moves down its concentration gradient, driven by diffusion.
- As Na^+ ions move across the wall, the solutions in the two compartments are no longer electrically neutral. Positive charge (from the Na^+) leaves the outside and builds up on the inside. This leads to an electric field across the wall.
- The electric fields points from the inside to the outside. This field is the direction that opposes motion of additional Na^+ ions.
- In time, the electric field caused by the initial movement of ions points from the inside to the outside. This field is the direction that opposes motion of additional Na^+ ions and will prevent any more Na^+ ions from moving. As this point the system is in equilibrium.

The result is that the concentration difference in Na^+ ions across the wall has been used to form a difference in electrical potential across the cell. The relation between concentration differences and electrical potential is given by the Nernst equation, which equates the electrical potential, eV, with the chemical potential, μ, caused by the concentration difference, i.e.,

$$\mu = \left(\frac{\partial F}{\partial N}\right)_{T,V} = -k_B T \frac{\partial ln Z}{\partial N} = -k_B T \frac{\partial ln \frac{\xi^N}{N!}}{\partial N} = k_B T \, lnN \; + \; constant \qquad (1.1)$$

for $N >> 1$. Thus

$$V = \frac{k_B T}{e} ln \frac{[Na^+]_{out}}{[Na^+]_{in}} \qquad (1.2)$$

We see immediately that V is on the order of $\frac{k_BT}{e} \approx 25mV$. Before we worry about details, let's think about how big this is on the scale of the electrical noise expected for this process.

1.2 Thermal Fluctuations in Voltage

Because there is a pore, there is a conductance G across the cell. This leads to a fluctuation in the potential, known as the Johnson noise, of size

$$\delta V = \sqrt{\frac{4k_BT\Delta f}{G}} \approx \sqrt{\frac{4k_BT}{C}} = \sqrt{\left(\frac{k_BT}{e}\right)\left(\frac{L}{\epsilon_m}\right)\frac{e}{\pi a^2}} \tag{1.3}$$

where we used

$$\Delta F \approx \frac{1}{\tau} = \frac{G}{C} \tag{1.4}$$

as an estimate of the bandwidth and recall that $C = \epsilon_m$ (area/thickness), so that for a thin dielectric sphere of thickness L and radius a, $C = \epsilon_m \frac{4\pi a^2}{L}$. For most all cells, the ratio $\frac{\epsilon_m}{L}$ is

$$c_m \equiv \frac{\epsilon_m}{L} \approx 1.0x10^{-14}\frac{F}{\mu m^2}. \tag{1.5}$$

For a neuron of radius $a = 10\mu m$, the noise level is found to be $\delta V \approx 10\mu V$. **The important result that for cells the noise level is much less than the thermal voltage** k_BT/e, where

$$\frac{k_BT}{e} \approx 25mV \tag{1.6}$$

Only at the smallest structure, the synaptic vesicle with radius $a \approx 10^{-2}\mu m = 10nm$, will the noise level approach the thermal voltage, so that for $a \approx 10^{-2}\mu m$ we have $\delta V \approx 10mV$. Actually, the case of vesicles is interesting, in that we can turn the argument around and look at the fluctuation in the number of ions across the cell. In synaptic vesicles, the membrane potential ΔV is set by a hydrogen ion, or pH gradient, with $pH_{in} \approx 5$ and $pH_{out} \approx 7.5$. Then

$$\Delta V = \frac{4k_BT}{e} ln \frac{[H^+]_{out}}{[H^+]_{in}} = \frac{4k_BT}{e}\left(pH_{in} - pH_{out}\right) \tag{1.7}$$

and

$$\delta V = \frac{\partial \Delta V}{\partial [H^+]_{in}} \delta [H^+]_{in} = \frac{k_BT}{e}\frac{\delta [H^+]_{in}}{[H^+]_{in}} \tag{1.8}$$

We equate noise level this with the expression for Johnson noise to get

$$\frac{\delta [H^+]_{in}}{[H^+]_{in}} = \sqrt{\frac{4e^2}{k_BTC}} = \sqrt{\left(\frac{e}{k_BT}\right)\frac{1}{c_m}\frac{e}{\pi a^2}} \tag{1.9}$$

An interesting number is the value of the radius a for which the fluctuations in ion concentration are of order unity, i.e., $\frac{\delta[H^+]_{in}}{[H^+]_{in}} \approx 1$. We call this a_{crit}, where

$$a_{crit} = \sqrt{\frac{e}{\pi}\left(\frac{e}{k_B T}\right)\frac{1}{c_m}} \approx 15nm \tag{1.10}$$

This is very close to the radius of vesicles.

A slightly different way to look at the noise issue is to recall that $Q = \Delta N e = C\Delta V$, where N is the net charge imbalance across the membrane. If we substitute this expression for C into the formula for Johnson noise, the "Signal-to-Noise" ratio for the cell is

$$\frac{"Signal"}{"Noise"} \equiv \frac{\Delta V}{\delta\left(\Delta V\right)} = \frac{1}{2}\sqrt{\frac{e\Delta V}{k_B T}\Delta N} \tag{1.11}$$

The dependence on the square root of ΔN is intuitive.

Note that the above expressions need to be modified if the conductance is not set by a static pore, but a pore that fluctuates open and closed. In the latter case, the fluctuations cut off at some high temporal frequency. But the major story holds.

FIGURE - chapt-1-channel-noise.eps

In the larger picture, the cell membrane may have selectively permeable channels to more than one ion. Thus the final potential may represent a steady state rather than an equilibrium value. In fact, nature uses two ions, K^+ and Na^+, to set two potentials, one low and one high. The presence of a voltage-dependent (nonlinear) conductance, one of the major findings of the century, allows the cell to switch between these two levels. Let's review the gist of this - the details will be the topic of another lecture.

In the simplest, or Hodgkin Huxley cell, there are three major conductances, those due to K^+, Na^+, and Cl^-. The equilibrium potential for each of these ions is

- $V_{K^+} = \frac{k_B T}{e} ln \frac{[K^+]_{out}}{[K^+]_{in}} \approx -75mV$
- $V_{Na^+} = \frac{k_B T}{e} ln \frac{[Na^+]_{out}}{[Na^+]_{in}} \approx +50mV$
- $V_{Cl^+} = \frac{k_B T}{e} ln \frac{[Cl^-]_{out}}{[Cl^-]_{in}} \approx -50mV$

The steady state potential for a system with these three ions and associated membrane permeabilities P_{Na^+}, P_{K^+}, and P_{Cl^-}, is

$$V_{SS} = \frac{k_B T}{e} ln \frac{P_{K^+}[K^+]_{out} + P_{Na^+}[Na^+]_{out} + P_{Cl^-}[Cl^-]_{in}}{P_{K^+}[K^+]_{in} + P_{Na^+}[Na^+]_{in} + P_{Cl^-}[Cl^-]_{out}} \approx -50mV \tag{1.12}$$

This relation is derived by considering the diffusion equation for the total flux of ions through the cell membrane; we will derive this equation in a future lecture. The important point is that the steady state potential is dominated by the ion that has the maximal conductance. The resting level is dominated by the K^+ conductance.

1.3 Fundamentals of the Action Potential

The essential ingredient that allows signaling is that the conductance for Na^+ is voltage dependent. A nice way to think of this, which we will discuss in detail, is that the current-voltage relationship has an essential nonlinearity. Thus for small disturbances of the membrane potential, the cell returns to the resting potential. However, for current injections beyond some critical value, the potential will jump to a new equilibrium point. A simplified model makes use of a voltage dependent change in the conductance for one of two ions. To be concrete, we take a cell with a solely Ohmic potassium current, G_{K^+}, and a voltage dependent sodium conductance, $G_{Na^+}(V)$, that has a value of zero below a threshold potential, V_{th}, and that is constant above V_{th} with value $G_{Na^+}(V_\infty)$.

FIGURE - chapt-1-channel-i-v.eps

FIGURE - chapt-1-brutal-i-v.eps

Thus we have a current-voltage relation given by

$$I(V) = \begin{cases} G_{K^+}V - G_{K^+}V_{K^+} & \text{if } V < V_{th} \\ (G_{K^+}G_{Na^+}(V_\infty))\, V - (G_{K^+}V_{K^+} + G_{Na^+}(V_\infty)V_{Na^+}) & \text{if } V > V_{th} \end{cases}$$

where, in this approximation, V_{Na^+} and V_{K^+} are the Na^+ and K^+ Nernst potential for sodium and potassium, respectfully. This relation is discontinuous at V_{th} and Ohmic below and above this potential.

We consider a pulse of current that causes the cell to change from the lower to the upper curve. This represents the front of the action potential. The shift in potential from $V = V_{K^+}$ to $V = \frac{G_{K^+}V_{K^+} + G_{Na^+}(V_\infty)}{G_{K^+} + G_{Na^+}(V_\infty)}$ occurs in roughly $10^{-4}s$. On the longer time scale of $10^{-3}s$, relaxation processes associated with the Na^+ current and the activation of an additional voltage dependent K^+ current cause the front to decay, so we are left with a pulse.

FIGURE - chapt-1-ap-iv-vs-time.eps

The critical lesson is that neurons use two voltage levels, and at least one voltage dependent conductance, to shift between the two levels.

FIGURE - chapt-1-neoctx-pyramidal-1.eps

FIGURE - chapt-1-neoctx-pyramidal-2.eps

We now know how neurons signal, and that the signaling, at least in principle, operates well above the physical limits to membrane noise. We put off the issue of variability in the transmission of spikes between cells - suffice it to say that at some synapses, e.g., those formed as calyces, the failure rate is very low indeed.

1.4 Separation of Dendritic Integration and Communication

How does a neurons separate the integration of synaptic inputs from the decision making that leads to the production of an action potential? We require a range of voltages over which the cell can integrate, that is summate, synaptic inputs. This range must clearly be larger than the amplitude of thermal noise that may erroneously activate a Na^+-based action potential. The activation range of the Na^+ is sharp; it turns on through the action of 4 charges and thus has a range of Δ V $> k_BT/4e$ 6 mV.

The range of synaptic integration corresponds to the difference between the K^+ reversal potential (the lowest voltage for inhibitory inputs) and the activation of the Na^+-based action potential, a range of about 2-times $k_BT/4e$ 50 mV. This is very large compared to the noise level across the membrane. But how does the probability of an erroneous action potential scale with this range? We consider a model calculation to address this issue.

$R_m \equiv$ Membrane Resistance

$I_{ch} \equiv$ Max channel current

$\Delta V \equiv$ Membrane voltage from "rest" level to threshold level

$N \equiv$ Number of Na^+channels in cell

$n \equiv$ Number of simultaneous channel openings required to elicit an action potential. Thus $n = \frac{I_{thresh}}{I_{channel}} = \frac{\Delta V/R_m}{I_{ch}} = \frac{\Delta V}{R_m I_{ch}}$

The rate of threshold events due to thermal noise, denoted Γ, follows the prescription laid down by Kramers for the thermal escape over an activation barrier for chemical systems.

$$\begin{aligned}
\Gamma &= \frac{1}{\tau_m}\binom{N}{n}\left[e^{-\frac{e\Delta V}{k_BT}}\cdot e^{-\frac{e\Delta V - R_m I_{ch}}{k_BT}}\cdot e^{-\frac{e\Delta V - 2R_m I_{ch}}{k_BT}}\cdots 1\right] \qquad (1.13)\\
&= \frac{1}{\tau_m}\binom{N}{n}\prod_{j=0}^{n} e^{-\frac{e\Delta V - jR_m I_{ch}}{k_BT}}\\
&= \frac{1}{\tau_m}\binom{N}{n} e^{-\frac{e}{k_BT}\sum_{j=0}^{n}(\Delta V - jR_m I_{ch})}\\
&= \frac{1}{\tau_m}\binom{N}{n} e^{-\frac{e}{k_BT}\left(n\Delta V - \frac{n^2}{2}R_m I_{ch}\right)}\\
&= \frac{1}{\tau_m}\binom{N}{n} e^{-\frac{e\Delta V}{k_BT}\frac{n}{2}}
\end{aligned}$$

where τ_m is the membrane time constant of the cell and we used $\sum_{k=0}^{n} k \simeq \frac{n^2}{2}$ and $\Delta V = nR_m I_{ch}$.

We can simply this further by expanding the combinatorial factor under the assumptions that both $n >> 1$ and $N >> 1$ but with the ordering $n << N$. Then, using Stirling's formula,

$$\begin{aligned}\binom{N}{n} &\equiv \frac{N!}{n!(N-n)!} \\ &\simeq \frac{e^{-N}N^N}{e^{-n}n^n e^{-(N-n)}(N-n)^{N-n}} \\ &\simeq \left(\frac{N}{n}\right)^n \frac{N^N}{n^N N^{N-n}\left[1-\frac{n}{N}\right]^{N-n}} \\ &\simeq \left(\frac{N}{n}\right)^{2n} \frac{1}{1-(N-n)\frac{n}{N}}\end{aligned} \tag{1.14}$$

For the case that $1-(N-n)\frac{n}{N}$ is near one, we have

$$\binom{N}{n} \sim \left(\frac{N}{n}\right)^{2n} = \left(\frac{NR_mI_{ch}}{\Delta V}\right)^{2n} \tag{1.15}$$

Thus the rate of threshold events is approximated as

$$\Gamma \sim \frac{1}{\tau_m}\left[\left(\frac{NR_mI_{ch}}{\Delta V}\right)^4 e^{-\frac{e\Delta V}{k_BT}}\right]^{n/2} \tag{1.16}$$

One thing we see is that term in the brackets can exceed unity for N large. This sets a scale for N, channel number

$$\left(\frac{NR_mI_{ch}}{\Delta V}\right)^4 e^{-\frac{e\Delta V}{k_BT}} \quad < \quad 1 \tag{1.17}$$

or

$$N < \frac{\Delta v}{I_{ch}R_m} \quad e^{\frac{e\Delta V}{4k_BT}} \tag{1.18}$$

To get an estimate, we take $\Delta V = 50$ mV (about 2 k_BT/e), $R_m = 10^9$ Ω, I_{ch} = 2 pA (peak spontaneous Na^+). We find $N \sim 50$ or order 10^2 channels per spike initiation zone.

We now consider the rate of threshold events for the case of $I_{max} \simeq I_{thresh}$, which correxponds to no excess channels, or $N \simeq n$, We have $\binom{N}{n} = \binom{N}{N} = 1$, $n = \frac{\Delta V}{R_mI_{ch}} \sim 10$ and take $\tau_m \sim 10^{-2}s$, so

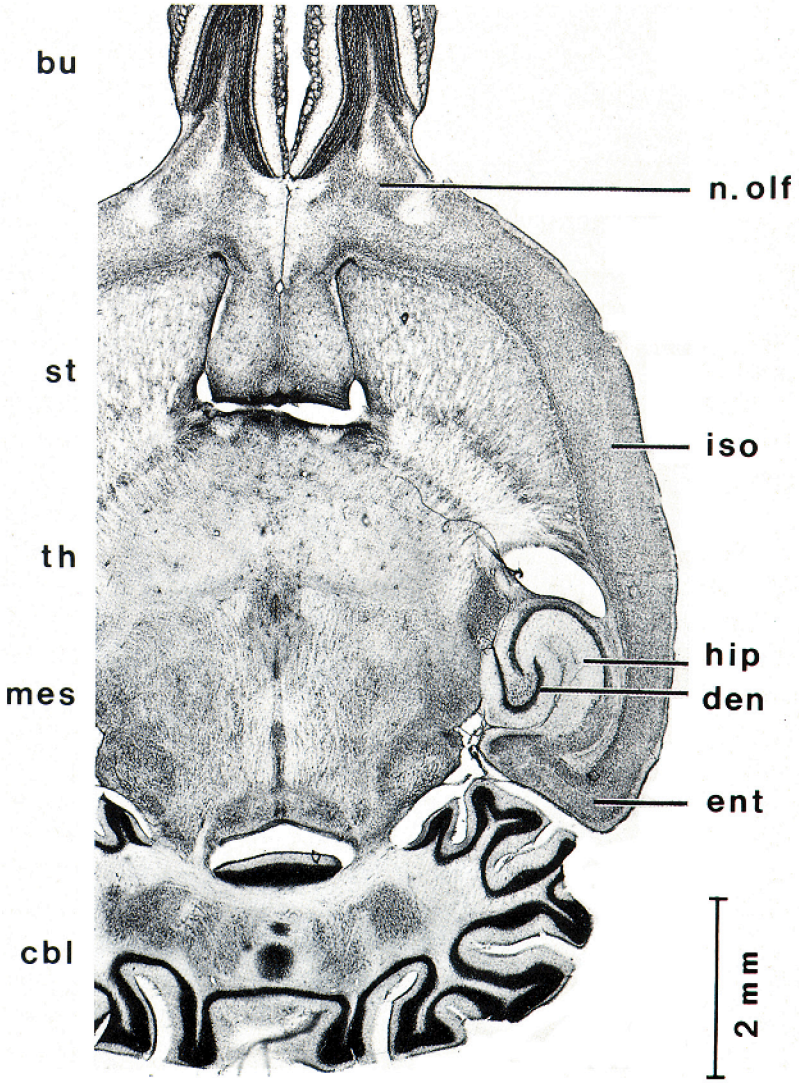
$$\Gamma \simeq \frac{1}{\tau_m} e^{-\frac{e\Delta V}{k_BT}\frac{n}{2}} \quad \sim \quad 10^{-3}\mathrm{s}^{-1} \tag{1.19}$$

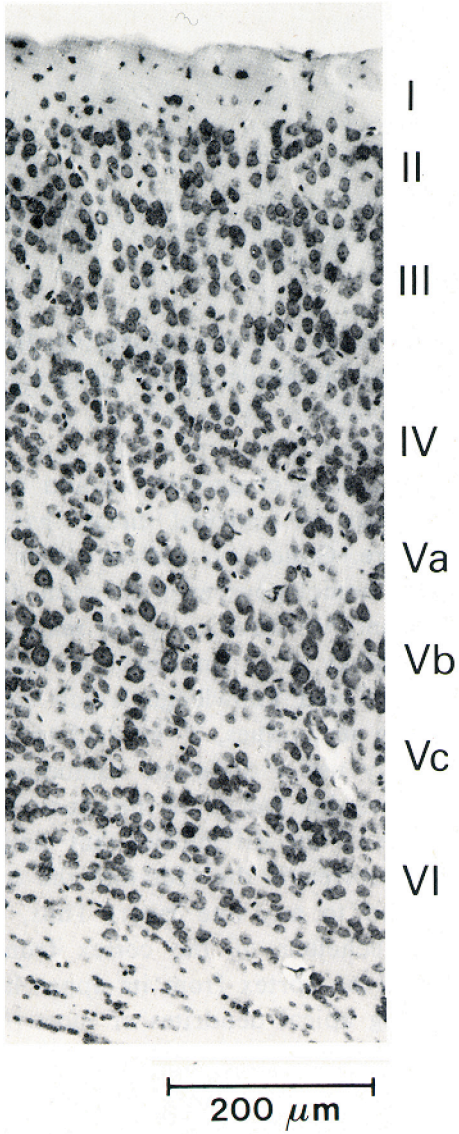
which corresponds to one random action potential every 20 minutes or so. There

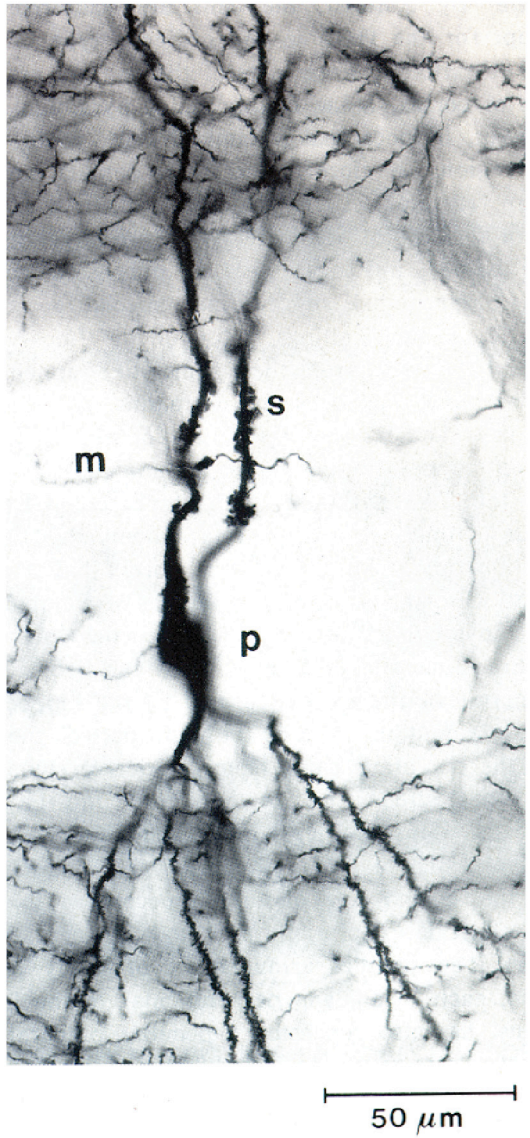
it is - free will three times an hour! A serious issue is that, from the perspective of noise immunity, it is better to have many channels that support a small current than one channel that can support a large, threshold current. The price for this is an increased energy utilization for protein synthesis. The trade off between noise immunity and energetics is an interesting an open research project.

A final issue is that synaptic activation depends on a chemical cascade that is initiated by the activation of a high-threshold Ca^{2+} current. This current peaks at potentials of about + 5 mV. Thus there is headroom of order k_BT/e that separates the turn-on of the action potential from the turn-on of synaptic transmission, so that dendritic integration *per se* cannot lead to synaptic release, or communication.

FIGURE - chapt-1-voltage-scales.eps







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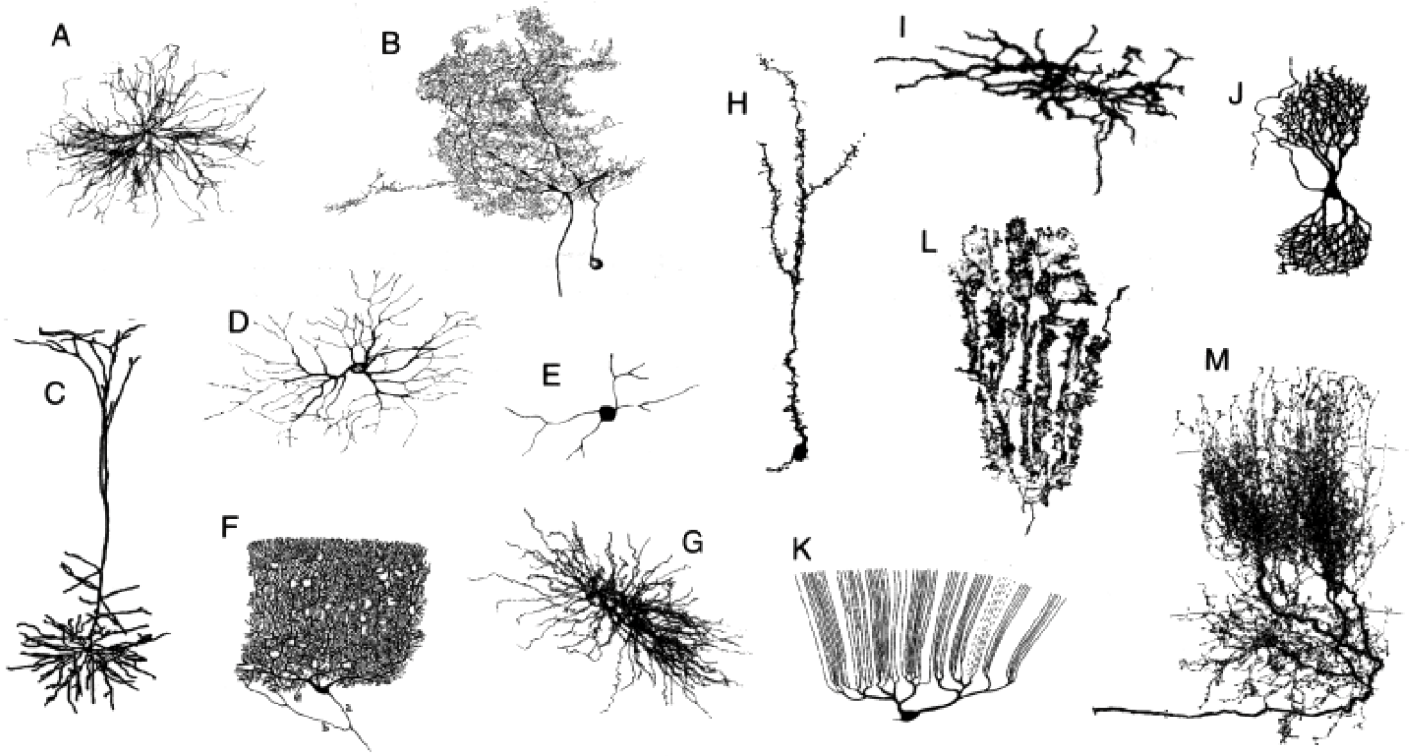

(A) α motoneuron in spinal cord of cat (2.6 mm). Reprinted by permission from Cullheim, Fleshman, and Burke (1987). **(B)** Spiking interneuron in mesothoracic ganglion of locust (0.54 mm). Unpublished data from G. Laurent, with permission. **(C)** Layer 5 neocortical pyramidal cell in rat (1.03 mm). Reprinted by permission from Amitai et al., (1993). **(D)** Retinal ganglion cell in postnatal cat (0.39 mm). Reprinted by permission from Maslim, Webster, and Stone (1986). **(E)** Amacrine cell in retina of larval tiger salamander (0.16 mm). Reprinted by permission from Yang and Yazulla (1986). **(F)** Cerebellar Purkinje cell in human. Reprinted by permission from Ramón y Cajal (1909). **(G)** Relay neuron in rat ventrobasal thalamus (0.35 mm). Reprinted by permission from Harris (1986). **(H)** Granule cell from olfactory bulb of mouse (0.26 mm). Reprinted by permission from Greer (1987). **(I)** Spiny projection neuron in rat striatum (0.37 mm). Reprinted by permission from Penny, Wilson, and Kitai (1988). **(J)** Nerve cell in the nucleus of Burdach in human fetus. Reprinted by permission from Ramón y Cajal (1909). **(K)** Purkinje cell in mormyrid fish (0.42 mm). Reprinted by permission from Meek and Nieuwenhuys (1991). **(L)** Golgi epithelial (glia) cell in cerebellum of normal-reeler mouse chimera (0.15 mm). Reprinted by permission from Terashima et al., (1986). **(M)** Axonal arborization of isthmotectal neurons in turtle (0.46 mm). Reprinted by permission from Sereno and Ulinski (1987).

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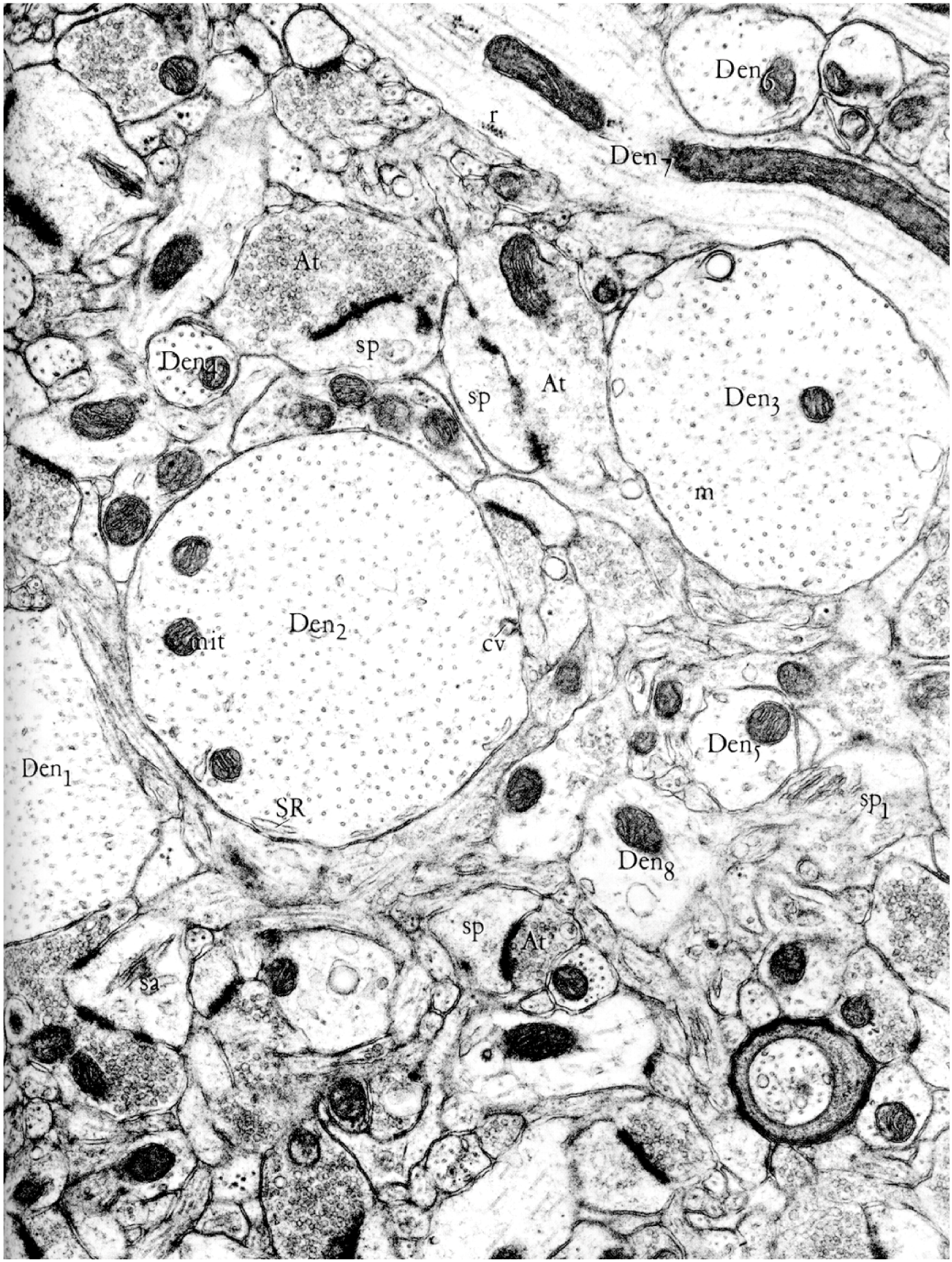

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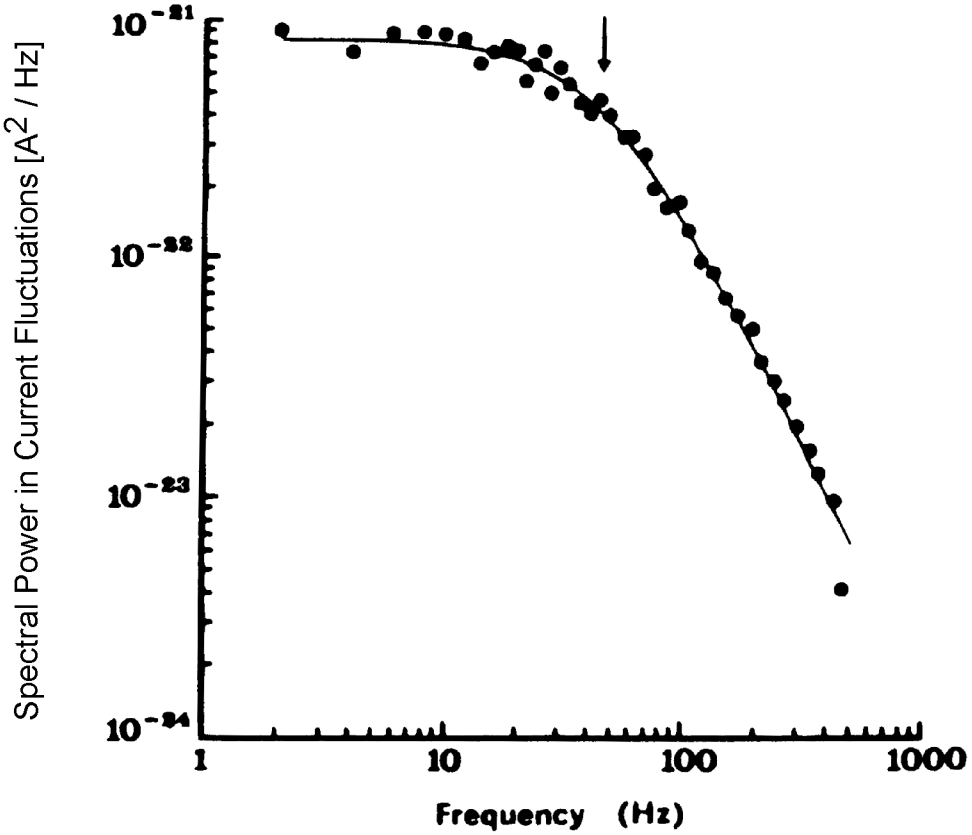
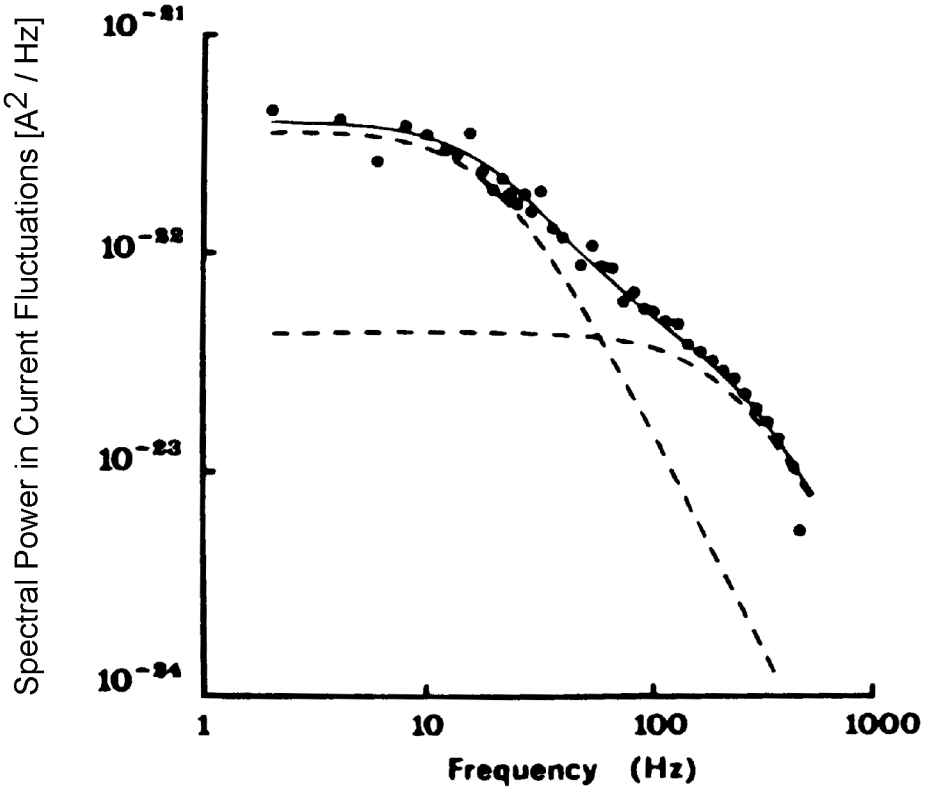
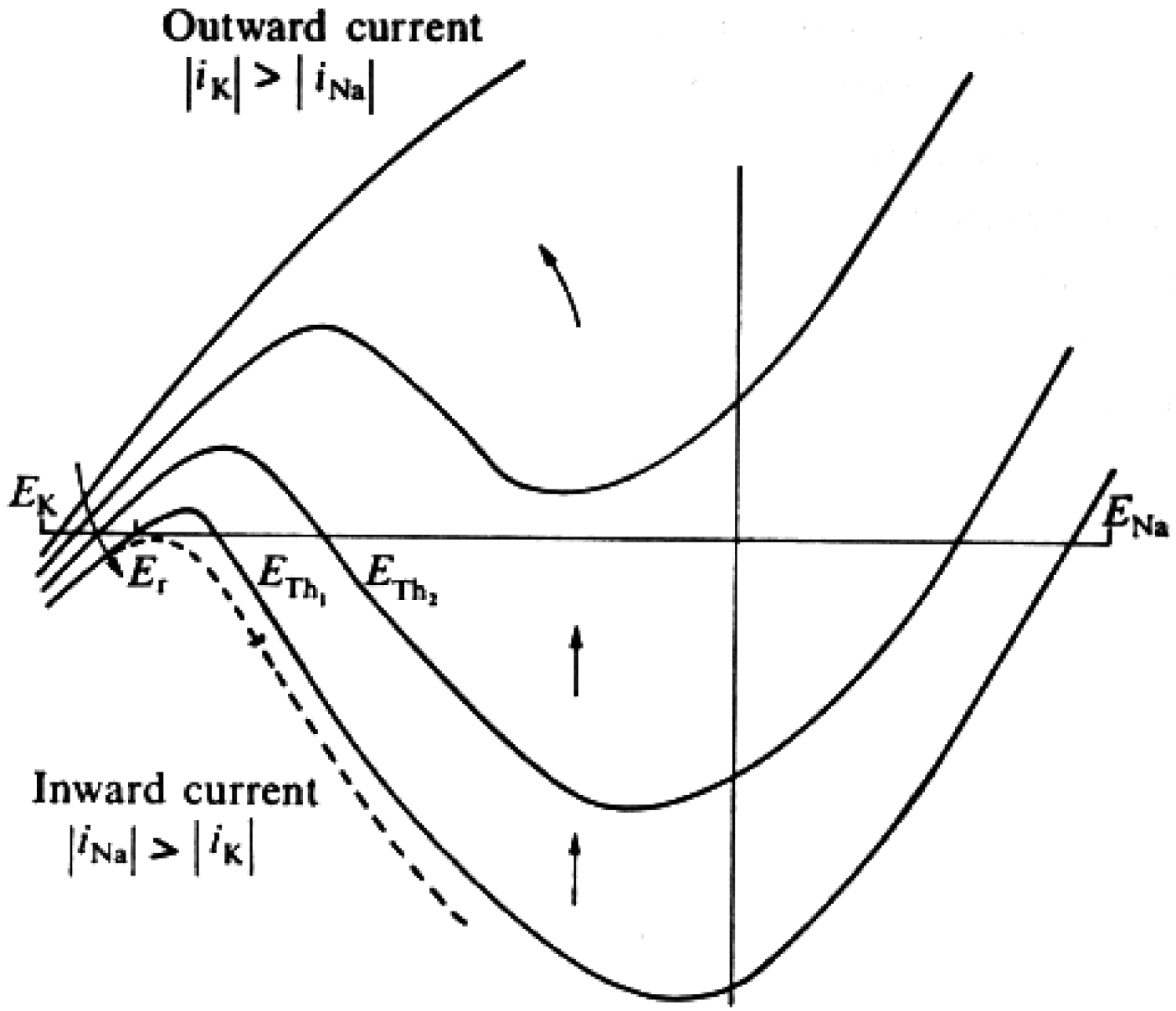




chapt_1_channel_noise.eps

I-V curves for Squid Axon from Action Potential Trigger to Recovery



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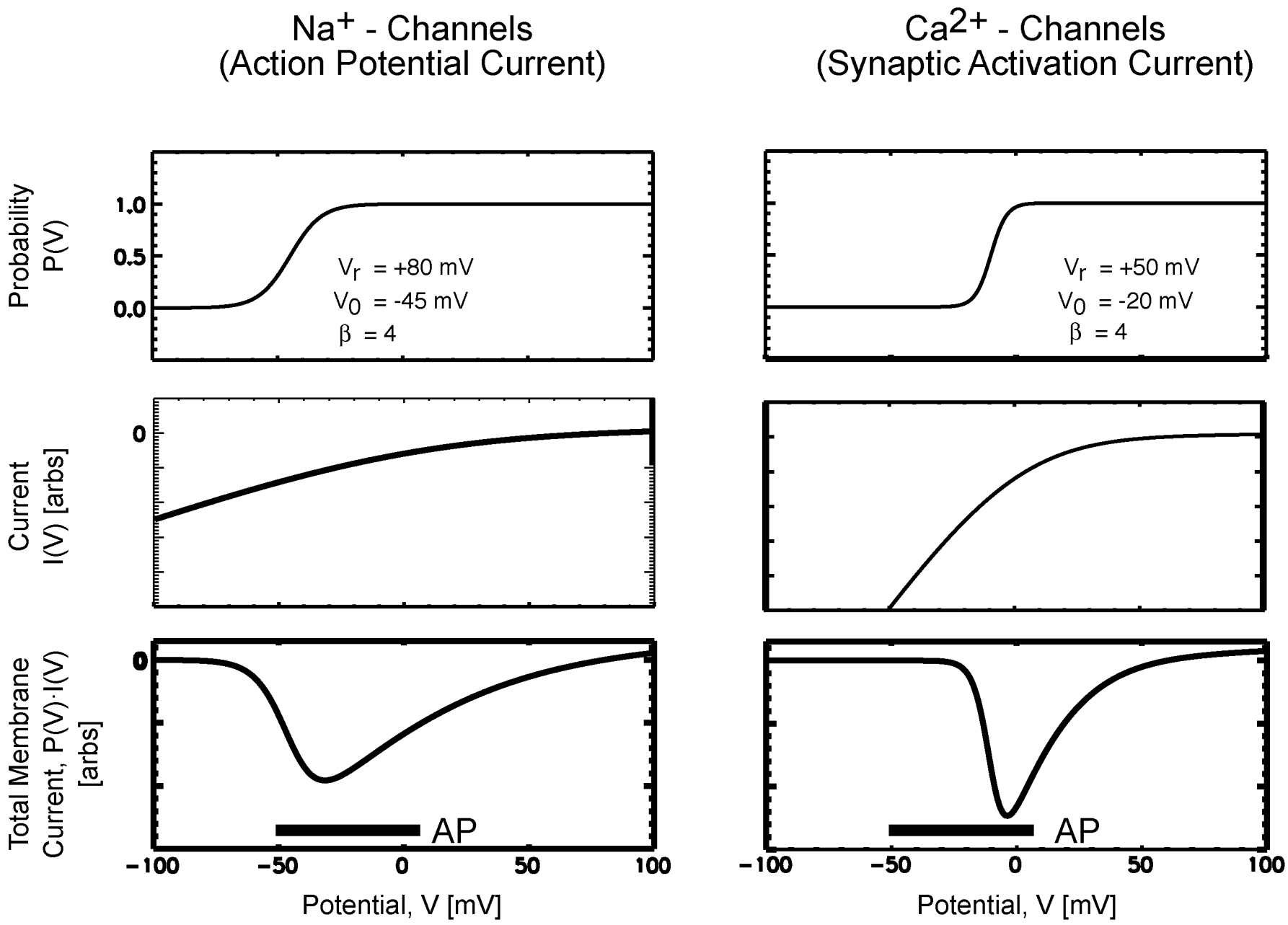

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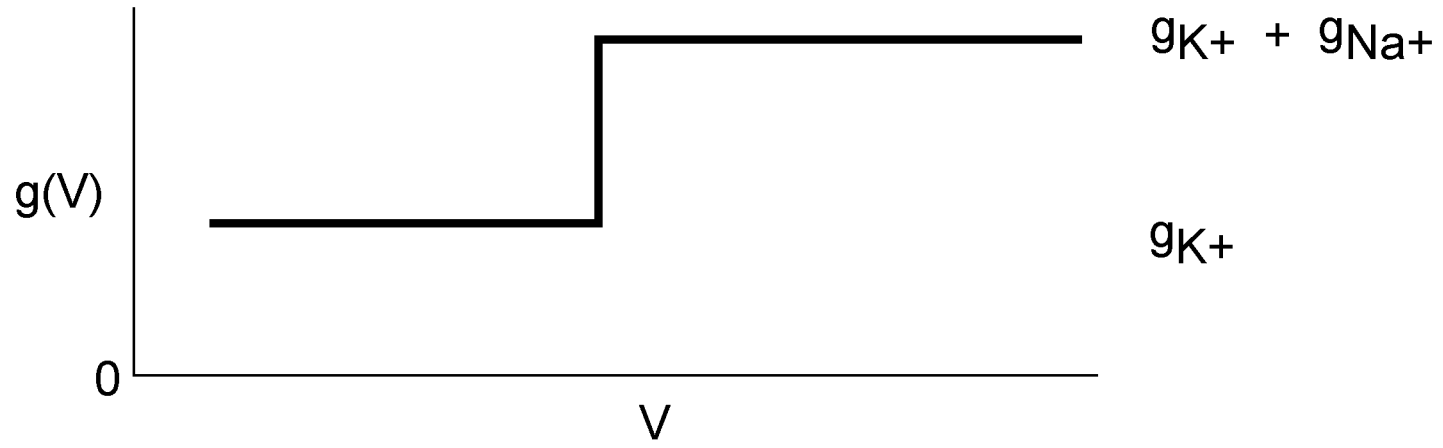

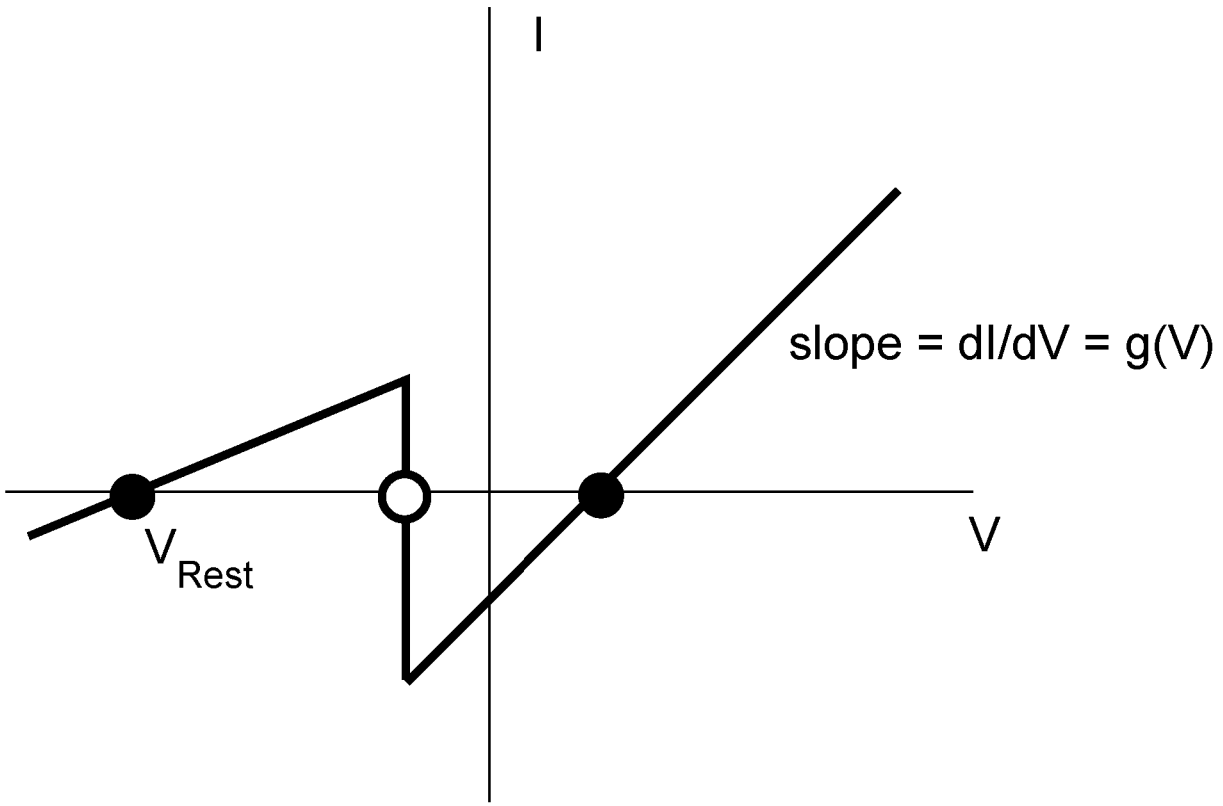

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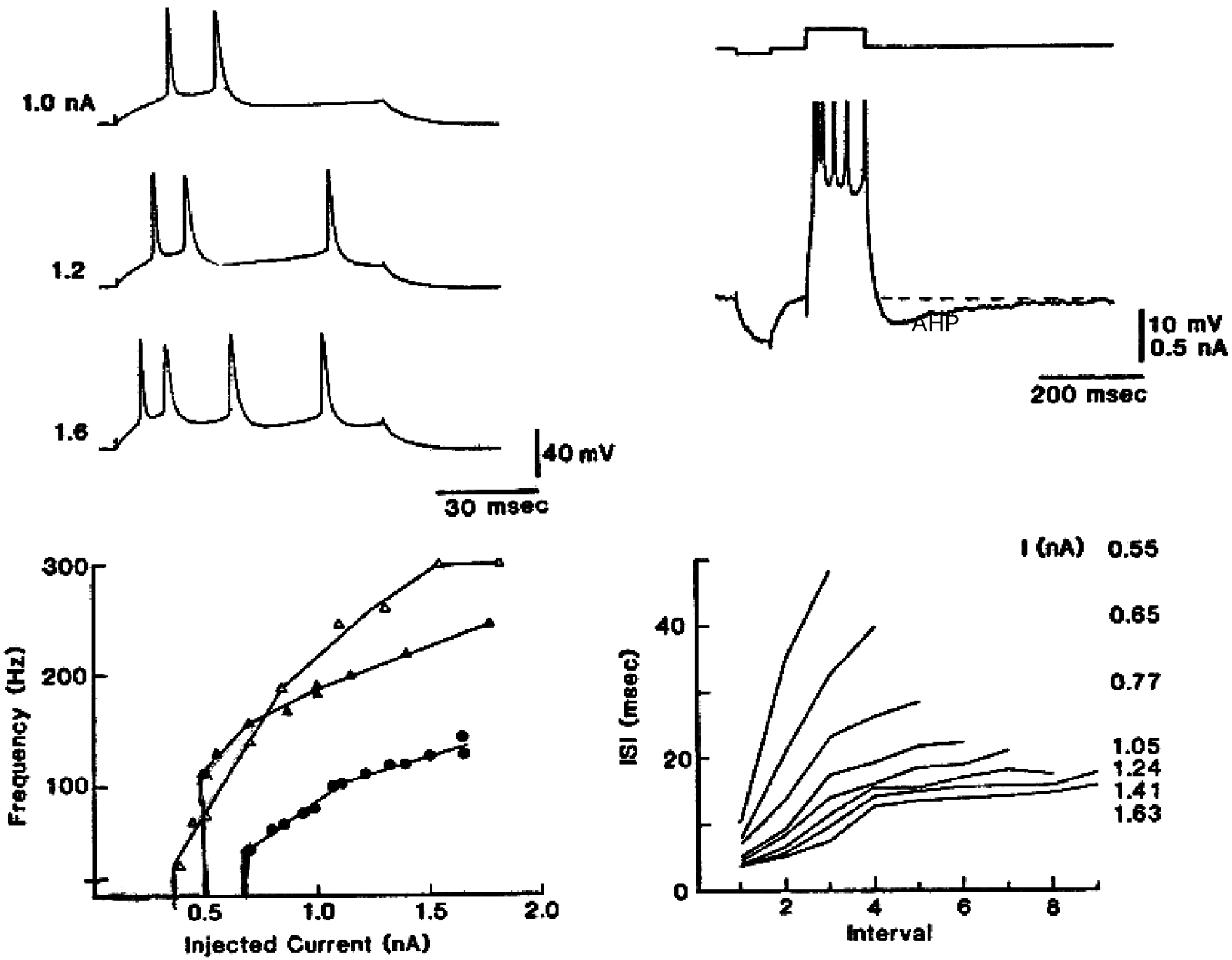
Regular Neocortical Pyramidal Cell



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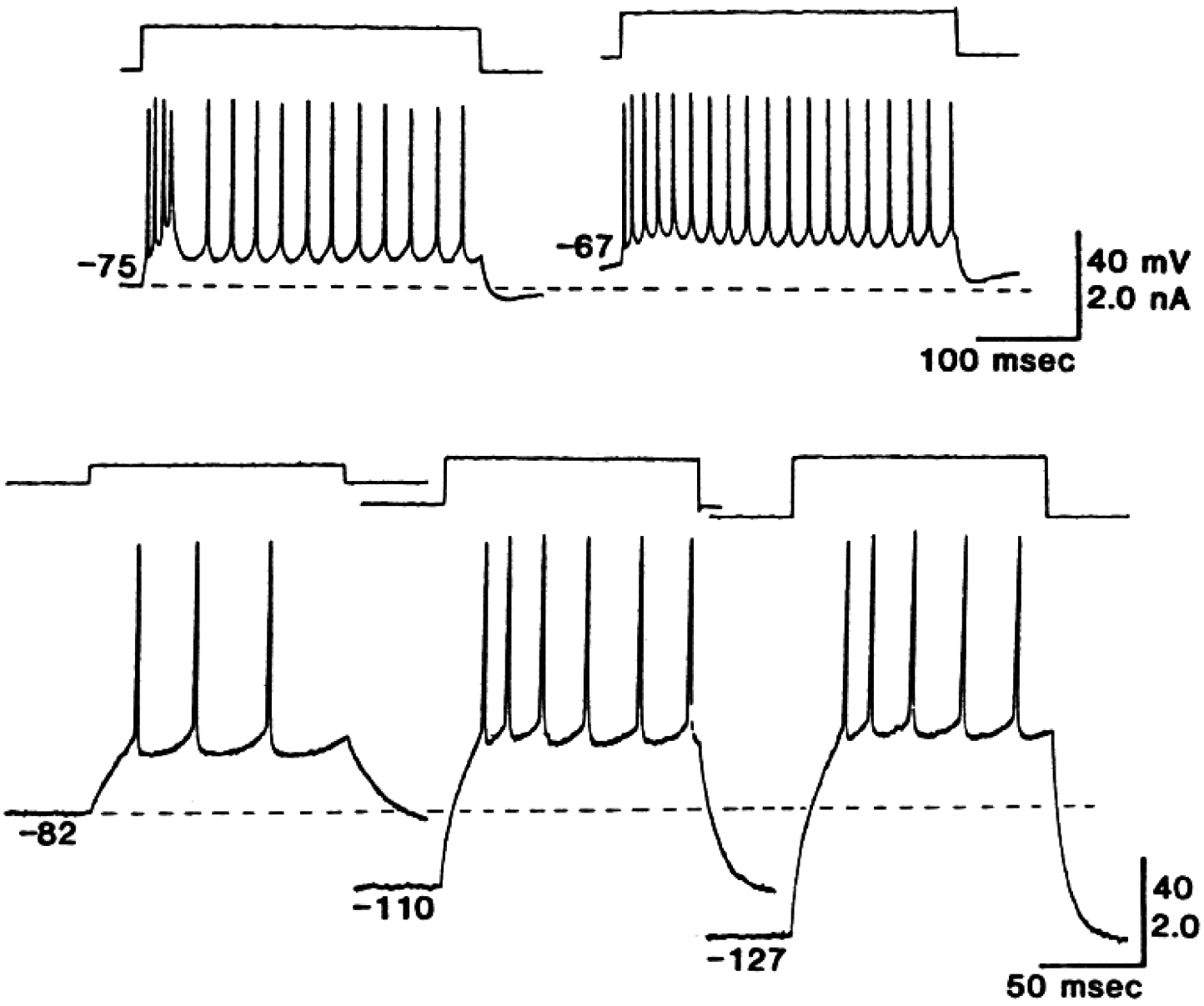
Bursting vs. Regular Neocortical Pyramidal Cell



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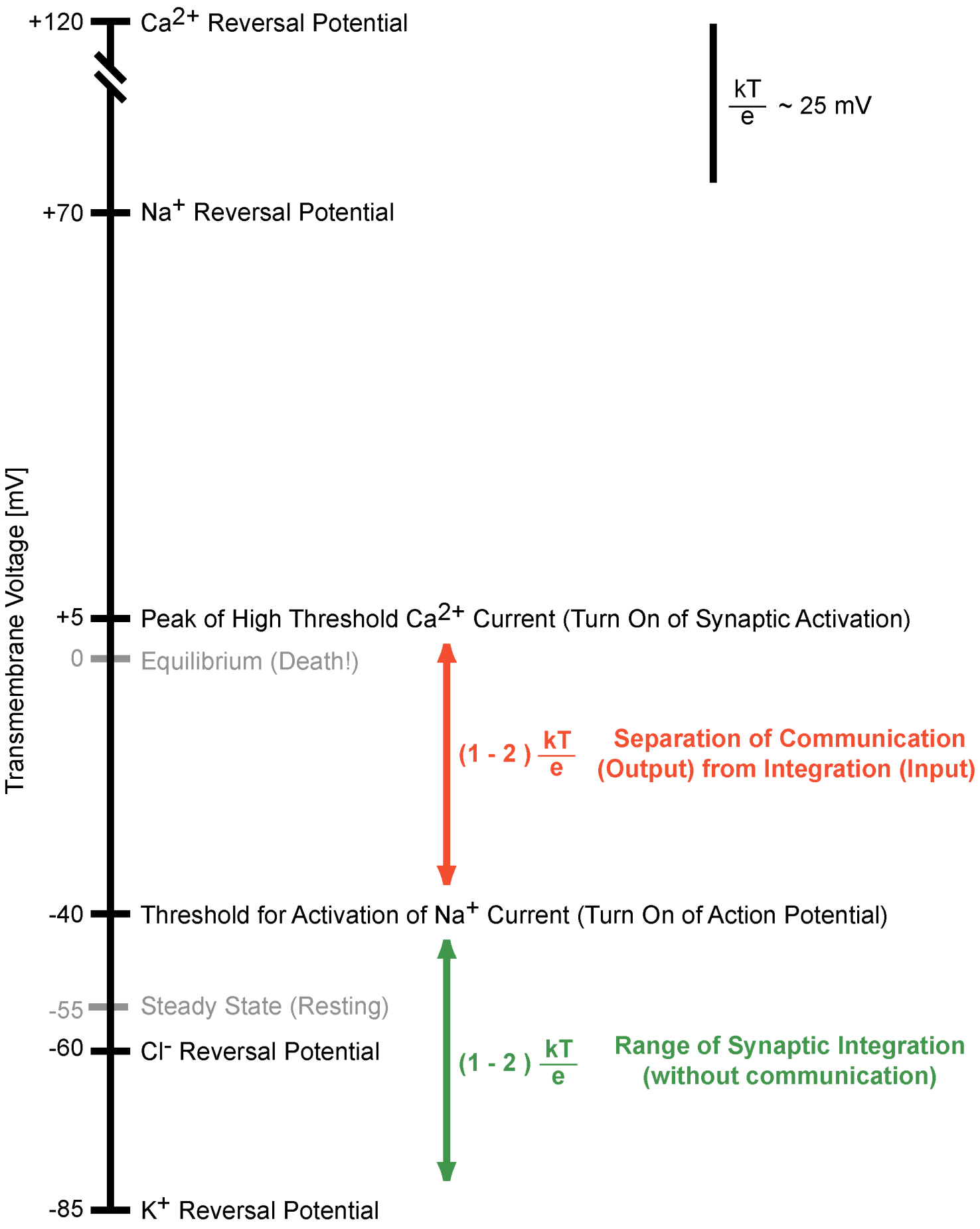

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