



Lecture 2: Ion channels & membrane potential

- Reading assignment from Kandell, Schwartz & Jessell:
 - Chapter 5 – Ion Channels
 - Chapter 6 – Membrane potential
- Lecture 1 left off having introduced neurons and action potentials.
- Lecture 2 will complete our introduction to the nervous system, and then delve into ion channel biophysics.



Knee-Jerk Spinal Reflex Circuit

- Different classes of neurons (sensory, motor or interneuronal) have different morphologies to best serve their functionality.
- All behavioral & computational functions are carried out by sets of interconnected neurons.
- In this example, a single sensory event triggers a cascade of signals in the spinal cord that result in extension of the leg.
- Signals are also sent to higher brain structures for further processing, but does not necessarily require that cortex “get involved” → **distributed processing**.

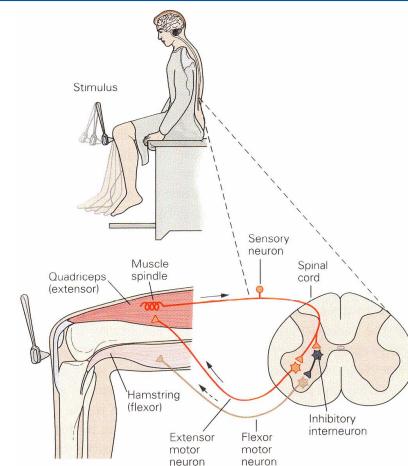


Figure 2-5 The knee jerk is an example of a monosynaptic reflex system, a simple behavior controlled by direct connections between sensory and motor neurons. Tapping the kneecap with a reflex hammer pulls on the tendon of the quadriceps femoris, an extensor muscle that extends the lower leg. When the muscle stretches in response to the pull of the tendon, information regarding this change in the muscle is conveyed by afferent (sensory) neurons to the central nervous system. In the spinal cord the sensory neurons act directly on extensor motor neurons that contract the quadriceps, the muscle that was stretched. In addition, the sensory neurons act indirectly, through interneurons, to inhibit flexor motor neurons that would otherwise contract the opposing muscle, the hamstring. These actions combine to produce the reflex behavior. In this schematic drawing each extensor and flexor motor neuron represents a population of many cells.



Divergence (fan-out) & Convergence (fan-in)

- The previous circuit was greatly (overly) simplified.
- Sensory neurons often **diverge** – allows a single sensory neuron to exert wide and diverse influence.
- Motor neurons often receive **converging** inputs – allows a single motor neuron to integrate diverse information from many sources.
- Sensory signals are typically called **afferent** while motor signals are typically called **efferent**.

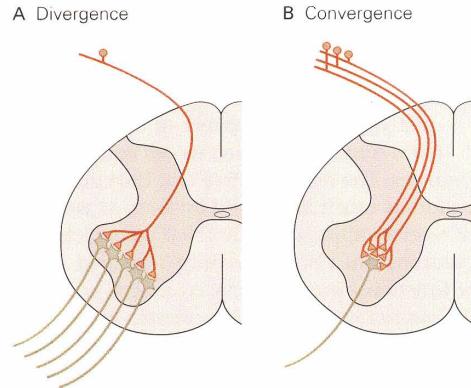


Figure 2-6 Diverging and converging neuronal connections are a key organizational feature of the brain.

- A. In the sensory systems receptor neurons at the input stage usually branch out and make multiple, divergent connections with neurons that represent the second stage of processing. Subsequent connections diverge even more.
- B. By contrast, motor neurons are the targets of progressively converging connections. With convergence, the target cell receives the sum of information from many presynaptic cells.



Feed-forward & Feedback Inhibition

- The previous two circuits were still greatly (overly) simplified.
- Reciprocal feed-forward inhibition** assures that extensor and flexor muscles are not simultaneously strongly activated.
- Negative feedback inhibition** helps regulate drive signal.
- The BIG PICTURE here is that neural circuits can be quite complex and sophisticated.
- Intriguing to consider how they were “designed” and “built” – beyond the scope of this course.

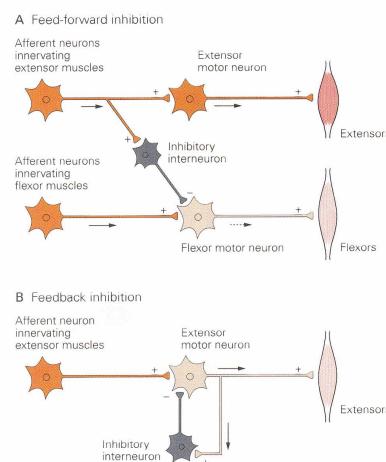


Figure 2-7 Inhibitory interneurons can produce either feed-forward or feedback inhibition.

- A. Feed-forward inhibition is common in monosynaptic reflex systems, such as the knee-jerk reflex (see Figure 2-5). Afferent neurons from extensor muscles excite not only the extensor motor neurons, but also inhibitory neurons that prevent the firing of the motor cells in the opposing flexor muscles. Feed-forward inhibition enhances the effect of the active pathway by suppressing the activity of other, opposing, pathways.
- B. Negative feedback inhibition is a self-regulating mechanism. The effect is to dampen activity within the stimulated pathway and prevent it from exceeding a certain critical maximum. Here the extensor motor neurons act on inhibitory interneurons, which feed back to the extensor motor neurons themselves and thus reduce the probability of firing by these cells.



Signaling Organization

- All neurons have **input**, **integrating-triggering**, **conductive** and **output** signals.
- Different signals used determined in part by **electrical properties** of cell membrane.

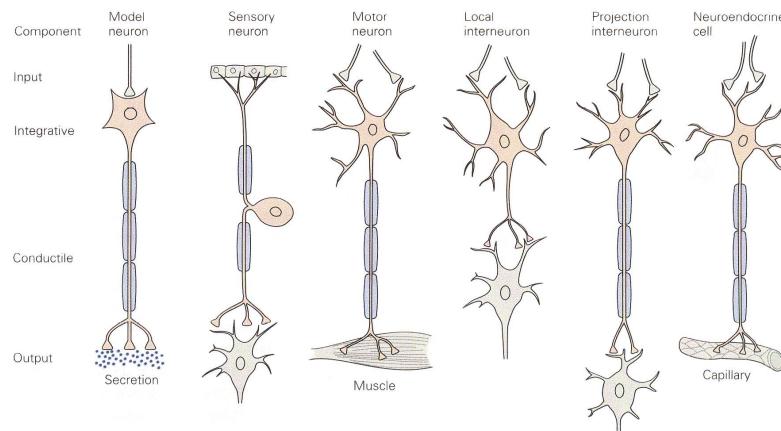


Figure 2-8 Most neurons, regardless of type, have four functional regions in common: an input component, a trigger or integrative component, a conductile component, and an output component. Thus, the functional organization of most neurons can be schematically represented by a model neuron. Each component produces a characteristic signal: the

input, integrative, and conductile signals are all electrical, while the output signal consists of the release of a chemical transmitter into the synaptic cleft. Not all neurons share all these features; for example, local interneurons often lack a conductile component.



Resting Membrane Potential

- Neurons maintain a difference in electrical potential across the cell membrane.
- Roughly -65 mV (outside arbitrarily defined as 0 V / ground).
- Potential difference created by:
 - Unequal distribution of charged ions (e.g., Na^+ and K^+) inside/outside of cell membrane.
 - Selective membrane permeability to K^+ (also Na^+).
- Mechanism:
 - Membrane protein pumps Na^+ out and K^+ in.
 - Ion channels let K^+ leak out.

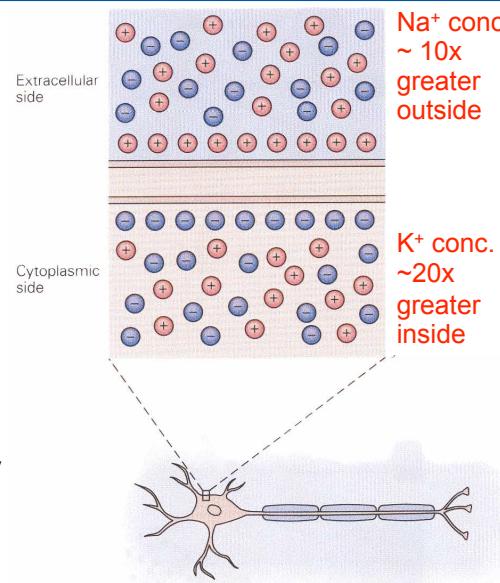


Figure 2-9 The membrane potential of a cell results from a difference in the net electrical charge on either side of its membrane. When a neuron is at rest there is an excess of positive charge outside the cell and an excess of negative charge inside it.



A 2nd Look at Action Potentials

- Neurons are *excitable cells* – can rapidly change membrane potential.
- Rapid change can serve as a signaling mechanism – *action potential*.
- Slight decrease in membrane potential (e.g., $-65 \text{ mV} \rightarrow -55 \text{ mV}$) makes membrane much more permeable to Na^+ than K^+ .
- This further reduces membrane potential and further increases Na^+ over K^+ permeability.
- This **positive feedback** loop creates sharp ($\ll 1 \text{ ms}$) depolarization event (**rising edge of the action potential**).
- Action potentials are “all or nothing” and are actively propagated along axon.

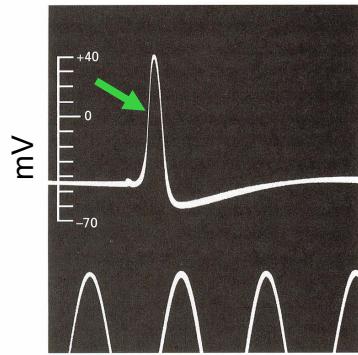


Figure 2-3 This historic tracing is the first published intracellular recording of an action potential. It was obtained in 1939 by Hodgkin and Huxley from the squid giant axon, using glass capillary electrodes filled with sea water. Time marker is 500 Hz. The vertical scale indicates the potential of the internal electrode in millivolts, the sea water outside being taken as zero potential. (From Hodgkin and Huxley 1939.)



Depolarization and Hyperpolarization

- Axonal action potentials are long range.
- Receptor and synaptic potentials are more local, short range.
- These signals decay on the order of millimeters.
- Both types result from a change in the membrane potential; the baseline (-65 mV) potential is the reference level.
 - A reduction (e.g., $-65 \text{ mV} \rightarrow -55 \text{ mV}$) termed **depolarization**.
 - This makes action potentials more likely, and is thus **excitatory**.
 - An increase (e.g., $-65 \text{ mV} \rightarrow -75 \text{ mV}$) termed **hyperpolarization**.
 - This makes action potentials less likely, and is thus **inhibitory**.



Putting it All Together

1) Receptor potential is graded and local; 1st representation of stretch.
• “Analog like”

2) Action potentials are all or nothing and long range;
2nd representation.
• “Digital like”

3) Neurotransmitter release to communicate to next neuron is statistical; 3rd representation.
• “Probabilistic like”

4) Synaptic potential is graded and local...

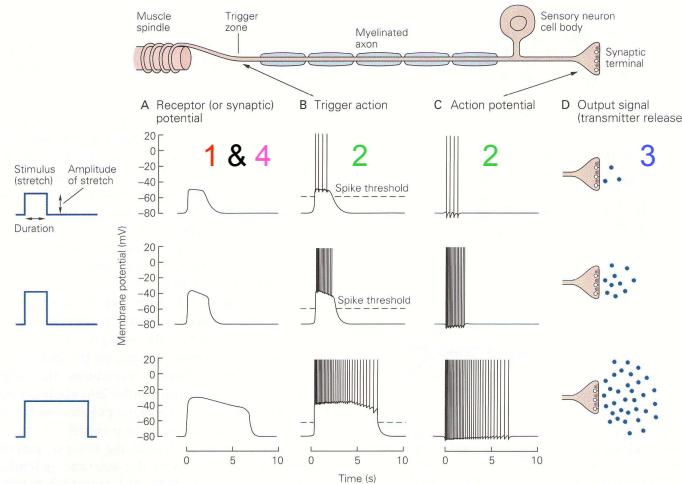


Figure 2-10 A sensory neuron transforms a physical stimulus (in our example, a stretch) into electrical activity in the cell. Each of the neuron's four signaling components produces a characteristic signal.

A. The input signal (a receptor or synaptic potential) is graded in amplitude and duration, proportional to the amplitude and duration of the stimulus.

B. The trigger zone integrates the input signal—the receptor potential in sensory neurons, or synaptic potential in motor neurons—into a trigger action that produces action potentials that will be propagated along the axon. An action potential is generated only if the input signal is greater than a certain *spike threshold*. Once the input signal surpasses this threshold, any further increase in amplitude of the input signal increases the frequency with which the action potentials are generated, not their amplitude. The *duration* of the input signal determines the number of action potentials. Thus, the graded nature of input signals is translated into a frequency code of action potentials at the trigger zone.

C. Action potentials are all-or-none. Every action potential has the same amplitude and duration, and thus the same waveform on an oscilloscope. Since action potentials are conducted without fail along the full length of the axon to the synaptic terminals, the information in the signal is represented only by the frequency and number of spikes, not by the amplitude.

D. When the action potential reaches the synaptic terminal, the cell releases a chemical neurotransmitter that serves as the output signal. The total number of action potentials in a given period of time determines exactly how much neurotransmitter will be released by the cell.



Passive & Active Signal Summary

Table 2-1 Comparison of Local (Passive) and Propagated Signals

Signal type	Amplitude (mV)	Duration	Summation	Effect of signal	Type of propagation
Local (passive) signals					
Receptor potentials	Small (0.1–10)	Brief (5–100 ms)	Graded	Hyperpolarizing or depolarizing	Passive
Synaptic potentials	Small (0.1–10)	Brief to long (5 ms to 20 min)	Graded	Hyperpolarizing or depolarizing	Passive
Propagated (active) signals					
Action potentials	Large (70–110)	Brief (1–10 ms)	All-or-none	Depolarizing	Active

- Since all or none, action potentials are essentially identical in shape.
- Information can not be coded / conveyed in the shape of the pulse.
- Information is coded / conveyed in the frequency emission.



Knee-Jerk Spinal Reflex Circuit – Revisited

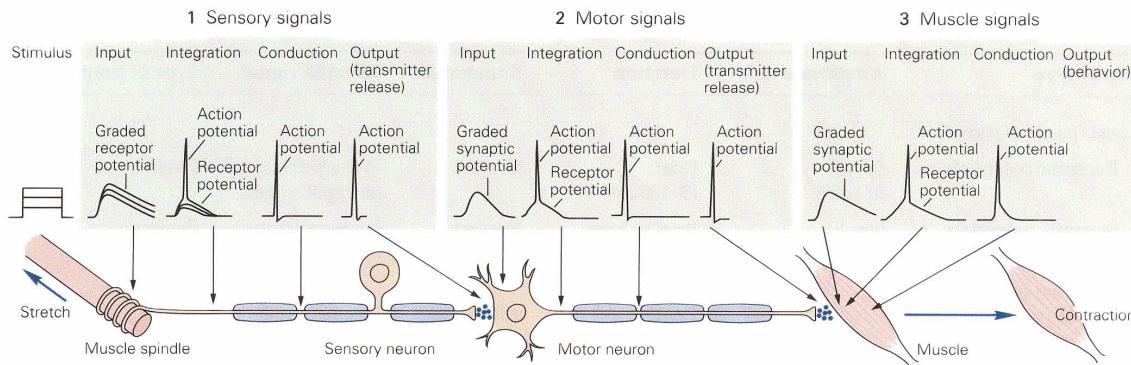


Figure 2-11 The sequence of signals that produces a reflex action.

1. The stretching of a muscle produces a receptor potential in the terminal fibers of the sensory neuron (the dorsal root ganglion cell). The amplitude of the receptor potential is proportional to the intensity of the stretch. This potential then spreads passively to the integrative segment, or trigger zone, at the first node of Ranvier. There, if the receptor potential is sufficiently large, it triggers an action potential, which then propagates actively and without change along the axon to the terminal region. At the terminal the action potential leads to an output signal: the release of a chemical neurotransmitter. The

transmitter diffuses across the synaptic cleft and interacts with receptor molecules on the external membranes of the motor neurons that innervate the stretched muscle. 2. This interaction initiates a synaptic potential in the motor cell. The synaptic potential then spreads passively to the trigger zone of the motor neuron axon, where it initiates an action potential that propagates actively to the terminal of the motor neuron. The action potential releases transmitter at the nerve-muscle synapse. 3. The binding of the neurotransmitter with receptors in the muscle triggers a synaptic potential in the muscle. This signal produces an action potential in the muscle, causing contraction of the muscle fiber.



Ion Channels

- Neuronal signaling depends on rapid changes in membrane potential.
- I.e., action potentials require ~ 500 V/s slew rate.
- Enabled by **ion channels**: membrane proteins found in all cells in body.
- Ion channels in neurons are tuned for rapid information processing.
- Ion channels are heterogeneous: different types of channels appear in different parts of nervous system (and neuron) & carry out specific signaling tasks.
- Malfunctioning of ion channels \rightarrow neurological disease.
- Ion channels are site of action of drugs, poisons (chemical inhibitor) and toxins (protein causing disease).



Ion Channels continued

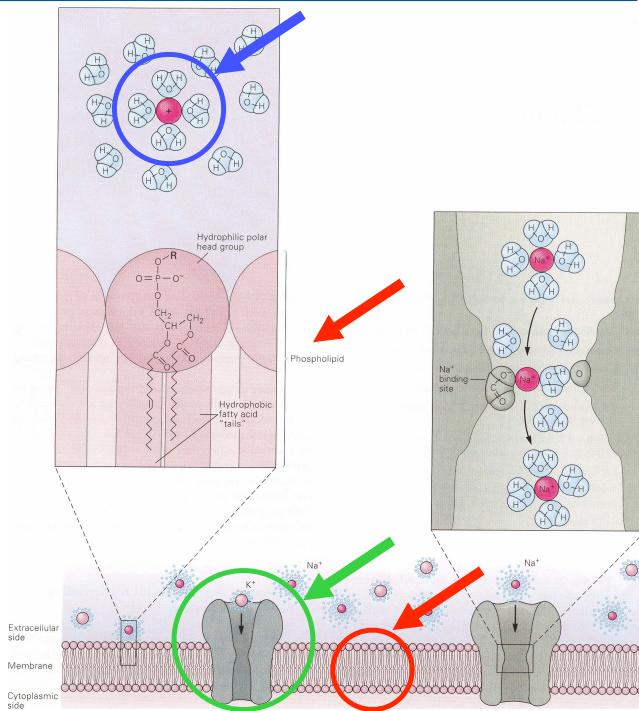
- Three properties of ion channels:
 - 1) Conduct ions → ionic current (up to 10^8 ions/channel/s)
 - 2) Recognize and select specific ions:
 - i.e., K^+ channels typically 100x more permeable to K^+ than Na^+ .
 - i.e., Na^+ channels typically 10-20x more permeable to Na^+ than K^+ when active; else not permeable
 - 3) Open/close (regulated) in response to specific electrical, mechanical or chemical signals:
 - **voltage-gated channels** regulated by membrane potential.
 - **mechanically-gated channels** regulated by pressure/stretch.
 - **ligand*-gated channels** regulated by chemical transmitters.
 - **resting channels** are not regulated; normally open.
- BIG PICTURE: we need to understand the fundamental operation of ion channel conductivity, selectivity and gating in order to understand information processing and representation in the nervous system.

* **Ligand** – an ion, a molecule, or a molecular group that binds to another chemical entity to form a larger complex.



Cell Membrane

- Cell membrane:
 - 6-8 nm thick.
 - double layer of phospholipids* (a.k.a. lipid bi-layer)
 - integrated proteins (channels).
- Fatty acid “tails” are hydrophobic.
- “Head” group is hydrophilic.
- Cations (+ ions) electrostatically attract the slight negative charge on oxygen (H_2O is charge neutral but dipolar).
- Membrane impermeable to ions due to size and energetics of cation- H_2O complex.

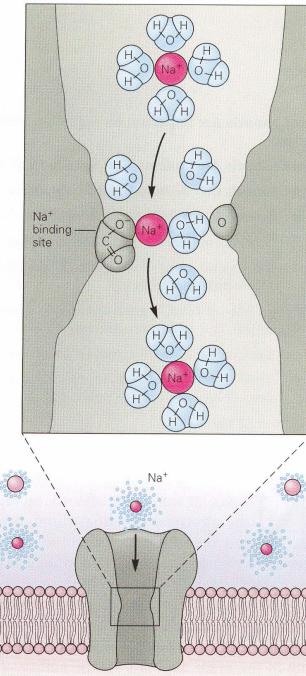


* **Lipid** – any of a group of organic compounds, including the fats, oils, waxes, sterols, and triglycerides, that are insoluble in water but soluble in nonpolar organic solvents, are oily to the touch, and together with carbohydrates and proteins constitute the principal structural material of living cells.
Phospholipids – any of various phosphorous-containing lipids that are composed mainly of fatty acids, a phosphate group & a simple organic molecule.



Ion Channels

- Ion channels are not just holes in the membrane!
- They are specialized proteins*.
- Ionic selectivity can not be based solely on ion diameter – K⁺ selective channels exist and K⁺ crystal radius is 0.133 nm; Na⁺ is 0.095 nm.
- Ion mobility & diffusion constant depends on size including shell of water.
- Smaller ions → stronger E field → attract H₂O more strongly → larger H₂O shell → lower mobility.
- Ok, but now selectivity puzzle is just flipped – Na⁺ selective channels exist but K⁺ is effectively “smaller” species.



* Proteins -- any of a group of complex organic macromolecules that contain carbon, hydrogen, oxygen, nitrogen, and usually sulfur and are composed of one or more chains of amino acids. Proteins are fundamental components of all living cells and include many substances, such as enzymes, hormones, and antibodies, that are necessary for the proper functioning of an organism. They are essential in the diet of animals for the growth and repair of tissue.



Ion Channels continued

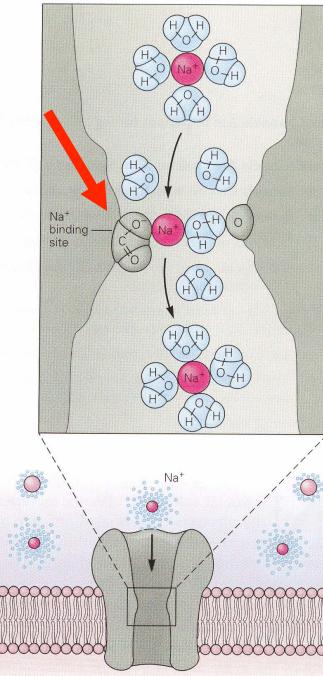
- Could be that ions must bind to specific carrier protein, which transports ion through membrane.
- This does exist (we'll learn about pumps), but it's not the answer.
- Ion conductance is way too high (10^8 ions/channel/s) for pumps (~100 ions/pump/s) to explain.
- So, must be some other mechanism...



Ion Channels continued

Answer, narrow region acting as molecular sieve*:

- 1) Ion sheds most of its H₂O of hydration.
- 2) Ion forms weak chemical bonds (electrostatics) with polar (charged) amino acids on walls.
- 3) Will happen only if free energy of binding > energy to shed H₂O of hydration.
 - Free energy: electrostatics (Coulomb's law) inversely proportional to distance.
 - Na⁺ small → can get close to amino acid that may have high E → large enough free energy to satisfy 3) above.
 - If amino acid instead has low E, then free energy of binding < energy to shed H₂O (which is high for Na⁺ b/c of its high E holding H₂O tightly).
 - But low E amino acid w/ large K⁺ can satisfy 3) above, even though K⁺ can't get as close, b/c H₂O is not held as tightly.
- 4) Electrostatic and diffusion forces propel ion through channel.



* Molecular sieve – molecular structures designed specifically to filter molecules based on size, e.g. oxygen out of air.



Ion Channel Electrical Characteristics

- Ion channels are either open or closed.
- When open, their I-V curve is essentially linear like a resistor (in most cases, but there are rectifiers as well).
- Single-channel resistance (R) in GΩ range; conductivity (G) more often used.
- Ion flux driven by electrostatic and diffusion forces, not by the channel.

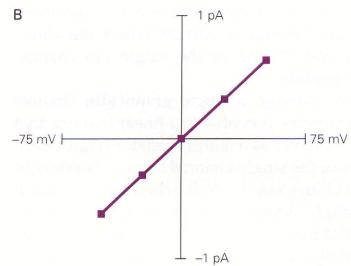
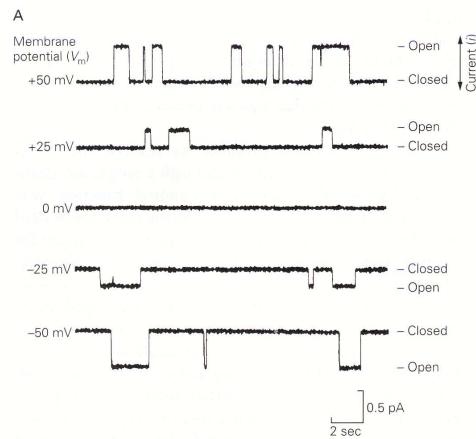


Figure 6-2 Characteristics of the current in a single ion channel. The data presented here were obtained from a channel formed by the addition of gramicidin A molecules to the solution bathing an artificial lipid bilayer.

A. The channel opens and closes in an all-or-none fashion, resulting in brief current pulses through the membrane. If the electrical potential (V_m) across the membrane is varied, the current through the channel (i) changes proportionally. V_m is measured in millivolts (mV); i is measured in picoamperes (pA).

B. A plot of the current through the channel versus the potential difference across the membrane reveals that the current is linearly related to the voltage; in other words, the channel behaves as an electrical resistor that follows Ohm's law ($i = V/R$ or $i = \gamma \times V$). (Data courtesy of Olaf Anderson and Lyndon Providence.)



Physical Models of Ion Channel Gating

- Ion channels have 2 or more conformational states, which are relatively stable.
- Switching between states is termed **gating**.
- Relatively little is known about molecular mechanisms of gating.
- Gating commonly involves widespread changes in channel's conformation (B).
- Ball and chain model only rarely the case (C)

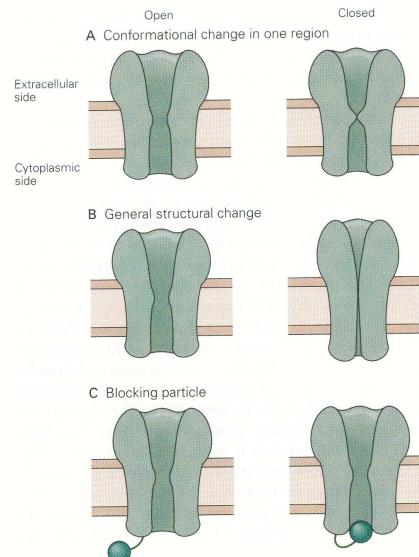


Figure 6-5 Three physical models for the opening and closing of ion channels.

- A. A localized conformational change occurs in one region of the channel.
B. A generalized structural change occurs along the length of the channel.
C. A blocking particle swings into and out of the channel mouth.



Controlling Ion Channel Gating

- Three regulatory mechanisms control gating (time a channel remains open and active):
 - Chemical ligand binding
 - Membrane potential
 - Mechanical stretch of membrane

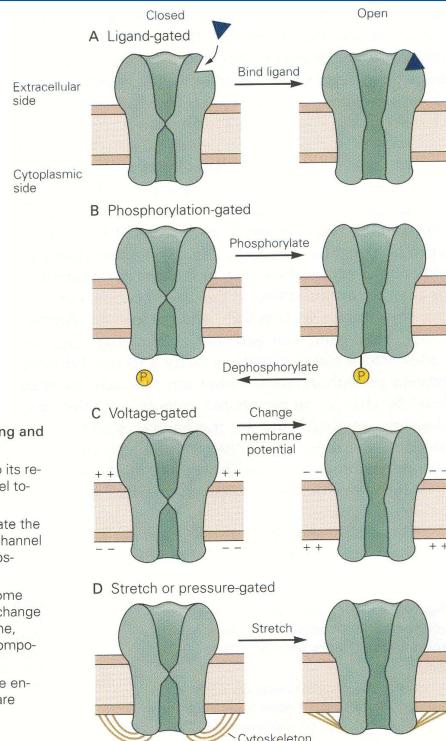


Figure 6-6 Several types of stimuli control the opening and closing of ion channels.

- A. Ligand-gated channels open when the ligand binds to its receptor. The energy from ligand binding drives the channel toward an open state.
B. Protein phosphorylation and dephosphorylation regulate the opening and closing of some channels. The energy for channel opening comes from the transfer of the high-energy phosphate, P_i .
C. Changes in membrane voltage can open and close some channels. The energy for channel gating comes from a change in the electrical potential difference across the membrane, which causes a conformational change by acting on a component of the channel that has a net charge.
D. Channels can be activated by stretch or pressure. The energy for gating may come from mechanical forces that are passed to the channel through the cytoskeleton.



Inactivation / Refractory State

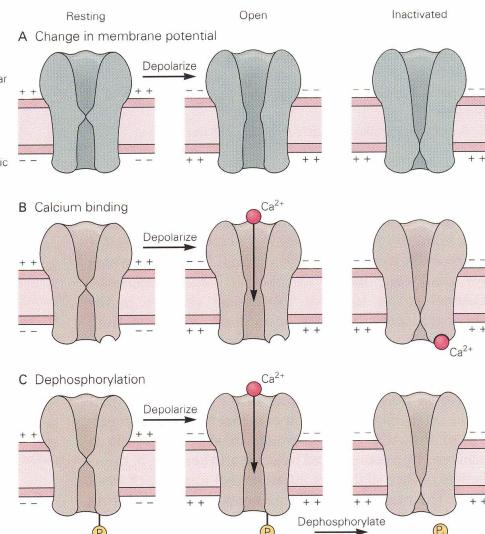
- Many voltage-gated channels enter a refractory state after activation.
- Termed “inactivation”.
- In Na^+ and K^+ channels inactivation due to intrinsic conformational change (A).
- This is what prevents a channel from staying open indefinitely.

Figure 6-7 Three mechanisms by which voltage-gated channels become closed and nonactivatable (the refractory state).

A. Many voltage-gated channels enter a refractory (inactivated) state after the transition from the resting (closed) state to a transient open state upon membrane depolarization. They recover from the refractory state and return to the resting state only after the membrane potential is restored to its original value.

B. When voltage-dependent Ca^{2+} channels are opened in response to depolarization, the internal Ca^{2+} level rises. The internal Ca^{2+} may then inactivate the channel by binding to a specific recognition site.

C. An increase in internal Ca^{2+} concentration in voltage-gated Ca^{2+} channels may produce inactivation through dephosphorylation of the channel. At pathologically high concentrations, Ca^{2+} may even produce an irreversible inactivation of the channel owing to the recruitment of protein-splitting enzymes activated by the Ca^{2+} ions.



Rest of Chapter 5

- We've covered topics in Chapter 5 up to, but not including, the section titled, “The structure of ion channels is inferred from biophysical, biochemical, and molecular biological studies.”
- We will not cover this section or beyond.
- Feel free to read if you are interested in learning more.



Membrane Potential

- Reading assignment from Kandell, Schwartz & Jessell:
 - Chapter 6 – Membrane Potential
- Information carried within & between neurons w/ electrical & chemical signals.
- Transient electrical signals (action potentials) critical for transmitting time-sensitive data rapidly and over long distances.
- Action potentials produced by temporary changes in current flow in/out of cell.
- This in turn changes the electrical potential across the cell membrane (membrane potential).
- Current flow controlled by ion channels in membrane (recall Lecture 3).



Resting and Gated Ion Channels

- Resting channels
 - Normally open.
 - Not influenced by membrane potential.
 - Important for maintaining resting membrane potential.
- Gated channels
 - Normally closed.
 - Probability of opening is a function of external factors.
 - External factors: membrane potential or stretch, ligand binding
- So, how are transient electrical signals generated?
 - Chapter 6: resting channels establish resting potential, and the resting potential can be perturbed.
 - Chapter 7: voltage-gated channels generate action potentials.



Separation of Charges Across Membrane

- At rest, excess of + charge outside of cell membrane; - charge inside.
- Membrane maintains this separation by blocking diffusion.
- Membrane potential definition:

$$V_m = V_{in} - V_{out}$$

- Resting membrane potential (V_r) = V_m when gated channels are closed.
- V_r typically = -60 mV to -70 mV.
- Electric current carriers are positive (cations) and negative (anions) ions.
- Direction of current flow defined as direction of net movement of + charge.

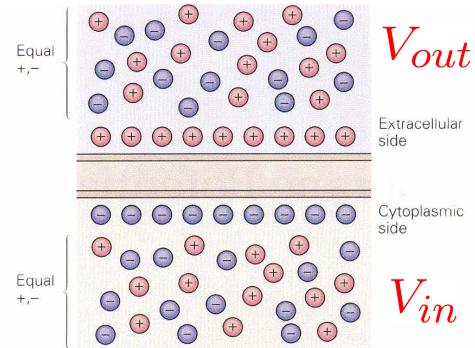


Figure 7-1 The membrane potential results from a separation of positive and negative charges across the cell membrane. The excess of positive charges (red circles) outside the membrane and negative charges (blue circles) inside the membrane of a nerve cell at rest represents a small fraction of the total number of ions inside and outside the cell.



Recording the Membrane Potential

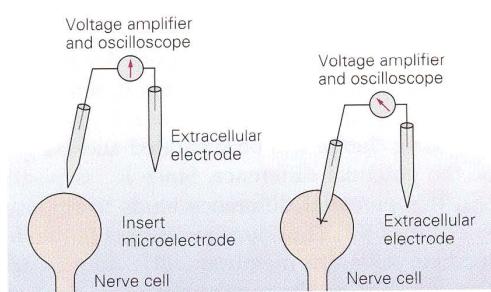


Figure 7-2A The recording setup.

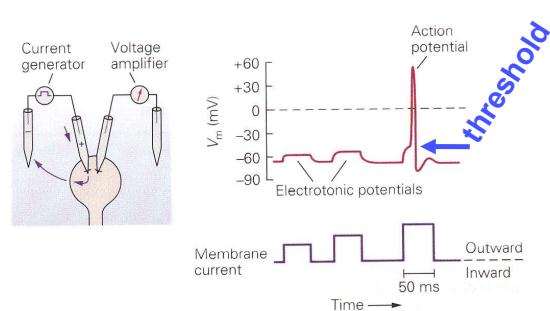


Figure 7-2C Depolarization.

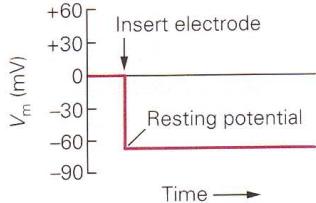


Figure 7-2B Oscilloscope display.

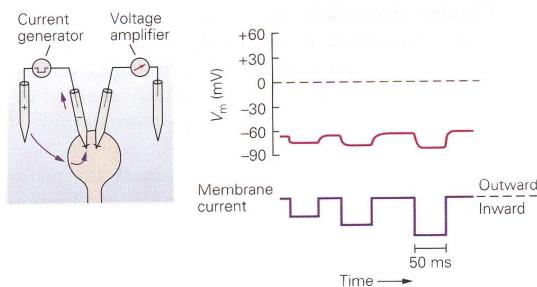


Figure 7-2D Hyperpolarization.



Resting Potential Determined by Resting Ion Channels

- No ion species is distributed equally inside/outside membrane.
- Table shows giant squid axon concentrations; ionic concentrations in vertebrates are 2-3x lower, but concentration gradients similar.

Table 7-1 Distribution of the Major Ions Across a Neuronal Membrane at Rest: the Giant Axon of the Squid

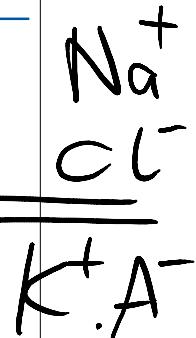
Species of ion	Concentration in cytoplasm (mM)	Concentration in extracellular fluid (mM)	Equilibrium potential ¹ (mV)
K ⁺	400	20	-75
Na ⁺	50	440	+55
Cl ⁻	52	560	-60
A ⁻ (organic anions)	385	—	—

¹The membrane potential at which there is no net flux of the ion species across the cell membrane.



Concentration Gradients & Resting Potential

- For simplicity, we first consider glia.
- Simply because glial membranes are permeable to only K⁺, not to all species present (we'll consider this case next).
- A high concentration of K⁺ and A⁻ exists inside the cell.
- A high concentration of Na⁺ and Cl⁻ exists outside the cell.
- Intuitively, species that can not transport through the ion channels must stay put (inside or outside of cell).
- Intuitively, species (i.e., K⁺) that can transport through the ion channels can potentially do so – but there must be a driving force.
- Recall driving forces at work in semiconductor p-n junctions?
(Diffusion down concentration gradients & electric-field induced drift)





Concentration Gradients & Resting Potential

Now the physics (akin to semiconductor device physics):

- 1) K⁺ diffuse inside→outside cell, down concentration gradient, creating diffusion current. (*Recall how electrons diffuse from n-type into p-type material, down concentration gradient, in a p-n junction.*)
- 2) Thus, outside accumulates a slight excess of + charge (K⁺) and inside accumulates a slight excess of - charge (lack of K⁺; *recall exposed donor atoms left behind when electrons move*).
- 3) Excess charges attract, forming sheet charges along membrane. (*Recall how inversion charge in MOS capacitor forms sheet along semiconductor-SiO₂ interface.*)
- 4) Sheet charges create electric (E) field, pointing from outside→in (+→-).
- 5) E-field applies force (drift) on K⁺ ions in direction of E-field (outside→in). This creates **drift current**. (*Recall holes (+) drift in direction of E-field.*)
- 6) At equilibrium (no net current flow), a specific E-field exists such that **drift current** is equal and opposite **diffusion current**.



Sketch of Drift and Diffusion Currents

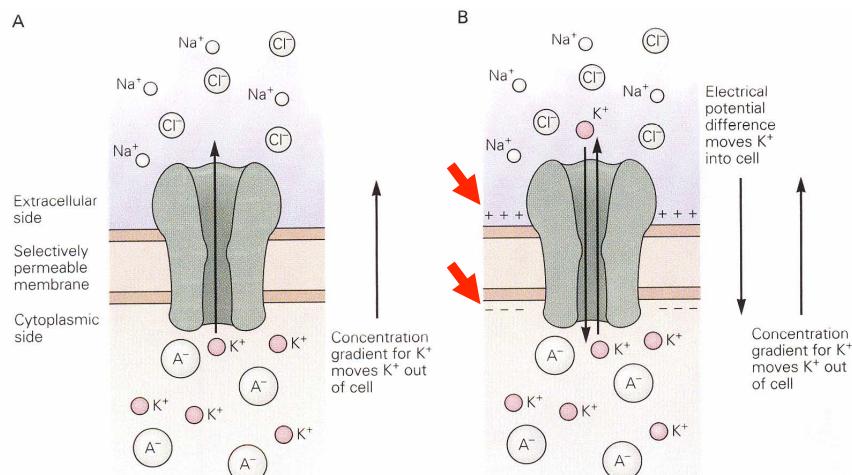


Figure 7-3 The flux of K⁺ across the membrane is determined by both the K⁺ concentration gradient and the electrical potential across the membrane.

- A. In a cell permeable only to K⁺ the resting potential is generated by the efflux of K⁺ down its concentration gradient.
- B. The continued efflux of K⁺ builds up an excess of positive

charge on the outside of the cell and leaves behind on the inside an excess of negative charge. This buildup of charge leads to a potential difference across the membrane that impedes the further efflux of K⁺, so that eventually an equilibrium is reached: the electrical and chemical driving forces are equal and opposite, and as many K⁺ ions move in as move out.



Concentration Gradients & Resting Potential

- The potential difference across the membrane associated with this specific E-field is termed the equilibrium potential (E_K).
(Recall the built-in potential in p-n junctions, V_o .)
- As per previous table, $E_K = -75 \text{ mV}$.
Note: don't be confused, here E is a voltage not an electric field.
(Potential is ϕ or V in standard electrical engineering notation.)
- Equilibrium potential for arbitrary ion X given by Nernst equation:

$$E_x = \frac{RT}{zF} \ln \frac{[X]_o}{[X]_i}$$

with R (gas constant), T (temperature in Kelvin), z (valence of the ion), F (Faraday constant) and $[X]_o$ and $[X]_i$ are chemical concentrations outside and inside of cell.



Calculating Resting Potential

- Since $RT/F = 25 \text{ mV}$ at room temperature (25° C), we can write:

$$E_x = \frac{25mV}{z} \ln \frac{[X]_o}{[X]_i}$$

- Or, including a factor of 2.3 to convert $\ln \rightarrow \log$:

$$E_x = \frac{58mV}{z} \log \frac{[X]_o}{[X]_i}$$

- And, with $z = 1$ for K^+ :

$$E_x = 58mV \log \frac{[20]}{[400]} = -75mV$$

- Recall expression for the built-in potential of a p-n junction ($kT/q = 25 \text{ mV}$):

$$V_o = \frac{kT}{q} \ln \frac{N_A N_D}{n_i^2} = \frac{kT}{q} \ln \frac{N_A}{n_i} \text{ for } N_D = n_i$$



Calculating Resting Potential

- Nernst Equation can be used to find the equilibrium (resting) potential of any ion that is present on both sides of a membrane permeable to that ion.
- See previous table (repeated here for convenience) for equilibrium potentials associated with each ion present in the giant squid axon:

Table 7-1 Distribution of the Major Ions Across a Neuronal Membrane at Rest: the Giant Axon of the Squid

Species of ion	Concentration in cytoplasm (mM)	Concentration in extracellular fluid (mM)	Equilibrium potential ¹ (mV)
K ⁺	400	20	-75
Na ⁺	50	440	+55
Cl ⁻	52	560	-60
A ⁻ (organic anions)	385	—	—

¹The membrane potential at which there is no net flux of the ion species across the cell membrane.



Concentration Gradients & Resting Potential

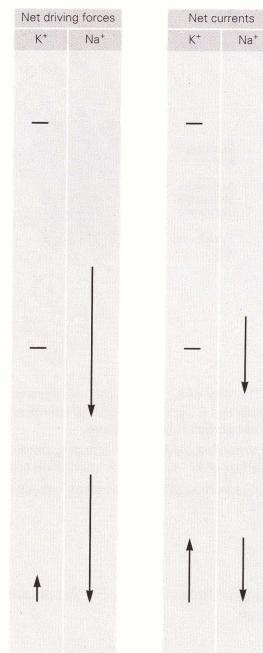
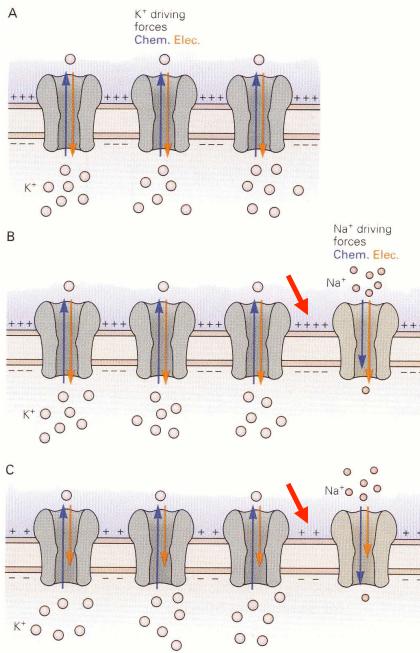
- Having considered simple glia, we now turn to neurons.
- Neurons at rest are permeable to Na⁺ and Cl⁻ ions, in addition to K⁺ ions.
- A⁻ ions unable to permeate; thus set aside.
- When multiple ion species can permeate membrane, a new resting potential is established such that net current flow is zero (steady state).
- To understand how resting potential is determined, must note that ion flux is the product of electrochemical driving force and membrane conductance to that ion:

$$\text{ion flux} = (\text{electrical driving force} + \text{chemical driving force}) \times \text{membrane conductance}$$

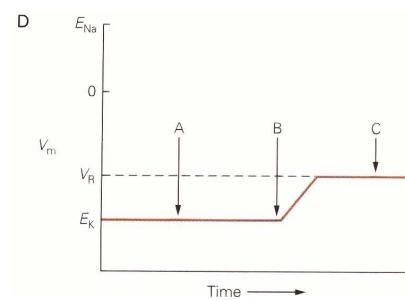
- There are relatively few **resting** Na⁺ channels (compared w/ resting K⁺ channels) so the conductance to Na⁺ is quite low.



Understanding Resting Potential w/ 2 Species



- V_R is close to E_K (not E_{Na}) b/c K⁺ channel conductance is higher.



Na⁺ - K⁺ Pump

- Now assume that the resting potential has been achieved.
- Passive movement of K⁺ out of cell = passive movement of Na⁺ into cell.
- But these concentrations gradients will eventually run down!!
- Need Na⁺ - K⁺ pump.
- Moves Na⁺ and K⁺ **against** their net electrochemical gradients.
- Moves Na⁺ out of cell; moves K⁺ into cell.
- Pump requires energy (ATP hydrolysis).
- Since energy put into system, this is NOT a system at equilibrium. It IS in steady state.
- Pump: membrane-spanning protein; 3 Na⁺ ions out for every 2 K⁺ ions in.



Another Quick Peek at Action Potentials

- Though we will study action potentials in depth soon enough, a quick peek is warranted now.
- If the membrane is depolarized past the “threshold voltage”, then voltage-gated Na⁺ channels open rapidly.
- Thus Na⁺ influx exceeds K⁺ efflux → further depolarization → even more voltage-gated Na⁺ channels open → ... (**positive feedback system**)
- Takes V_R very close to E_{Na} = + 55 mV.
- Why does membrane ever repolarize, to end action potential?
 - Voltage-gated Na⁺ channels gradually *inactivate*.
 - Voltage-gated K⁺ channels are slow, but eventually open.



Goldman Equation: V_R w/ Multiple Species

- Membrane conductance (1/resistance) is a convenient measure of how readily an ion crosses the membrane.
- Permeability (P, units of cm/s) is another convenient measure; similar to a diffusion constant.
- Membrane potential is easy to calculate w/ Goldman Equation:

$$V_m = \frac{RT}{F} \ln \frac{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_i}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_o}$$

- Species with highest concentration and permeability dominates – consider limit cases.



Equivalent Circuit Model

- So all of the preceding is well and good, but surely there is an easier / more intuitive way to model this behavior.
- Enter our good friend, the equivalent circuit model!
- Model elements:
 - Resistors – represent the ion channels.
 - Voltage sources – represent concentration gradients of relevant ions.
 - Capacitors – capacity of membrane to store charge.
 - Current sources – Na^+ - K^+ pump.
- All we need to do is determine element values and draw the schematic.
- Since this is stock-and-standard EE terrain, we won't unnecessarily belabor the development of the model. Just a quick overview.



Equivalent Circuit Model

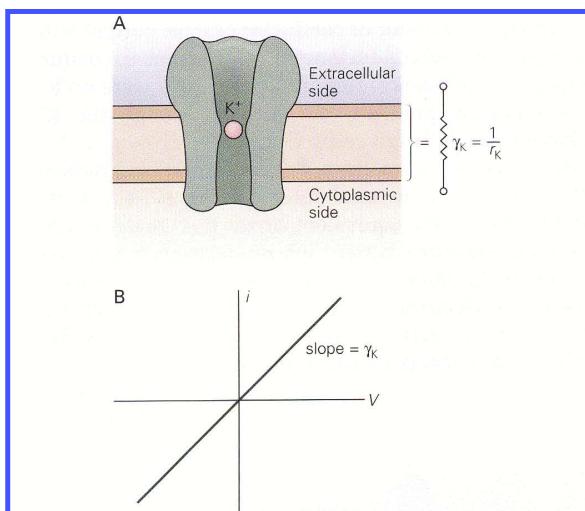


Figure 7-5. Electrical properties of a single K^+ channel.
A. A single K^+ channel can be represented as a conductor or resistor (conductance, γ , is the inverse of resistance, r).
B. The current-voltage relation for a single K^+ channel in the absence of a concentration gradient. The slope of the relation is equal to γ_{K} .

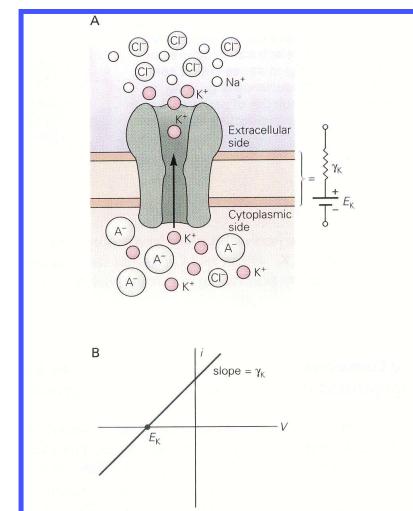


Figure 7-6 Chemical and electrical forces contribute to current flow.
A. A concentration gradient for K^+ gives rise to an electromotive force, with a value equal to the K^+ Nernst potential. This can be represented by a battery, E_{K} . In this circuit the battery is in series with a conductor, γ_{K} , representing the conductance of a channel that is selectively permeable to K^+ ions.
B. The current-voltage relation for a K^+ channel in the presence of both electrical and chemical driving forces. The potential at which the current is zero is equal to the K^+ Nernst potential.



Equivalent Circuit Model

Figure 7-7 All of the passive K^+ channels in a nerve cell membrane can be lumped into a single equivalent electrical structure comprising a battery (E_K) in series with a conductor (g_K). The conductance is $g_K = N_K \times \gamma_K$, where N_K is the number of passive K^+ channels and γ_K is the conductance of a single K^+ channel.

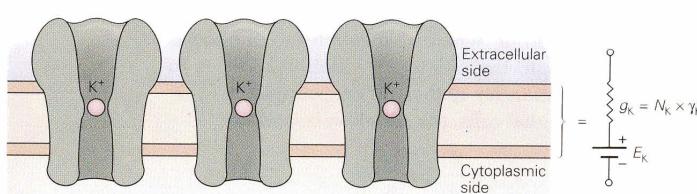
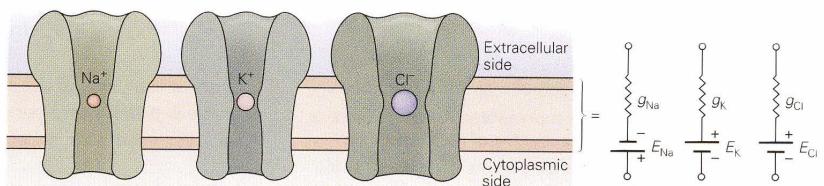


Figure 7-8 Each population of ion channels selective for Na^+ , K^+ , or Cl^- can be represented by a battery in series with a conductor. Note the directions of poles of batteries, indicating a negative electromotive force for K^+ and Cl^- and a positive one for Na^+ .



Equivalent Circuit Model

Figure 7-9 The passive current flow in a neuron can be modeled using an electrical equivalent circuit. The circuit includes elements representing the ion-selective membrane channels and the short-circuit pathways provided by the cytoplasm and extracellular fluid.

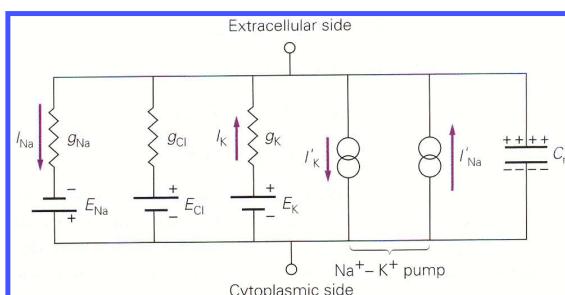
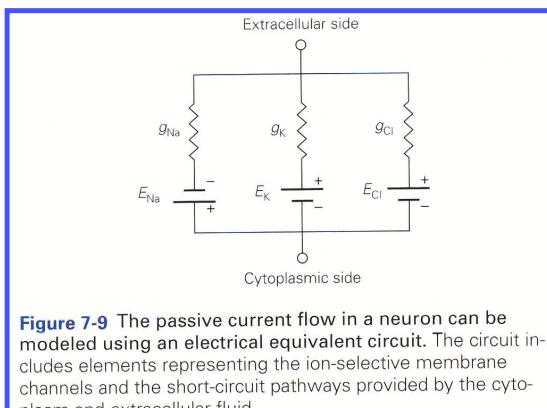


Figure 7-10 Under steady state conditions the passive Na^+ and K^+ currents are balanced by active Na^+ and K^+ fluxes (I'_Na and I'_K) driven by the Na^+-K^+ pump. The lipid bilayer endows the membrane with electrical capacitance (C_m). Note I'_Na is 50% greater than I'_K (and therefore I_{Na} is 50% greater than I_K) since the Na^+-K^+ pump transports three Na^+ ions out for every two K^+ ions it transports into the cell.