Electrical Properties of Neurons

Chapter 4

Content

Ion channels - Membrane

- Selectively permeable membrane of cell
  - Gases and water molecules can pass easily
  - Large molecules (ex. glucose) and charged molecules like ions or amino acids are unable

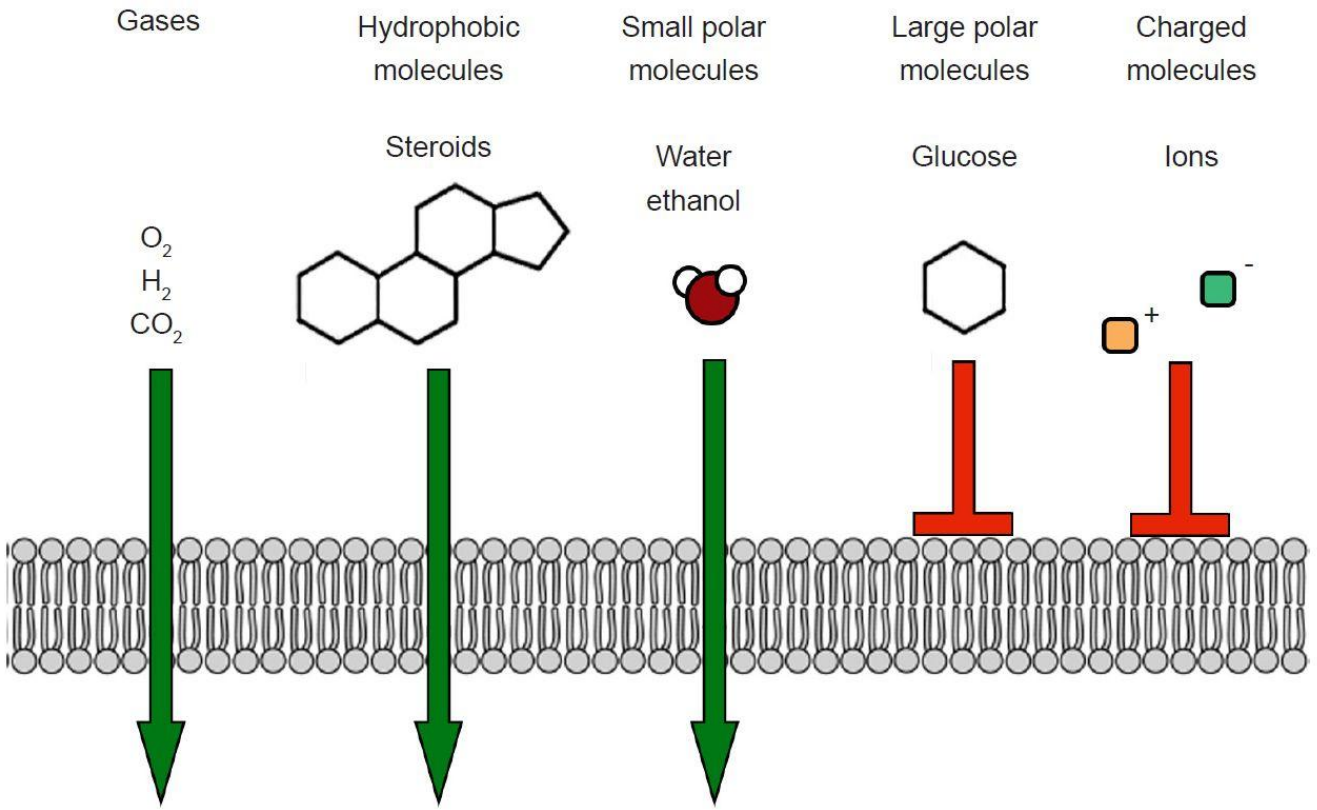


Figure 4.1 Selective permeability of molecules across the cell membrane.

Ion channels

- Transmembrane proteins have pores that are like "tunnels" allowing molecules and ions to pass
- Called ion channels
- Channels are passive (no cellular energy is required to move ions)
- Special molecular characteristics allow specific ions to pass and exclude other ions

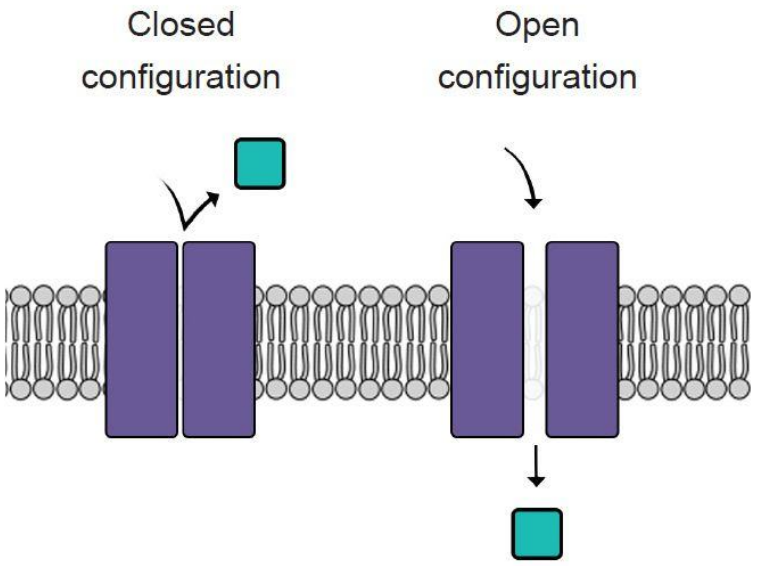


Figure 4.2 Ion channels (purple) are transmembrane proteins that can be open, allowing charged ions to cross the cell membrane through a molecular “tunnel” called the pore.

Ion channel features to allow different ions to pass through:

1. Pore size
    - Only ions of a diameter equal to or less than the diameter of the ion channel can pass through
    - Excludes larger diameter ions
2. Electrical charge
    - Charged amino acids line the inside of the pore
    - Their charge allows only certain ions to pass
        - Like charges repel and opposites attract
3. Hydration shell
    - Water molecules around an ion forms a “hydration shell”
    - Ion channel selectivity is derived from the
        - hydration shell radius
        - number of water molecules
        - orientation of water molecules

Hydration shell example

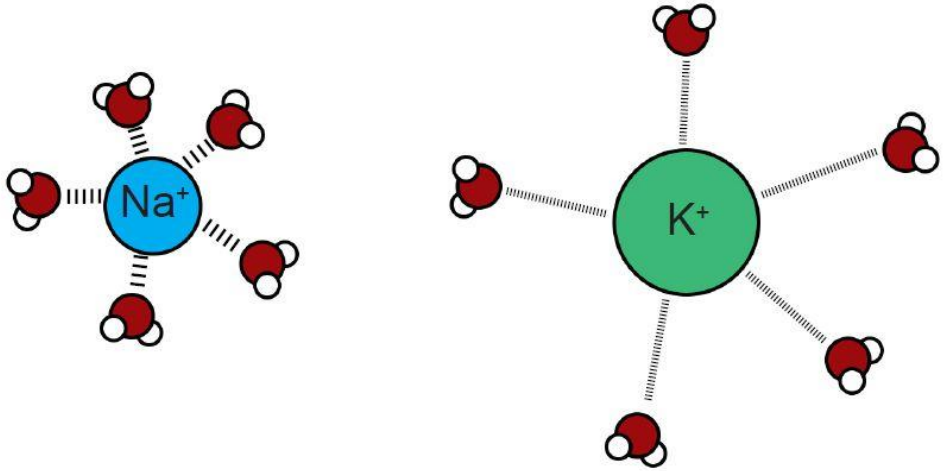


Figure 4.3 Ions dissolved in water are surrounded by a shell of water molecules. The potassium ion is larger, and the water molecules are farther apart, making the attraction weaker than in the sodium ion.

- K+ and Na+ are both too big to pass through K+ channel with their hydration shells intact
- K+ easily loses a water molecule from its hydration shell
  - It then fits through the channel
  - In addition, K+ is large enough to interact with amino acids lining the inside of the channel to facilitate its movement through
- It is harder (takes more energy) for Na+ to lose a water molecule
  - Therefore, it is not “energetically favourable” for the Na+ to pass through
  - Even when Na+ does lose a water molecule, it is too small to interact with the amino acids lining the inside of the channel

Classes of ion channels

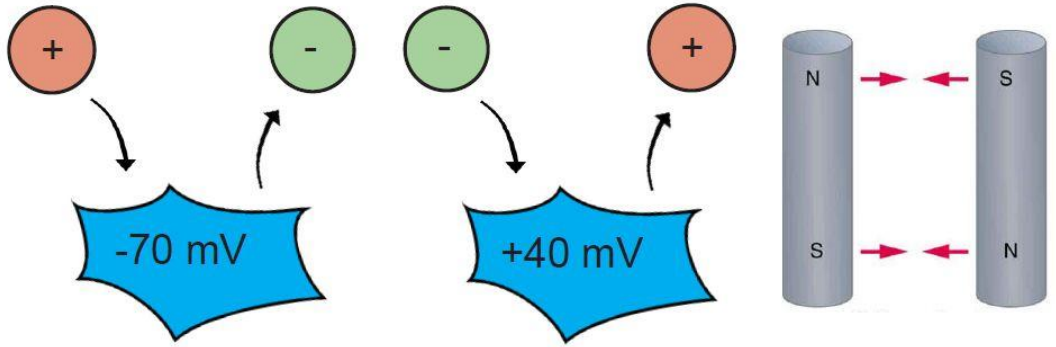
- Leak channels
  - Persistently open
  - Ex. Potassium (K^+) and chloride (Cl^-) leak channels
  - Movement depends solely on **electrochemical gradient** (next slide)
- Voltage-gated ion channels
  - Sensitive to the electrical potential of the surrounding membrane
  - Many remain closed at negative potentials (resting condition) and open at positive potentials (action potential)
- Ligand-gated ion channels (AKA ionotropic receptors)
  - Open in response to binding certain molecules
- Catch-all category of ion channels used by the sensory systems
  - Open and close in response to unique stimuli depending on what they are able to sense (hair cells in ears, Pacinian corpuscles in skin, Golgi tendon organ in muscles, and ion channels of photoreceptors in eyes)

The electrochemical gradient

- Movement of ions across channel depend on channel being present and open AND specific conditions inside and outside of cell
- Once open, two forces act on ions:
    1. Electrical gradient
    2. Chemical gradient
- Together these forces are known as the electrochemical gradient
- To predict forces acting on ion, need to know
    1. Charge of ion
    2. Relative concentrations of ions across membrane

Electrical gradient

Figure 4.4 The electrical gradient describes the forces acting on ions as they follow the rules of magnetism in physics - “opposites attract, and similar charges repel.”



- Refers to electrical forces acting on charged molecules (pull opposite charges together; push like charges away)
- At rest, interior of cell has negative charge (about -70 mV)
  - Positive charges are attracted while negative charges are repelled
- As neuron’s membrane potential (V_m) changes (e.g., to +40 mV), the force exerted by electrical gradient also changes

Chemical gradient

Figure 4.5 The chemical gradient describes the same forces acting on ions as diffusion, where ions move from areas of high concentration to low concentration.

- Natural process by which high concentration of substance will eventually diffuse to lower concentration and settle evenly over space
- Unaffected by biological movement of ions

Net flow into the cell

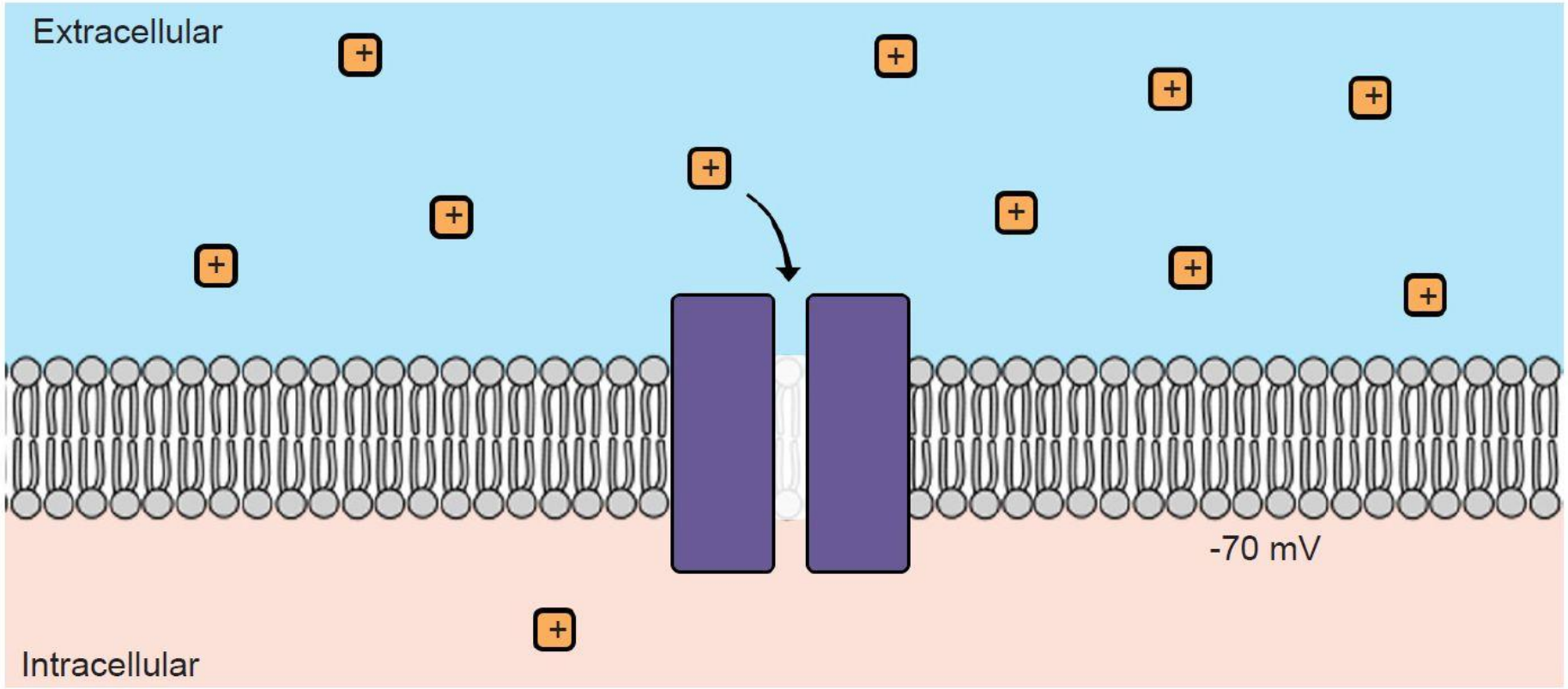


Figure 4.6 When a sodium channel opens (purple), sodium ions (orange) are acted on by two forces. They have a positive charge, which is attracted to the negatively-charged inside of the cell (electrical gradient). They are at a higher concentration outside the cell, which causes them to move to the inside of the cell with the lower concentration (chemical gradient).

Dynamic equilibrium

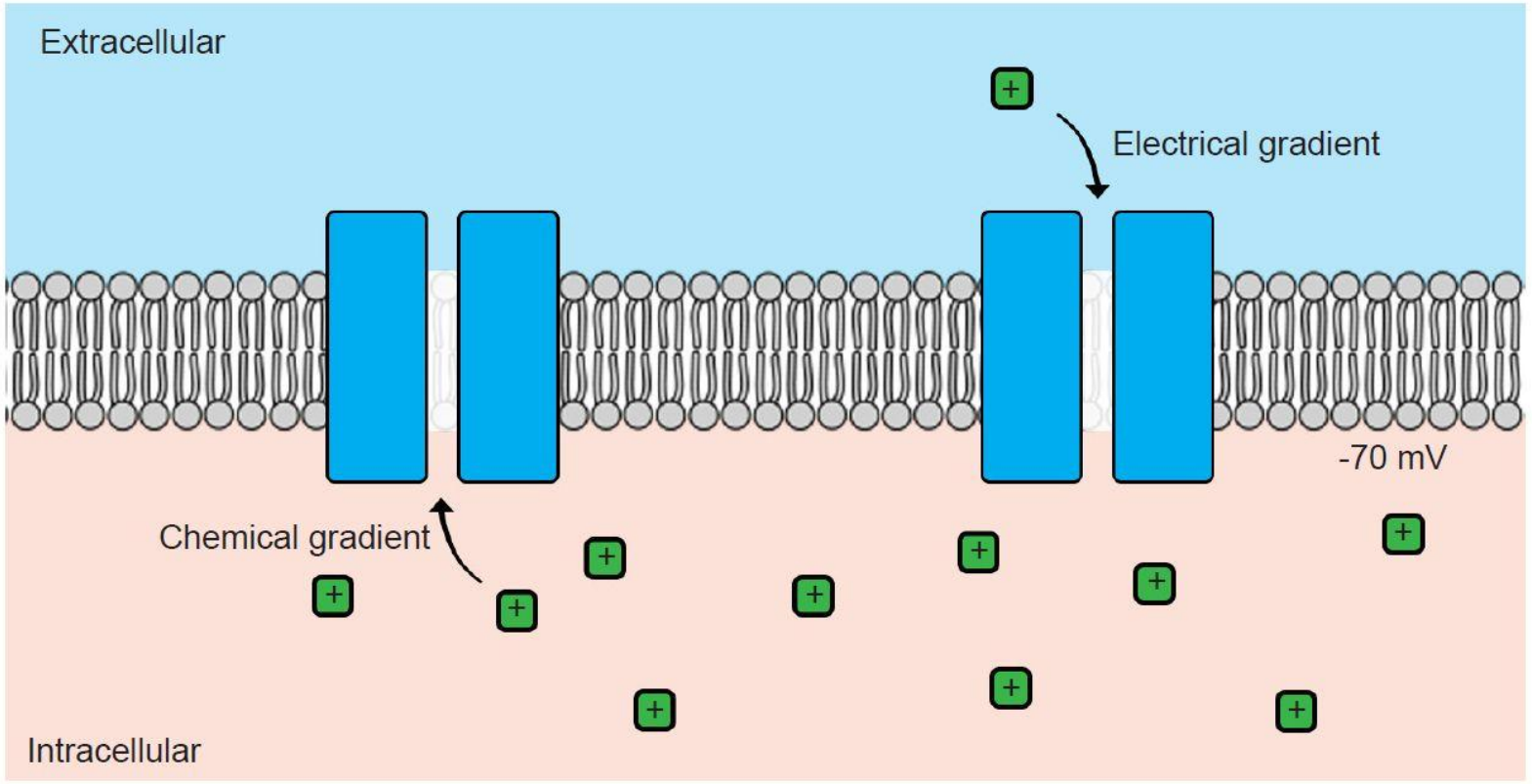


Figure 4.7 When a potassium channel opens (blue), potassium ions (green) are acted on by two opposing forces. They have a positive charge, which is attracted to the negatively-charged inside of the cell (electrical gradient). At the same time, they are at a higher concentration inside the cell, which causes them to want to move outside of the cell (chemical gradient). This process is at equilibium.

More on dynamic equilibrium

- Dynamic, because constant movement of ions **but**
- Equilibrium, because no net movement of charge
- Exact value of V_m is called equilibrium potential for the ion (abbreviated as E_x, where x is ion of interest)
- E_x differs for each ion

Ion concentrations

Ion	Abbreviation	Concentration outside $[X]_o$	Concentration inside $[X]_i$
Sodium	Na^+	140 mM	15 mM
Potassium	K^+	5 mM	150 mM
Chloride	Cl^-	120 mM	10 mM
Calcium	Ca^{2+}	1 mM	100 nM = 0.1 μM
Magnesium	Mg^{2+}	2 mM	0.5 mM
Miscellaneous anions	A^-	20 mM	100 mM

Table 4.8 Charged ions are unequally distributed across the cell membrane. Typical concentrations of ions in a mammalian neuron.

The Nernst equation

- Possible to calculate equilibrium potential (E_x) for each ion
- Use Nernst equation
- E_x = equilibrium potential (usually measured in mV)
- E_x is AKA reversal potential and Nernst potential
  - Voltage at which the net movement of the ion (i.e., into the cell, out of the cell) reverses direction

Meaning of equation elements

$$E_x = \frac{RT}{zF} \ln\left(\frac{[x]_o}{[x]_i}\right)$$

Equation 4.9 The Nernst equation calculates the reversal potential for a given ion *x*.

- E_x = equilibrium potential (usually measured in mV)
- R = ideal gas constant = 8.314 J/K*mol
- T = temperature in Kelvin (about 310K for biological temps)
- z = electrical charge of ion
- F = Faraday constant = 96,485 Coulombs/mol
- $[x]_o$ and $[x]_i$ = concentration of ions outside and inside of cell, respectively

Back-of-the-envelope equation

- Shortcut that condenses R and F constants and turns natural log into a base 10 logarithm and assumes physiological temperature

$$E_x \cong \frac{61}{z} \log\left(\frac{[x]_o}{[x]_i}\right)$$

Equation 4.10 The "back-of-the-envelope" equation is a shortcut to estimate the reversal potential for an ion x.

Example

- Calculate the equilibrium potential for calcium ions

Mathematical explanation of movement

- Nernst equation is useful for calculating reversal potential for individual ions assuming the appropriate ion channels are open
- However, not all ion channels are opened or closed at the same time
- Goldman-Hodgkin-Katz equation combines the Nernst potentials for three relevant ions (Na^+, K^+, and Cl^-)

Goldman-Hodgkin-Katz (GHK) Equation

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

Equation 4.11 The Goldman-Hodgkin-Katz equation is used to calculate the membrane potential given permeability of ions and their concentrations across the cell membrane.

- Combination of Nernst equations for equilibrium potentials for all 3 ions
- Introduces value of p (permeability)
  - Ability for ion to cross the membrane through ion channels
  - No units
- Higher the permeability of a given ion, closer the V_m to the E_x for that ion

The action potential

- Short-lasting change (1 or 2 milliseconds) in membrane potential
- Triggers release of neurotransmitters at axon terminal of a chemical synapse
- All-or-nothing response
  - Sub-threshold changes in V_m are called graded potentials
- V_m goes from negative to a more positive potential = depolarization
- Action potential threshold = ~ - 55 mV
- Change in membrane potential is due to movement of ions, especially Na^+ and K^+ through voltage-gated ion channels

Characteristic "shape" of action potential

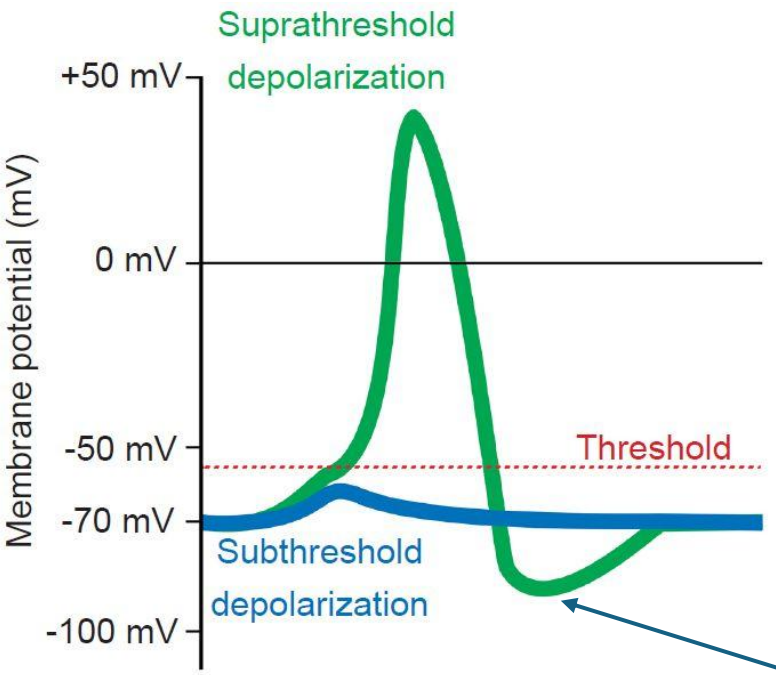


Figure 4.13 If the depolarization exceeds the action potential threshold, roughly -55 mV, the neuron will fire an action potential (green).

hyperpolarization

Steps of action potential

1. Depolarization from incoming (input) neurons
2. Opening of voltage-gated Na^+ channels
3. Opening of voltage-gated K^+ channels
4. Inactivation of voltage-gated Na^+ channels
5. Deactivation of voltage-gated K^+ channels

Some steps may overlap during action potential

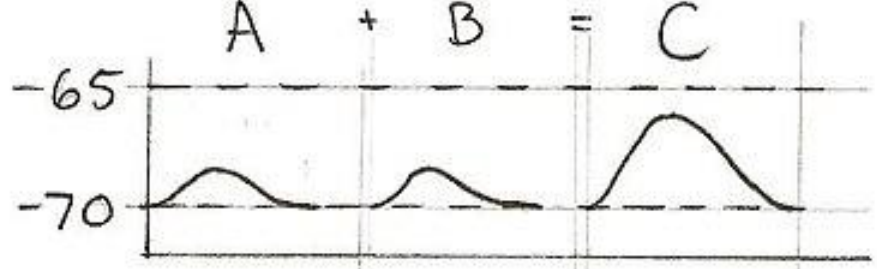
Step 1: Depolarization from incoming neurons

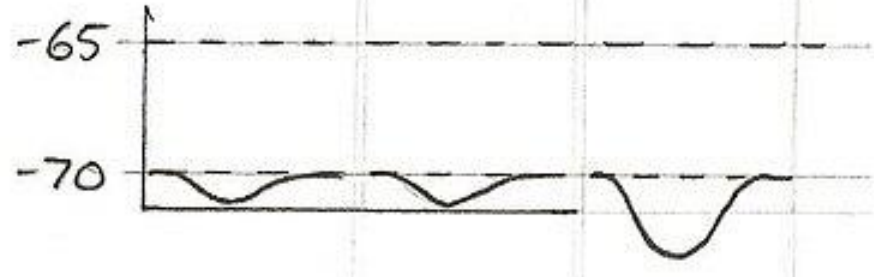
- Presynaptic neurons release neurotransmitters causing some ion movement via postsynaptic ligand-gated ion channels
- Small deviations in membrane voltage = postsynaptic potentials (PSPs)
- Release of excitatory neurotransmitters leads to excitatory PSPs (EPSPs) – depolarizations (negative to less negative V_m)
- Release of inhibitory neurotransmitters leads to inhibitory PSPs (IPSPs) – hyperpolarizations (negative to more negative V_m)
- Often multiple EPSPs are required to bring V_m above threshold potential

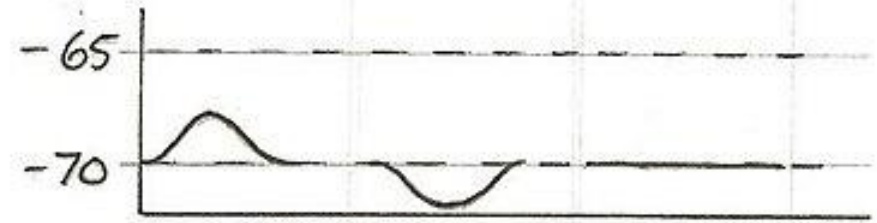
Summation of EPSPs

- Spatial summation
  - Two EPSPs from two adjacent inputs are triggered
- Temporal summation
  - Multiple EPSPs from same input occur close together in time
  - Adding a second EPSP during decay period may allow a large enough change in V_m to reach threshold

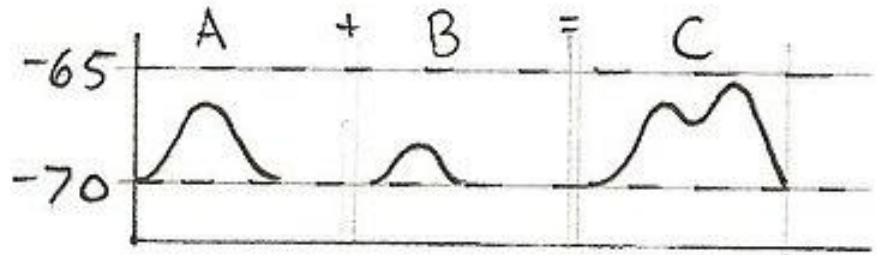
- When large enough total depolarization of membrane potential reaches soma, action potential is initiated at axon hillock







•Examples of spatial summation.



•An example of temporal summation

Step 2: Opening of voltage-gated Na^+ channels

- At rest, voltage-gated ion channels are almost all closed
- As V_m depolarizes, channels are more likely to open
- Electrochemical gradient allows us to predict movement of Na^+ ions
  - Positively charged sodium ions are drawn to negative inside
  - Ions move from area of high concentration (outside cell) to are of lower concentration (inside cell)
- Movement of Na^+ into cell causes V_m to depolarize to very positive potential
  - Peak of action potential can reach +40 mV

Voltage-gated Na^+ channels

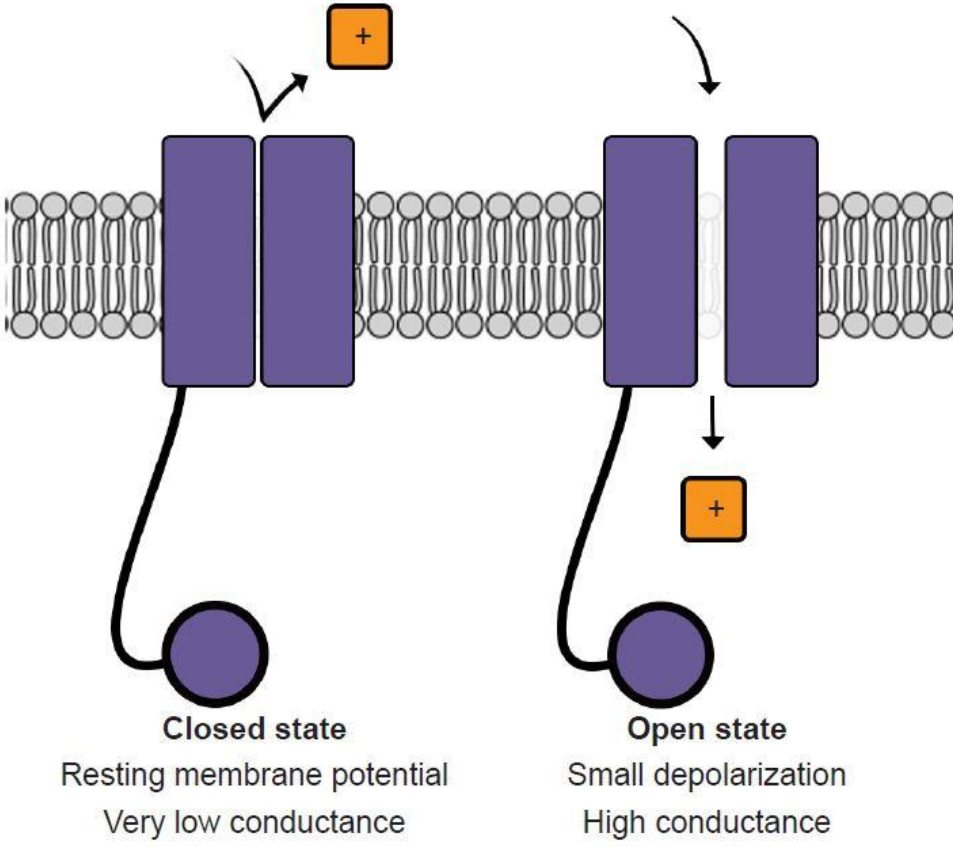


Figure 4.16 Voltage-gated Na^+ channels have a molecular structure that allows the channel to temporarily change structure in response to membrane voltage. A small depolarization to -50 mV causes the channels to open, while a large depolarization above -30 mV causes the channels to inactivate, blocking further sodium currents.

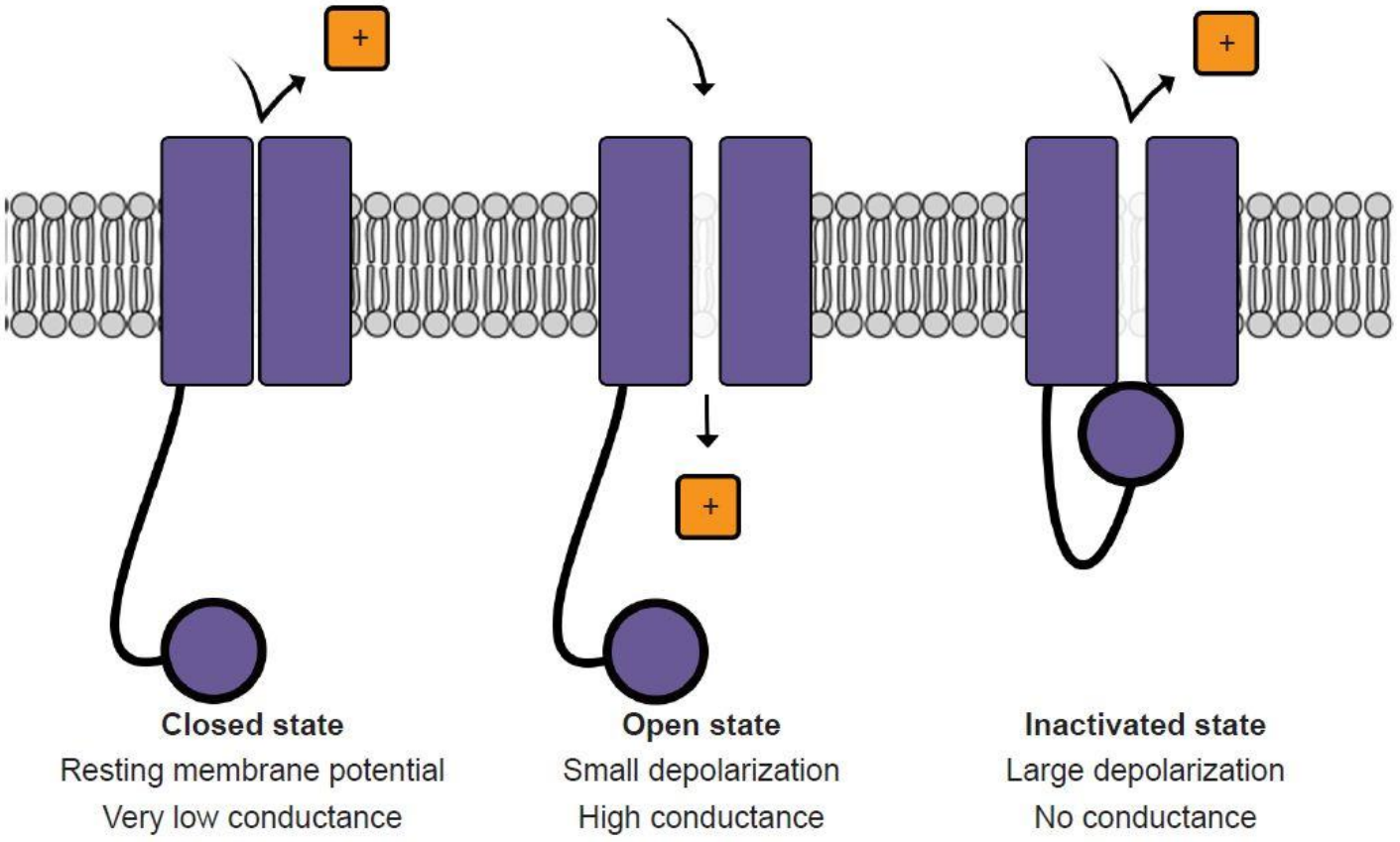
Step 3: Opening of voltage-gated K^+ channels

- Like voltage-gated Na+ channels, these K^+ channels open when cell starts to depolarize, allowing K^+ ions the move across cell membrane
- Again, knowledge of electrochemical gradient can be applied
  - Positive potential inside neuron repels K^+ ions
  - Relatively high concentration of K^+ inside pushes K^+ outside
- Interior of cell (and V_m) become more negative
- Cells become more negative than the resting membrane potential

Step 4: Inactivation of voltage-gated Na^+ channels

- In addition to the pore, these channels have inactivation gates
- When positive potential is reached, inactivation gate closes, preventing further movement of excitatory, depolarizing Na^+ ions
- Inactivation process is often faster than a millisecond

Voltage-gated Na^+ channels



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Step 5: Deactivation of voltage-gated K^+ channels

- Main current flow is outward as K^+ ions are driven out of cell through voltage-gated K^+ channels by electrochemical gradient
- Interior once again becomes more negative
- Deactivation of voltage-gated K^+ channels is much slower (a few milliseconds) than inactivation of Na^+ channels
- Hyperpolarizing current stops, which causes membrane potential to gradually return to the resting potential

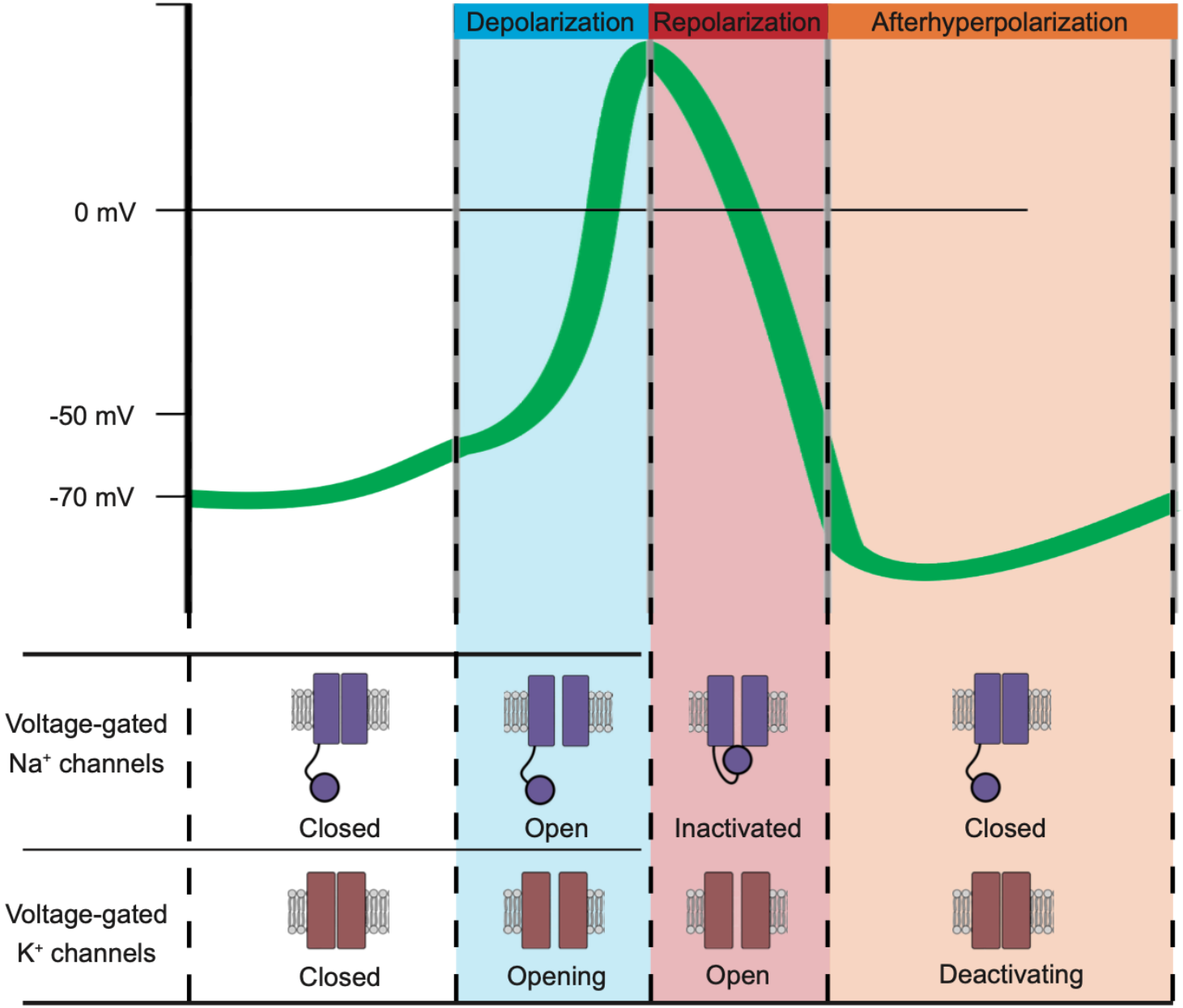


Figure 4.17 Voltage-gated ion channels open, inactivate, and deactivate at different times during the action potential.

Depolarization

- -70 mV to +40 mV (upward deflection of action potential)
- Lasts for 0.5 millisecond
- V_m becomes more positive because Na^+ enters cell through voltage-gated Na^+ channels (Step 2)
- Voltage-gated K^+ channels start to open (Step 3)

Repolarization

- +40 mV to –70 mV (rapid downwards deflection)
- Also lasts ~0.5 milliseconds
- Voltage-gated Na^+ channels have almost all inactivated (Step 4)
- K^+ are being drive out of the cell through voltage-gated potassium channels
- V_m becomes more negative

Afterhyperpolarization

- -70 mV to –80 mV and back to –70 mV (slow return to resting membrane potential)
- Can last for a few milliseconds
- Gradual deactivation of voltage-gated K+ channels (Step 5)

Clinical connection: Chronic pain

- Nociception = sensory system's process of encoding noxious stimuli
- Pain = perception that the body is experiencing injury or noxious stimulus
- Pain triggers a reflex to withdraw from stimulus to decrease severity of damage and/or creates memories to discourage future contact with pain-inducing situations
  - A healthy, protective sensation
- Dysregulation of somatosensory system can cause people to experience pain even in the absence of injurious stimuli, a condition called allodynia
- Allodynia is not completely understood, but linked to change in voltage-gated Na^+ channel properties that cause increase of excitability of pain-sensing neurons
- Not all chronic pain is allodynia

Randomness in ion channel properties

- Voltage-gated ion channels do not follow "if-then" precision
- More probabilistic in nature
  - At –70 mV, 0.1% chance to open
  - At –30 mV, 50% chance to open
  - At +20 mV, 99.9% chance to open

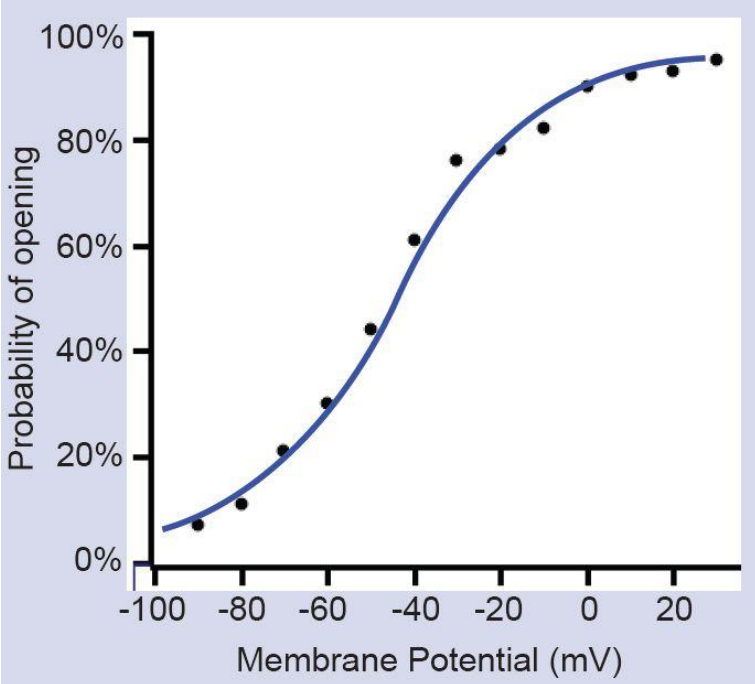


Figure 4.18 Opening of voltage-gated ion channels is probabilistic, with a greater likelihood of opening at depolarized potentials.

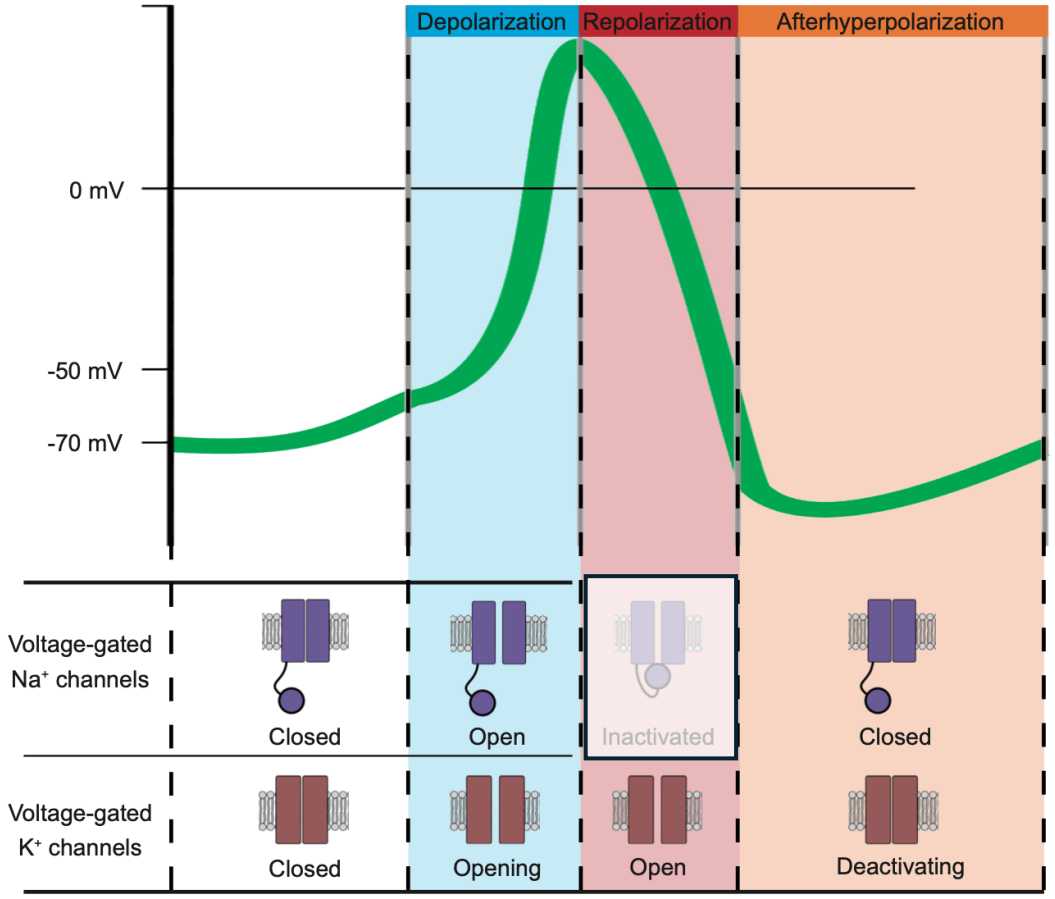
Changes in V_m

- Consider the individual ion that is moving
- When Na^+ ions move into the cell, membrane potential shifts towards E_{Na} which is +55 mV (a depolarization)
- During repolarization, voltage-gated K^+ channels open and V_m shifts towards E_K, which is -80 mV
- Consider GHK equation
  - As permeability to a given ion increases, V_m shifts towards equilibrium potential for that ion

Refractory periods

- Absolute refractory period
  - Time window when second action potential cannot be fired
  - Lasts ~0.5 milliseconds (up to 1 millisecond)
  - Due to voltage-gated Na^+ channels being inactivated (prevents Na^+ from being able to pass any more inward excitatory current)
- Relative refractory period
  - Time window when it is more difficult to fire an action potential compared to resting condition
  - Only some voltage-gated Na^+ channels have "reset" to closed (vs inactivated)
  - Plus, many voltage-gated K^+ channels are still open, allowing K^+ ions to move and neuron to be more negative
  - Lasts as long as afterhyperpolarization

Absolute refractory periods



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Relative refractory periods

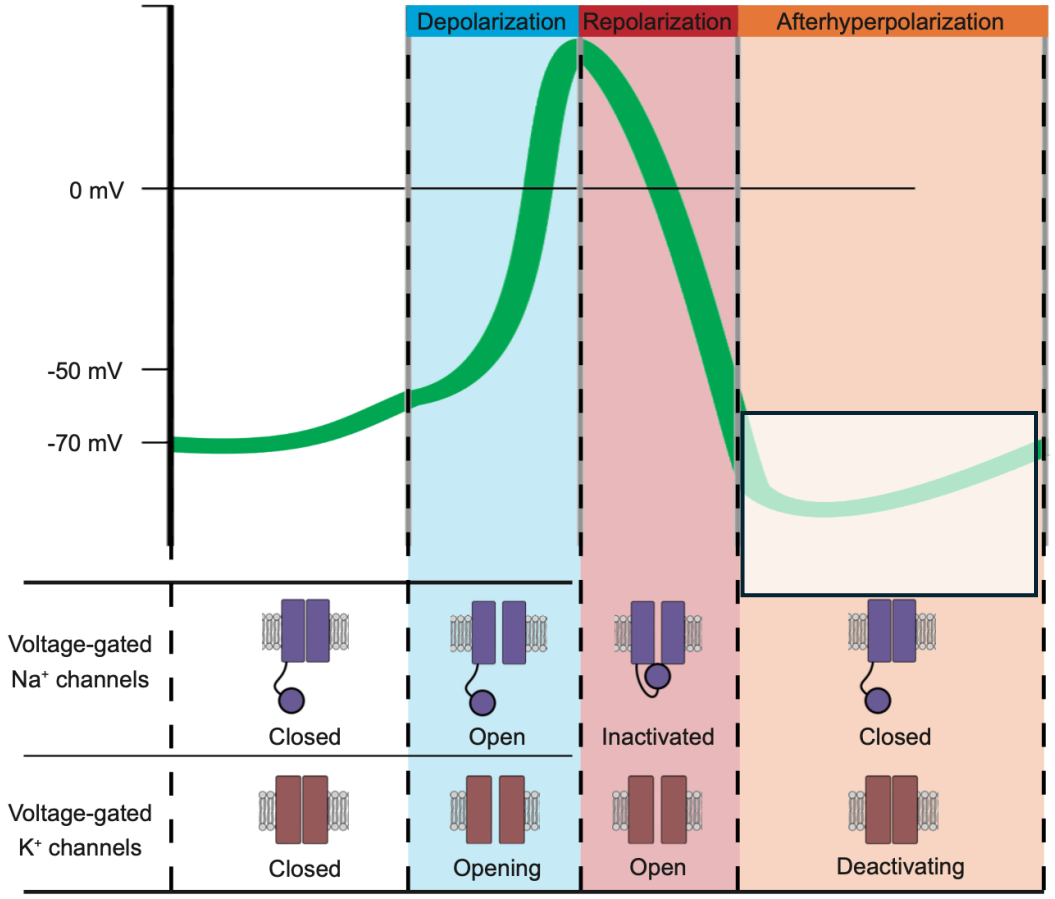

Figure 4.17 Voltage-gated ion channels open, inactivate, and deactivate at different times during the action potential.

The sooner after repolarization phase of the first action potential, the more difficult to reach threshold for a second action potential

Movement of action potentials

- Been discussing what happens at a single section of a cell membrane
- But, for action potential to travel from hillock to terminal, change in V_m must physically move down length of axon
- Ability to travel is possible because Na^+ entering cell are not restricted to cytoplasmic volume beneath ion channels
- Na^+ moves to area of lower concentration (chemical gradient) which is next section of membrane
- That section then becomes depolarized
- Next set of channels opens, allowing more Na^+ influx
- Repeats down axon
- Chain reaction

Action potentials are unidirectional

- Na^+ ions move down the concentration gradient (move forward)
- Previous patch of membrane is in absolute refractory period, making it impossible for action potential to travel backwards

Analgesia and motor signaling

- Lidocaine is an inhibitory of voltage-gated Na^+ channels
  - Blocking channels prevents action potentials from travelling up the afferent pathway, preventing incoming sensory inputs from area
- Similarly, outbound signals can be blocked
- Poison – efferent pathway is blocked, leading to paralysis
  - Pufferfish
    - Delicacy in Japan; dish is called fugu and can cause numbness of lips or even mild intoxication
    - Tetrodotoxin (TTX)
      - Produced by symbiotic bacteria (prevents predation)
      - Voltage-gated Na^+ channel inhibitor
      - Prevents phrenic nerve from sending signals to move the diaphragm
      - People can die of respiratory failure in hours after exposure to 1 mg of TTX

Figure 4.20 Pufferfish and other species likely evolved a symbiotic relationship with bacteria that produce the deadly TTX to prevent predation.

The role of myelin

- Increases conduction velocity, speed at which action potential travels
- Physically blocks leak K^+ channels, preventing positive charges from exiting the cell
- Influx of Na^+ is still required for signal to travel
- This influx happens at nodes of Ranvier (unmyelinated segments of axon)
- Nodes of Ranvier are dense with voltage-gated Na^+ channels
- Saltatory conduction (Italian *saltare* = "jump")

Saltatory conduction

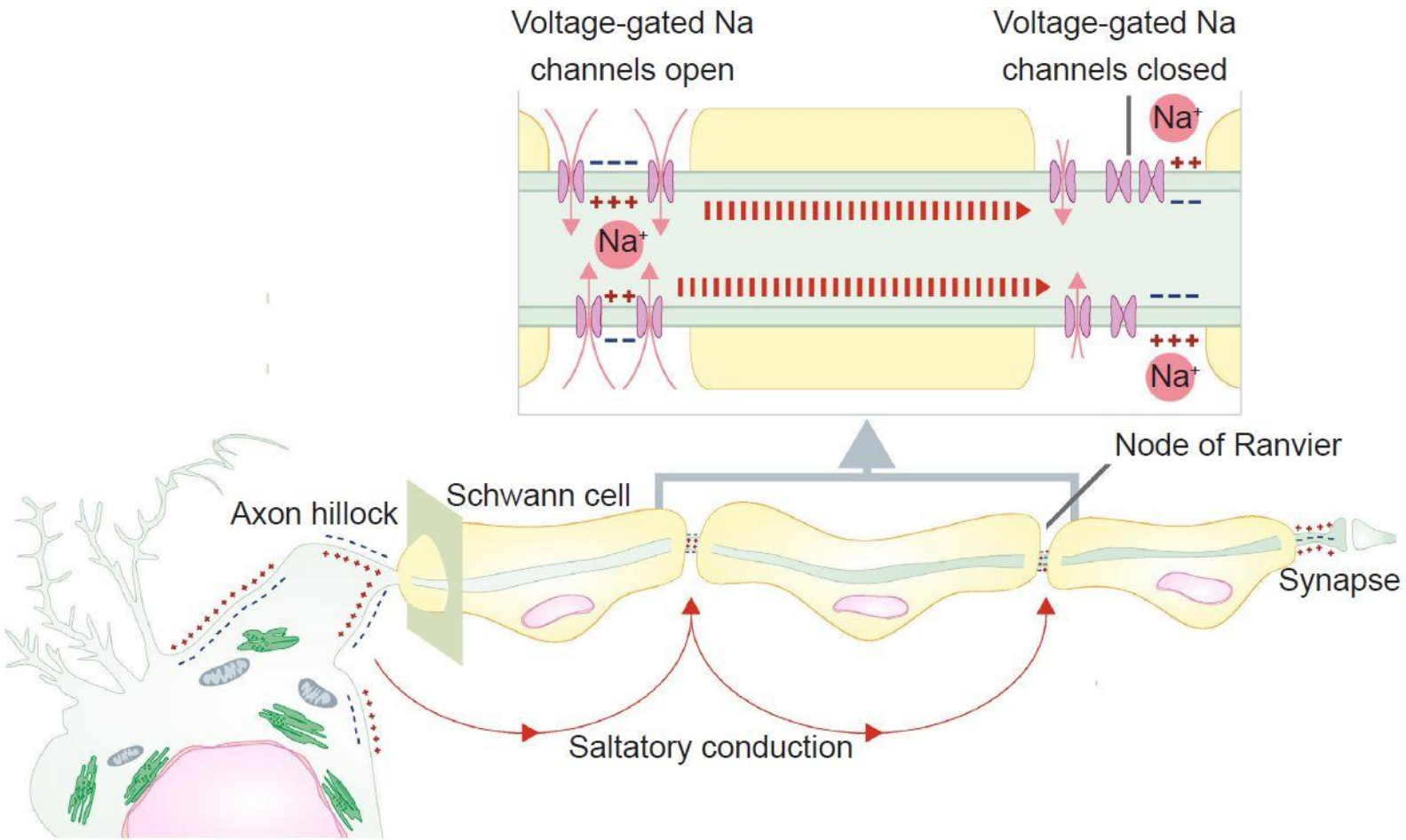

Figure 4.19 Movement of an action potential down a myelinated axon relies on saltatory conduction.