Neurophysiology for Computer Scientists

David S. Touretzky

Outline

1. Parts of a Neuron
2. Ionic Basis of the Resting Potential
3. Ionic Basis of the Action Potential
4. Ligand-Gated Channels
5. Second Messengers
6. Synaptic Transmission
7. Properties of Dendritic Trees

Parts of a Neuron

1. Cell body (soma)
2. Dendrites (apical, basal)
3. Axon

- Some cells lack dendrites, e.g., dorsal root ganglion cells in the spinal cord.
- Some cells lack axons, e.g., some types of amacrine cells in the retina.
- What is the difference between an axon and a dendrite?

  Presence of spikes.
  Distribution of channel types.
  Pre- vs. post-synaptic structures.

Properties of Neurons

1. Resting potential of –60 to –75 mV.
2. Sum inputs in a non-linear, temporal-dependent way.
3. Produce a spike (or burst of spikes) as output.
4. But only if input is above threshold.
5. On the downward side of the spike the cell can hyperpolarize: membrane potential drops as low as –90 mV.
6. Post-spike refractory period in which cells are much harder to excite.
7. Behavior can change in response to prolonged or repeated stimuli: “habituation,” “mode switching,” “fatigue,” etc.
8. Post-inhibitory rebound: if hyperpolarized by an inhibitory input, simply removing this input can result in a spike.

How are all these properties achieved?

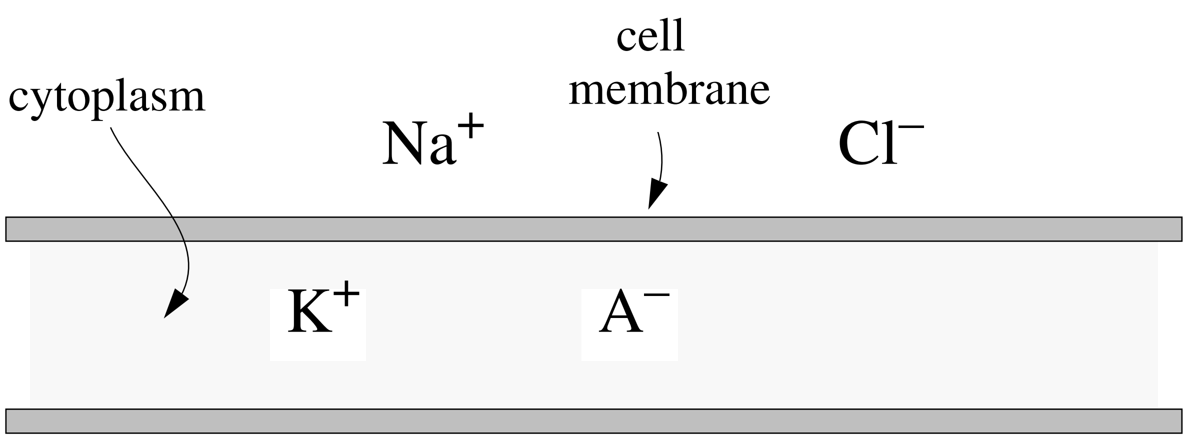
(Intra/Extra)-Cellular Ion Concentrations

Concentration values are in mM, for typical CNS neurons.

	Extracellular	Intracellular
Na^+	150	30
K^+	3	140
Ca^{2+}	1.2	0.1
Cl^-	130	8
A^-	25	162

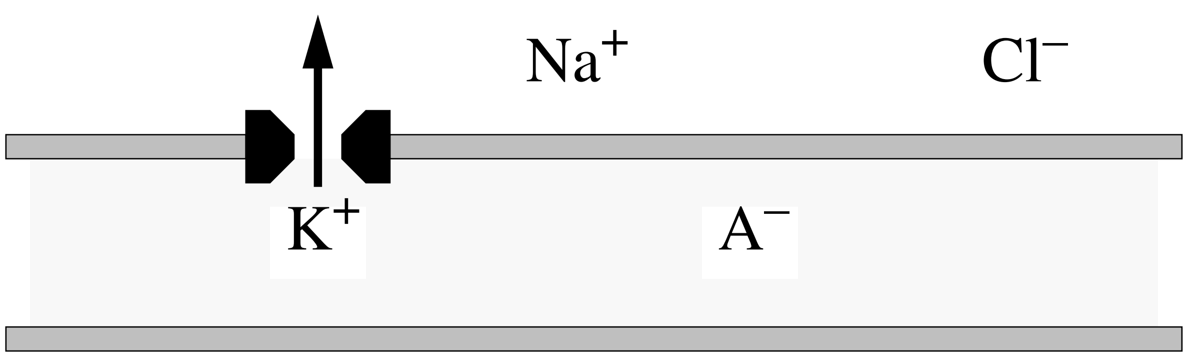
Positive and negative charges balance, both inside and outside.

The cell membrane is a lipid bilayer: acts like an insulator.



Passive Ion Channels

- Membrane contains channels selectively permeable to K^+. Concentration gradient favors K^+ flowing out of the cell.
  $[K^+]_i = 140$ mM $\quad [K^+]_o = 3$ mM
- K^+ ions continue to flow out the channel until the cell's membrane potential V_m is –96 mV.
- At this point, the outward concentration gradient for K^+ is exactly counterbalanced by the inward electrical force.
- The cell's negative internal charge attracts positive ions, but only K^+ can pass through the channel.
- Positive charges cluster along the outer wall of the membrane; negative charges are left to cluster along the inner wall.



Reversal Potential for K^+

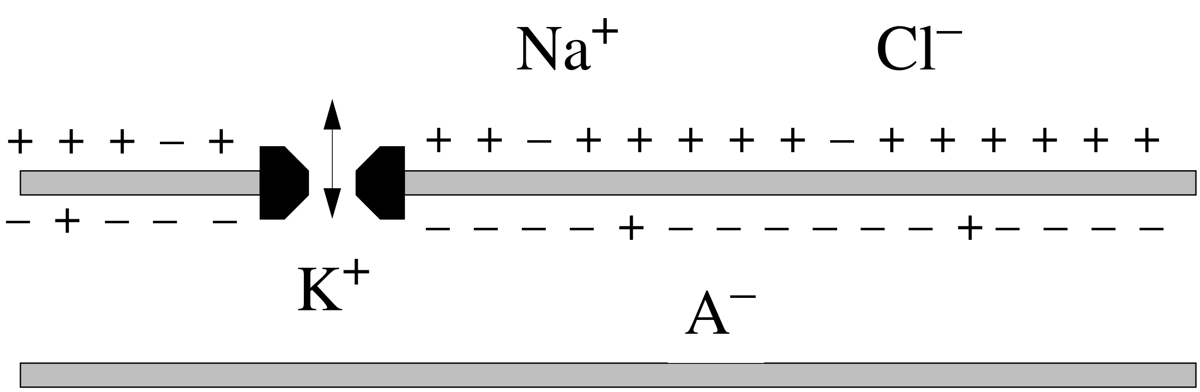
- The Nernst Equation defines the equilibrium potential:

$$E_K = \frac{RT}{zF} \cdot \ln \frac{[K]_o}{[K]_i}$$

- R = thermodynamic gas constant; T = temperature;
  z = valence (+1 for K^+); F = Faraday's constant

- k = (RT/zF) = 25 mV at room temp. $E_K = -96$ mV

- The cell membrane is only 50 Angstroms thick, so a –96 mV potential is like 192,000 volts across a 1 cm membrane.



Manipulating the Reversal Potential

- By changing the extracellular concentration of K^+, we can change the reversal potential.

- Example: suppose we want E_K to go from –96 mV to –75 mV.

$$K_o = \exp\left(\frac{E_K}{RT/zF}\right) \cdot K_i = \exp(-3) \cdot 140\text{mM} = 7\text{mM}$$

- Solution: increase extracellular K^+ from 3 mM to 7 mM.

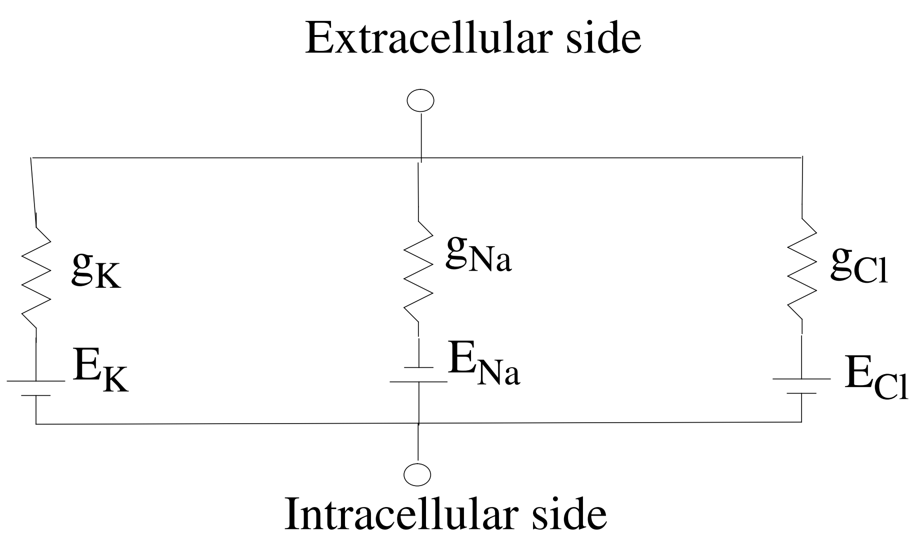
Two Other Ionic Currents

- Passive sodium channels allow an inward sodium leakage.

$$E_{Na} = 25\mathrm{mV} \cdot \ln \frac{[K]_o}{[K]_i} = 25\mathrm{mV} \cdot \ln \frac{150\,mM}{30\,mM} = +40\,\mathrm{mV}$$

- Passive chloride channels also allow an inward Cl^- leakage. $E_{Cl} = -75$ mV.

- There is a simultaneous flow of K^+, Na^+, and Cl^- ions into and out of the cell.



The Resting Potential

- The cell's membrane potential V_m is a weighted combination of the reversal potentials for the three ion species.

- The different ion channels have different conductivities: g_K, g_{Na}, and g_{Cl}.

- The Goldman-Hodgkin-Katz equation:

$$V_m = \frac{(E_K \times g_K) + (E_{Na} \times g_{Na}) + (E_{Cl} \times g_{Cl})}{g_K + g_{Na} + g_{Cl}}$$

- For typical cortical neurons the resting potential V_r is in the range of –60 to –75 mV.

- V_r is bounded from below by E_K and from above by E_{Na}.

The Sodium Pump

- Ions are constantly leaking into and out of the cell through the passive membrane channels.
- *Why doesn't the "battery" run down?*
- Electrogenic pumps maintain the cell's ionic balance.
- The sodium pump takes in 2 K^+ ions and expels 3 Na^+ ions on each cycle.
- The pump is powered by ATP.

The Action Potential

- Spikes are produced by voltage-sensitive membrane channels.
- Suppose V_m rises above –55 mV (the spike threshold.)

1. Voltage-gated Na^+ channels begin to open.
2. This increases g_{Na}, so more Na^+ ions enter the cell.
3. The membrane becomes further depolarized, causing more channels to open and even more Na^+ ions to enter the cell.
4. The Na^+ channels inactivate and close. They will reactivate (be ready to open again) when the membrane is repolarized.

- Why are spikes sharp? How does the membrane get repolarized again so quickly?

1. As V_m rises, voltage-gated K^+ channels begin to open.
2. This increases g_K, soK^+ ions leave the cell at a high rate.
3. The membrane potential drops. Since g_K is higher than normal, V_m can even temporarily drop to below Vr. This is the cause of after-hyperpolarization.
4. As V_m drops, the voltage-gated K^+ channels gradually close, and the passive current flows bring the cell back to V_r.

Channel Behavior

- The sodium channel has several states: open, closed (with several substates), and inactive.
- Each state corresponds to a movement of charge within the channel, causing a conformational change in the protein.
- A series of 3-4 conformational changes bring the channel from the closed state to the open state.
- State changes are stochastic, influenced by V_m.
- Normally the channel is closed. In the open state, ions can pass.
- When the channel passes to the inactive state, ions cannot pass.
- Repolarizing the membrane takes the channel out of the inactive state, allowing the activation gate to close until the membrane depolarizes again.
- Post-inhibitory rebound is caused by spontaneous channel openings after massive de-inactivation.

What About Calcium?

- Ca^{2+} is present in only small amounts in the cell: 0.1 mM compared to 140 mM for K^+.
- Extracellular concentration is also small: only 1.2 mM.
- Thus, Ca^{2+} doesn't contribute significantly to the resting potential or the normal (sodium) axonal spike.
- It can, however, contribute to some types of spikes.
- Ca^{2+} is crucial for triggering many important metabolic operations in neurons, such as transmitter release.
- Thus, when a little bit of extra calcium does enter the cell, it has a big effect.
- If a cell is overstimulated, too much Ca^{2+} can enter, which could poison it.
- This is how epileptic seizures can result in brain damage.

Types of Ionic Currents

- There are more than a dozen voltage-gated ion currents.
- Each has a different time course of activation and inactivation.
- $I_{Na,t}$ is the fast, transient sodium current responsible for action potentials.
- I_K is one of several currents responsible for repolarization after an action potential.
- I_{AHP} is a slow potassium current triggered by Ca^{2+} influx, responsible for adaptation of the action potential with repeated firing.
- Complex spike patterns in some cells are thought to involve as many as 10 distinct ion currents.
- Aplysia cell R15 (the "parabolic" cell) uses a combination of 7 channel types to produce its unusual firing pattern.

Ion Channels Are Proteins

- A channel is typically a single protein strand that passes through the membrane multiple times, forming a pore throught which ions can pass.
- Modifications to the amino acid sequence result in slight changes to the channel characteristics, e.g., conductance, activation voltage, open/close time.
- Humans and cows both have ion channels, but their characteristics are slightly different.
- Cells continually make new channels and reclaim existing ones.
- By modulating the rates of creation and reclamation, a cell can dynamically adjust the distribution of channels over the surface of its membrane.
- Some types of *learning* may may be implemented this way.

Propagation of the Action Potential

- A region of membrane is depolarized due to Na^+ channels opening.
- The depolarization spreads to nearby patches of membrane as ions flow into the cell.
- Channels in these new patches then begin to open.
- The “spike” is a traveling wave that begins at the soma.
- It can travel in either direction along an axon: prodromic or antidromic.
- Normally it only travels forward.
- Why doesn’t it reflect backward when it gets to the end of the axon?

Ligand-Gated Ion Channels

- In the dendrites and soma there are receptors sensitive to particular neurotransmitters.
- In the simplest case, the receptor and the ion channel are parts of the same complex. This is a ligand-gated ion channel.
- When transmitter binds to the receptor, the channel opens and ions flow.
- Whether a channel is excitatory or inhibitory depends on the kinds of ions it passes.
- For some inhibitory channels, binding of neurotransmitter *prevents* the channel from opening.
- This has no effect on the resting potential, but can enhance the cell's response to input, or permit a sequence of multiple spikes instead of just one.

Neurotransmitters

- Dozens of substances can act as neurotransmitters, including both simple molecules (ACh, glutamate, dopamine), and proteins (enkephalin, substance P.)

- A few you should know about:

glutamate	excitatory; pyramidal cells
GABA	inhibitory interneurons
ACh	neuromuscular junction (excit.)
	heart cells (muscarinic inhib.)
	hippocampus (modulatory)

- Many kinds of channels can be sensitive to the same neurotransmitter.

- $GABA_A$ receptor: fast shunting inhibition via Cl^- channel.

- $GABA_B$ receptor: slow, long-lasting inhibition via K^+. Not directly coupled to a single ion channel.

- Sometimes receptors are named after substances that enhance or block their response (agonists/antagonists), e.g., muscarinic vs. nicotinic ACh receptors.

Second Messenger Systems

- Instead of being directly coupled to a channel, a receptor can be coupled to a G protein.
- When transmitter binds to the receptor, this allowsGDP (guanosine 5'-diphosphate) bound to the α subunit to be converted to GTP (guanosine 5'-triphosphate).
- The GTP-α subunit complex then detaches from the receptor and can interact with a variety of targets, including ion channels.
- Second messenger systems produce slower but longer lasting effects than ligand-gated channels.
- It allows a single receptor to control several intracellular processes at once.
- The $GABA_B$ receptor is an example of a second messenger system.

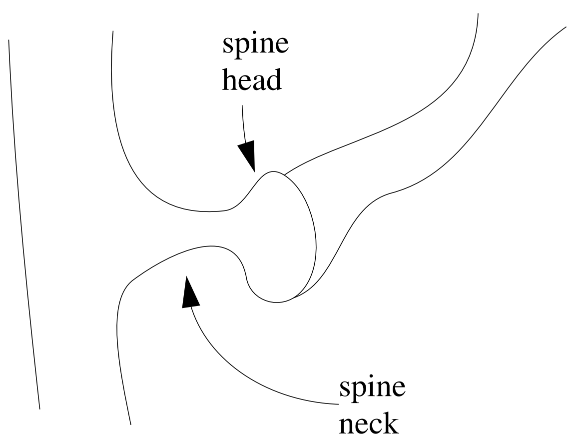
Transmitter Release

- The *synaptic bouton* contains voltage-sensitive Ca^{2+} channels that open when the spike depolarizes the membrane.
- Calcium enters the bouton and triggers metabolic reactions that result in transmitter release.
- A vesicle fuses with the membrane surface and dumps its transmitter into the synaptic cleft.
- This is a probabilistic process. A single spike may only result in release of a packet of transmitter 10% of the time.
- Some cells can release more than one type of transmitter. This was only discovered recently.

Properties of Dendrites

- Generally passive current flow; no spikes.
- The *cable equation* defines how current flows in dendritic segments.
- Must deal with resistance, capacitance, multiple current sources, branched dendritic trees.
- Many synapses in the brain are made onto dendritic spines.
- Why are there spines?

  a) small diameter neck gives high input impedance
  b) mini-chemical reactors



Dendritic Information Processing

- Local interactions in the dendritic tree are non-linear.
- Active membrane areas have been found in some dendrites, permitting dendritic spikes to occur.
- "Cold spots" are regions where shunting inhibition suppresses distal epsps, preventing them from traveling further toward the soma.
- The AND-NOT gate consists of a shunting inhibitory synapse downstream from an excitatory synapse.
- AND and OR gates can also be constructed based on interactions between nearby synapses.
- What do neurons compute? Possibly very complex functions, since there can be 10,000 synapses coming into a pyramidal cell.

Miscellaneous Items

- Terms to know:

epsp and *ipsp*
shunting inhibition
pyramidal cell
glutamate
GABA (γ-amino butyric acid)
$GABA_A$ vs. $GABA_B$ receptor

- How neuroscientists draw pyramidal cells: