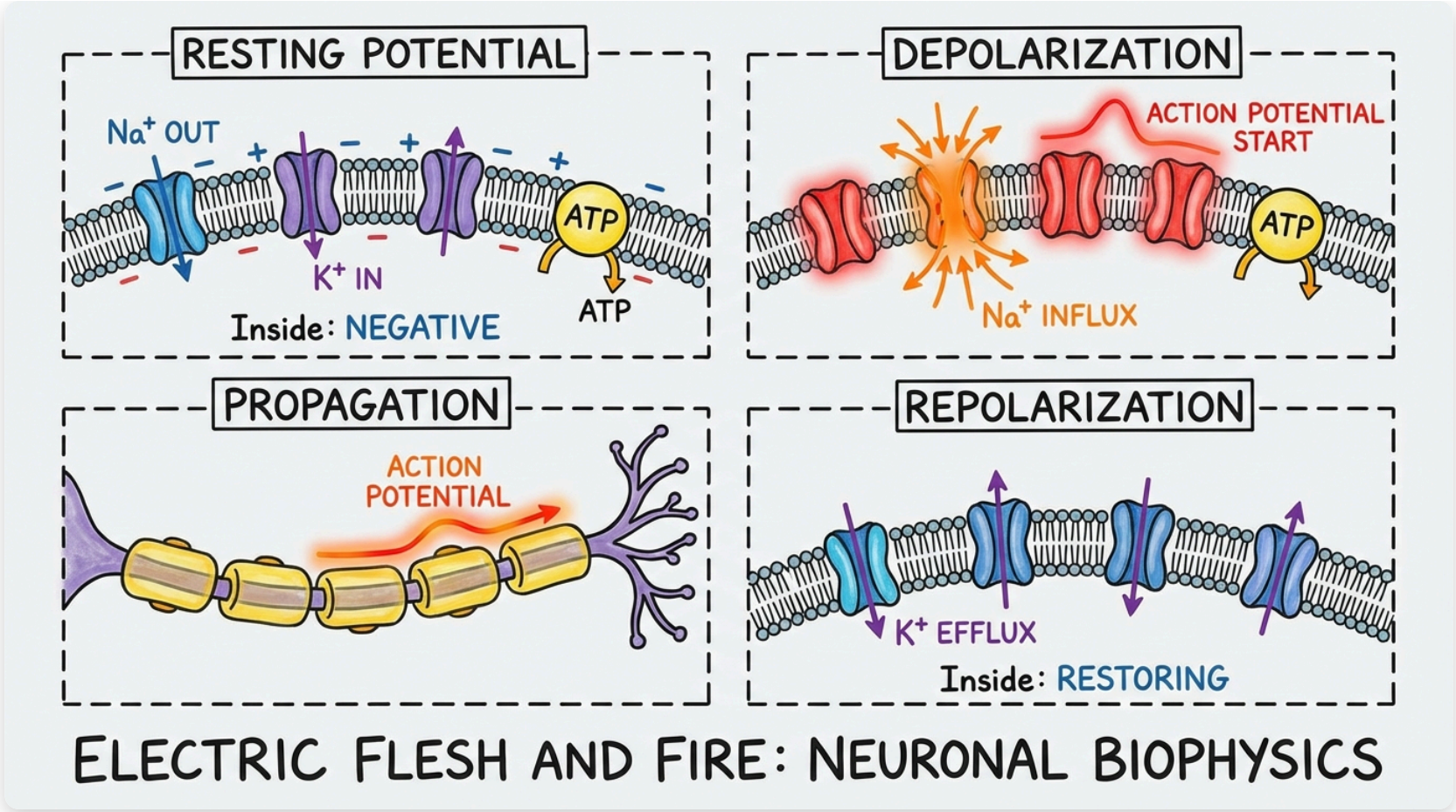
Electrical Neural Activity

Electric Flesh and Fire: The Biophysics of Thought Electrical Neural activity Visual Summary LECTURE OUTLINE (80 minutes) I. The Resting Membrane Potential (20 min) • Ion distributions and the Na^+/K^+-ATPase • The Nernst equation: equilibrium potentials for single ions • The Goldman-Hodgkin-Katz equation: multiple ion contributions • Why neurons rest at –70 mV, not at E_K II. The Action Potential: Ionic Mechanisms (20 min) • Hodgkin and Huxley's voltage clamp experiments • Voltage-gated Na^+ channels: activation and inactivation • Voltage-gated K^+ channels: delayed rectification • The absolute and relative refractory periods III. Propagation of the Action Potential (15 min) • Local circuit currents and the cable equation • Length constant and time constant • Continuous vs. saltatory conduction • Myelination and conduction velocity IV. Channel Diversity and Clinical Relevtic (15 min) • Channelopathies: from painlessness to paralysis • Multiple sclerosis and demyelination • Epilepsy as electrical storms • Pharmacology of ion channels V. Evolutionary Origins (10 min) • Bacterial action potentials and ancient ion channels • The thermodynamic cost of thought

- Here are 4 main points from the text:
- Neurons maintain a resting electrical charge across their membrane, typically at -70 mV, due to the movement and distribution of ions.
- An action potential is an electrical signal generated by neurons through the rapid opening and closing of voltage-gated sodium and potassium channels.
- Action potentials travel along the neuron, and myelination significantly increases their speed and efficiency.
- Disorders of ion channels, called channelopathies, cause various diseases like multiple sclerosis and epilepsy.

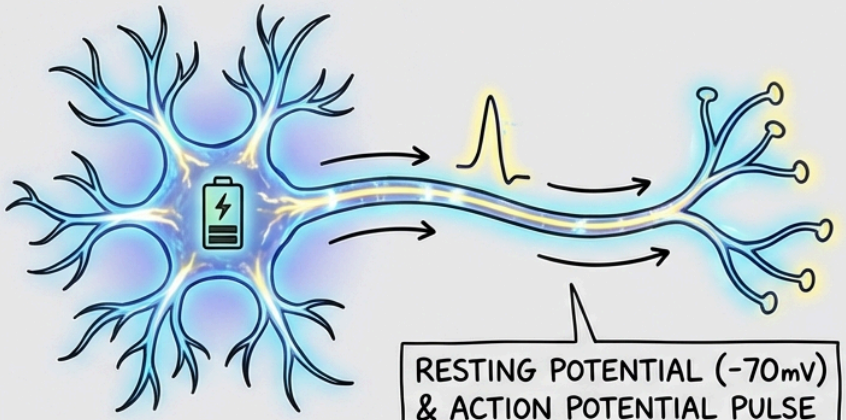

RESTING POTENTIAL
Na+ OUT
K+ IN
ATP
ATP
Inside: NEGATIVE
DEPOLARIZATION
ACTION POTENTIAL START
ATP
Na+ INFLUX
PROPAGATION
ACTION POTENTIAL
REPOLARIZATION
K+ EFFLUX
Inside: RESTORING
ELECTRIC FLESH AND FIRE: NEURONAL BIOPHYSICS

Brain's Battery

Your thoughts move at 120 meters per second—the speed of a Formula 1 car—yet this biological lightning is a million times slower than electricity in copper wire. Today we decode the most elegant hack in evolutionary history: how life transforms a 70-millivolt battery smaller than a virus into the computational foundation of consciousness. We'll discover why your brain burns 20% of your calories just maintaining electrical readiness, how two equations—the Nernst and Goldman—predict the voltage of every neuron on Earth, and how Hodgkin and Huxley's squid experiments revealed the molecular machinery underlying every thought. From the resting potential that sets the stage to the action potential that carries the signal, we'll trace the complete electrical journey within a single neuron—saving the chemical synapse for next time.

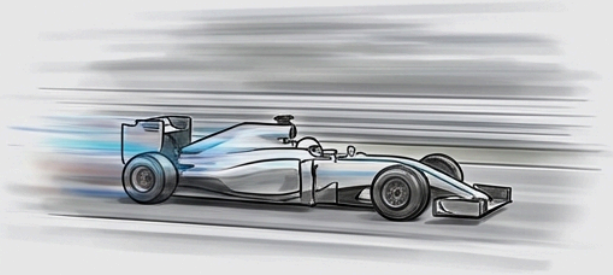
- Main Points:
- Thoughts travel at 120 meters per second within the brain. This biological electricity is much slower than electricity in wires.
- The brain uses tiny electrical signals as the foundation for consciousness.
- Your brain uses 20% of your body's calories to maintain its electrical readiness.
- Neurons send electrical signals using a process with a "resting potential" and an "action potential."

NEURON: BIOLOGICAL BATTERY & SIGNALING



RESTING POTENTIAL (-70mV)
& ACTION POTENTIAL PULSE

SPEED COMPARISON: THOUGHT vs. F1 CAR

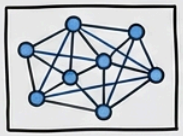


THOUGHT VELOCITY (~120 m/s)
> F1 TOP SPEED (~100 m/s)

ELECTROCHEMICAL BASIS & COMPUTATION

$$V = \frac{RT}{zF} \ln \frac{[X]_{out}}{[X]_{in}}$$

NERNST EQUATION



BRAIN COMPUTATIONAL POWER

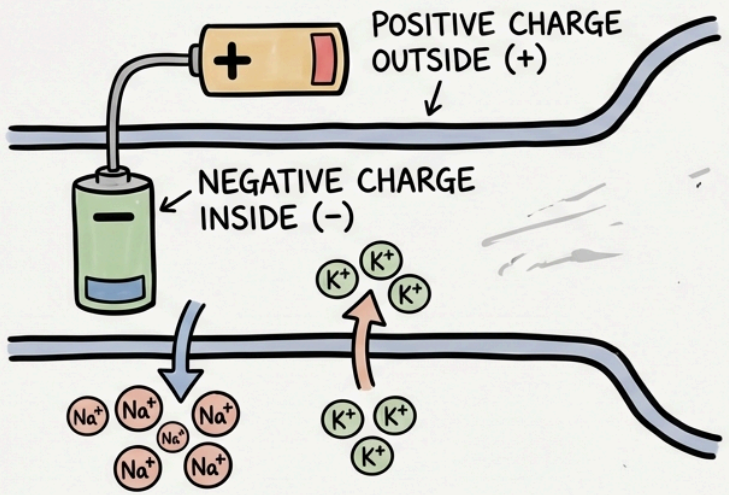
Electrical Signals

Today's journey: From the ion gradients that create the resting potential, through the voltage-gated channels that generate action potentials, to the cable properties that propagate signals along axons. We stop at the axon terminal—next class, we'll see what happens when electricity meets chemistry. The Resting Membrane Potential: A Battery Waiting to Fire The resting membrane potential is the voltage difference across the neuronal membrane when the cell is not actively signaling—typically around –70 mV (inside negative relative to outside). This isn't just a baseline; it's a loaded battery, an energetic reservoir that enables rapid electrical signaling. Understanding where this voltage comes from requires understanding ion distributions and the forces that create them.

- Main Points:
- The resting membrane potential is the voltage difference across a neuron's membrane when it is not actively signaling.
- This voltage typically measures around -70 mV, meaning the cell's inside is negative compared to its outside.
- It functions like a loaded battery, an energetic reservoir that allows for rapid electrical signaling.
- Ion distributions and the forces acting on them create this voltage difference.

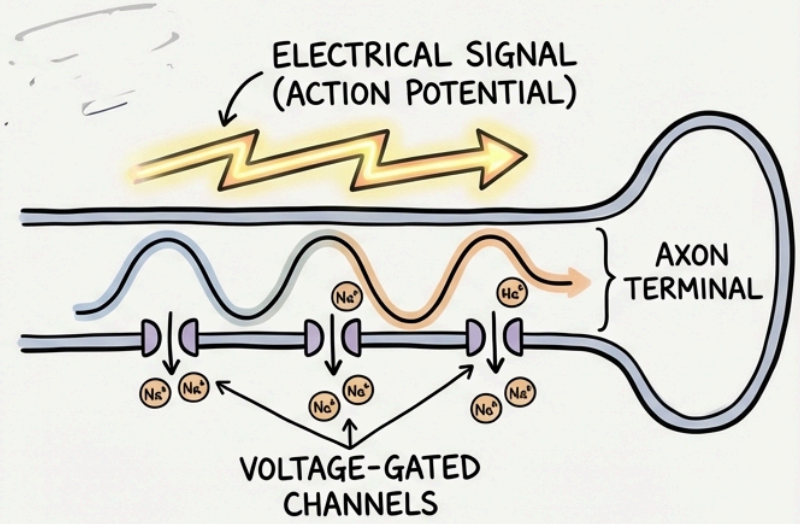
NEURON PHYSIOLOGY: AXON & SIGNALING

PANEL 1: RESTING POTENTIAL (LOADED BATTERY)



Key Ion Gradients: Higher Na^+ Outside
Higher K^+ Inside

PANEL 2: ACTION POTENTIAL (PROPAGATING WAVE)

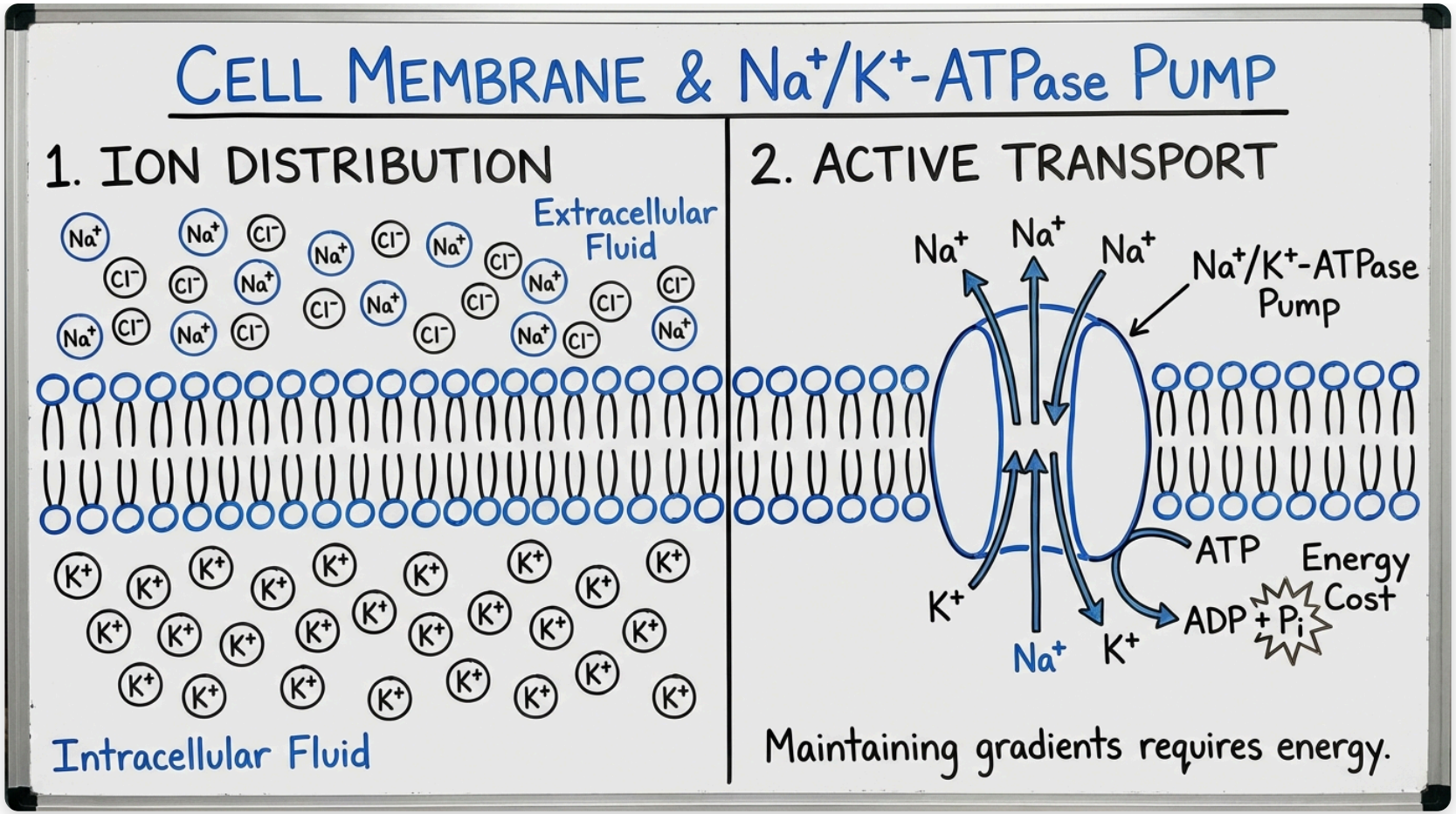


Dynamic wave propagating via channels

Ion Gradients

Ion Distributions: The Unequal Players - The intracellular and extracellular fluids have dramatically different ion compositions. Potassium (K^+) is concentrated inside cells (~140 mM intracellular vs. ~5 mM extracellular—a 28:1 ratio). Sodium (Na^+) shows the opposite pattern (~15 mM inside vs. ~145 mM outside—a 1:10 ratio). Chloride (Cl^-) is concentrated outside (~120 mM vs. ~10 mM inside). These gradients don't exist by accident—they're actively maintained by the Na^+/K^+-ATPase, a molecular pump that burns one ATP molecule to export 3 Na^+ and import 2 K^+. This pump consumes roughly 25% of all ATP in neurons—the energetic price of electrical readiness. -

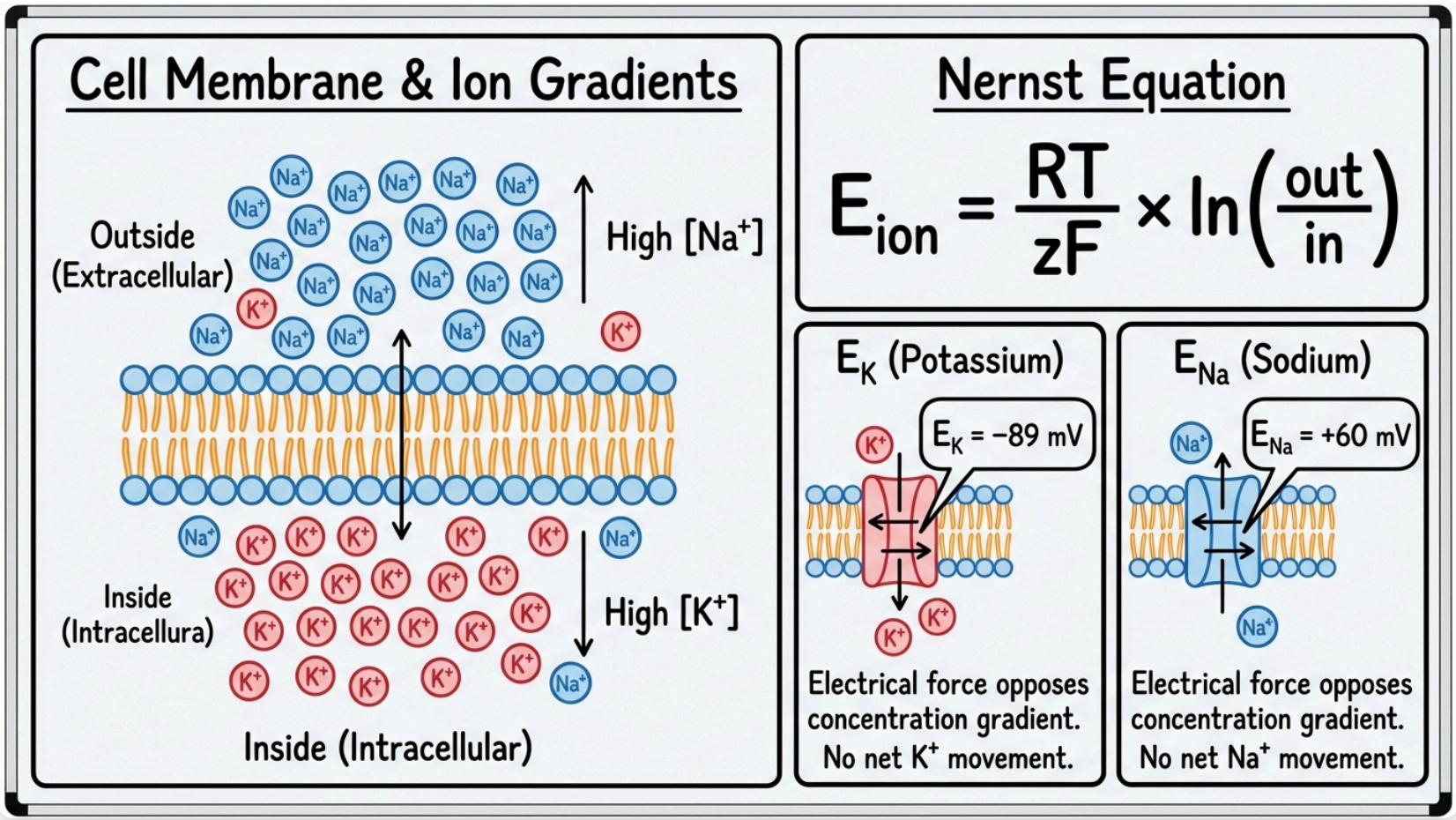
- Here are 5 main points from the text:
- Intracellular and extracellular fluids have very different ion compositions.
- Potassium (K^+) is concentrated inside cells, while sodium (Na^+) and chloride (Cl^-) are concentrated outside cells.
- The Na^+/K^+-ATPase, a molecular pump, actively maintains these ion differences.
- This pump uses one ATP molecule to move 3 sodium ions out of the cell and 2 potassium ions into the cell.
- The Na^+/K^+-ATPase consumes about 25% of all ATP in neurons, which is essential for electrical readiness.


CELL MEMBRANE & Na+/K+-ATPase PUMP
1. ION DISTRIBUTION
Extracellular Fluid
Intracellular Fluid
2. ACTIVE TRANSPORT
Na+/K+-ATPase Pump
ATP
ADP + Pi
Energy Cost
Maintaining gradients requires energy.

Nernst Equilibrium Potentials

The Nernst Equation: Predicting Equilibrium Potentials - If a membrane were permeable only to potassium, what voltage would result? Walther Nernst answered this in 1889 with his equation: E_ion = (RT/zF) × ln(_out/_in), or at body temperature: E_ion = 61.5/z × $\log_{10}$(_out/_in) mV. For potassium, with its 28:1 inside-to-outside ratio: E_K = 61.5 × log(5/140) = –89 mV. For sodium: E_Na = 61.5 × log(145/15) = +60 mV. These equilibrium potentials represent the voltage at which the electrical force on an ion exactly balances its concentration gradient—no net flow occurs. -

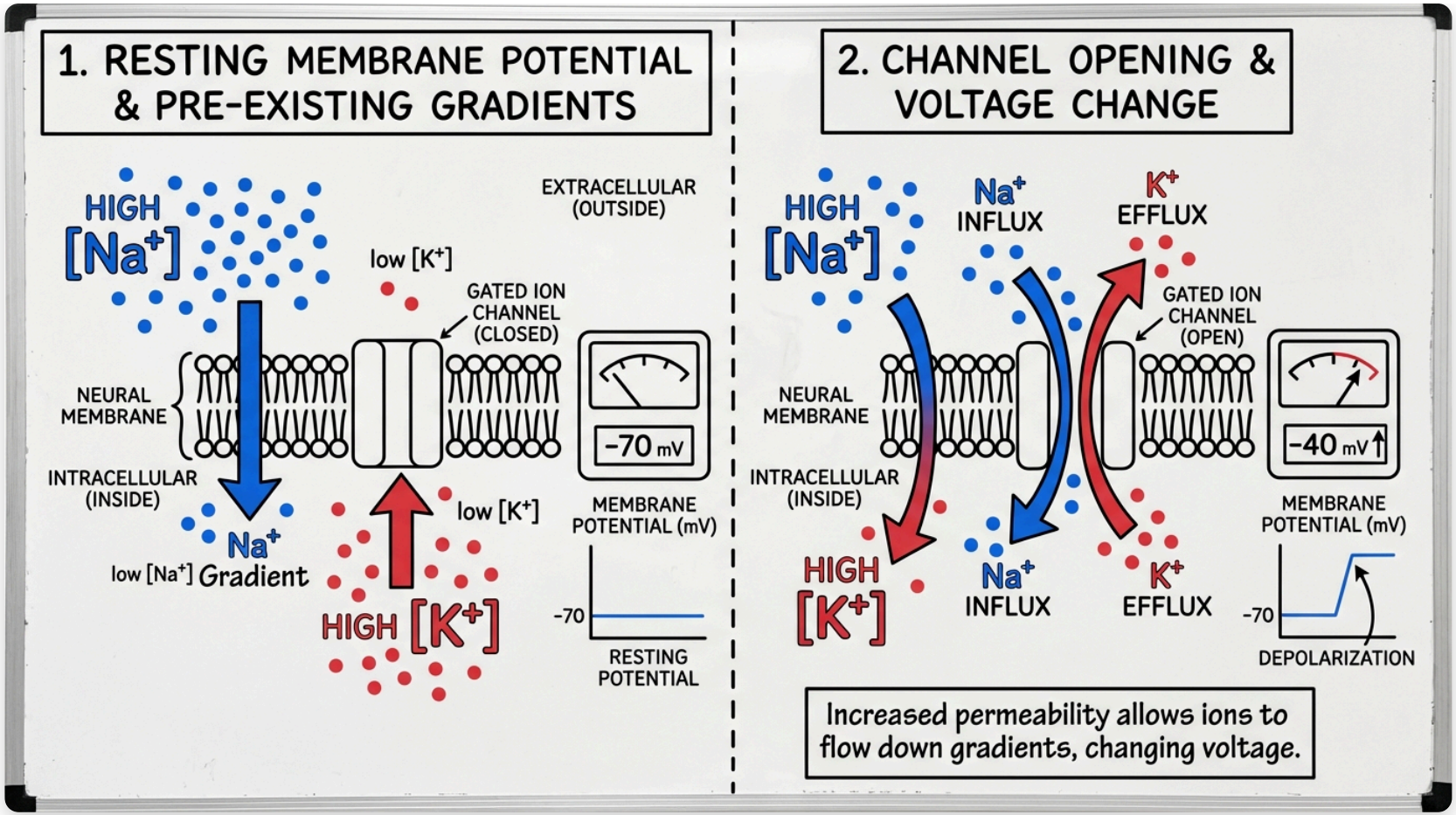
- Here are 4 main points from the text:
- Walther Nernst developed an equation to predict the electrical voltage across a membrane permeable to only one type of ion.
- The Nernst equation calculates an "equilibrium potential" for each specific ion.
- The equilibrium potential is the voltage where an ion's electrical force perfectly balances its concentration gradient, causing no net movement.
- For example, the Nernst equation predicts potassium's equilibrium potential at -89 mV and sodium's at +60 mV.


Cell Membrane & Ion Gradients
Outside
(Extracellular)
High [Na+]
Inside
(Intracellura)
High [K+]
Inside (Intracellular)
Nernst Equation
$E_{ion} = \frac{RT}{zF} \times \ln\left(\frac{out}{in}\right)$
E_K (Potassium)
E_K = −89 mV
Electrical force opposes concentration gradient.
No net K+ movement.
E_{Na} (Sodium)
E_{Na} = +60 mV
Electrical force opposes concentration gradient.
No net Na+ movement.

Nernst Voltage Principle

The Nernst equation reveals a profound truth: the voltage across a membrane is determined by ion concentrations and membrane permeability. Change either, and you change the voltage. Neurons exploit this principle continuously—they don't create new ions during signaling; they simply open and close channels that change permeability, allowing the pre-existing gradients to drive voltage changes.

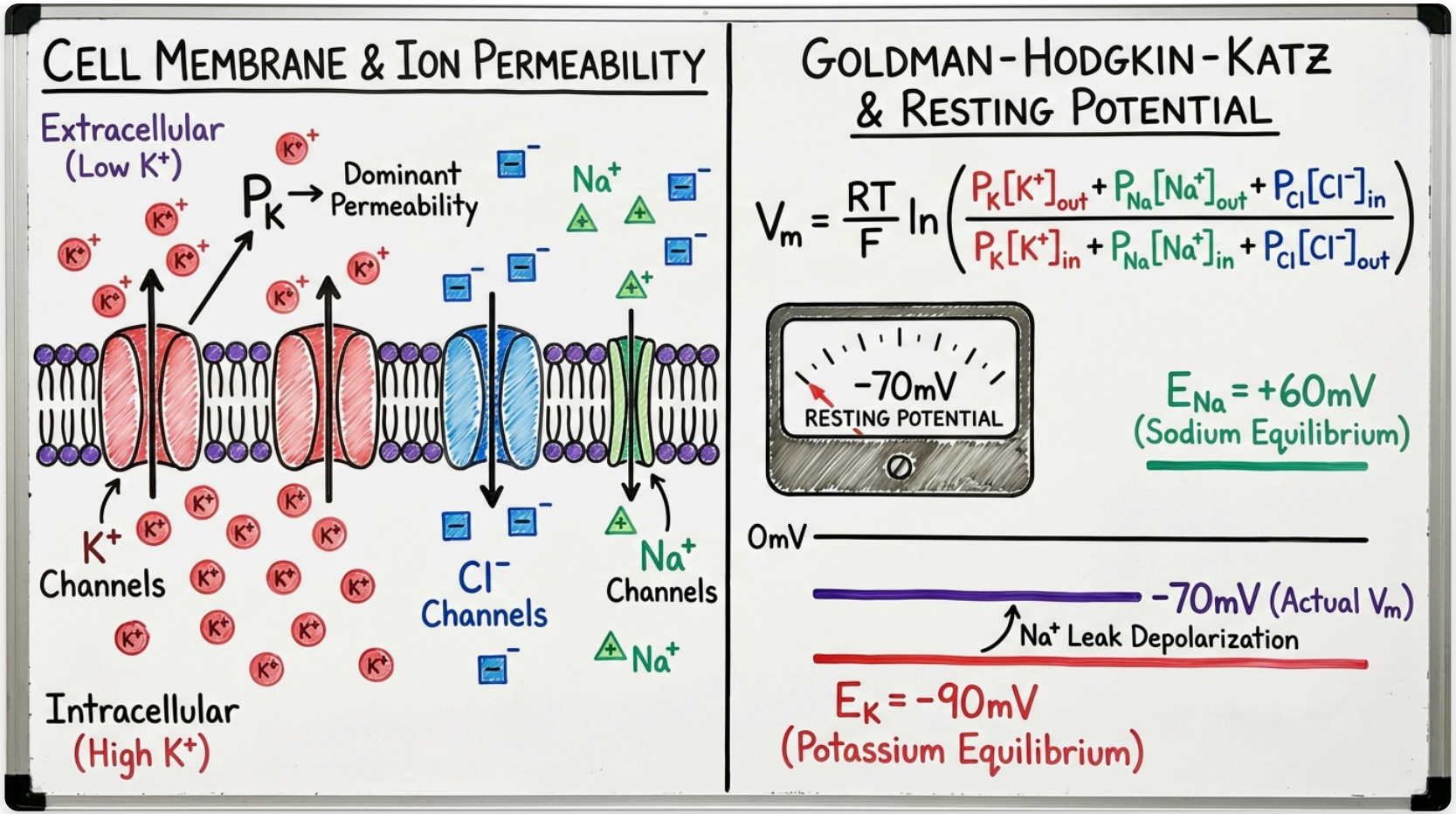
- → Membrane voltage is determined by ion concentrations and membrane permeability.
- → Changing ion concentrations or membrane permeability alters the voltage.
- → Neurons change their membrane voltage during signaling by altering permeability.
- → Neurons open and close channels to change membrane permeability.
- → Pre-existing ion gradients drive these voltage changes in neurons.


1. RESTING MEMBRANE POTENTIAL & PRE-EXISTING GRADIENTS
HIGH [Na+]
EXTRACELLULAR (OUTSIDE)
low [K+]
GATED ION CHANNEL (CLOSED)
NEURAL MEMBRANE
INTRACELLULAR (INSIDE)
-70 mV
MEMBRANE POTENTIAL (mV)
Na+
low [Na+] Gradient
low [K+]
HIGH [K+]
-70
RESTING POTENTIAL
2. CHANNEL OPENING & VOLTAGE CHANGE
HIGH [Na+]
Na+ INFLUX
K+ EFFLUX
GATED ION CHANNEL (OPEN)
NEURAL MEMBRANE
INTRACELLULAR (INSIDE)
-40 mV
MEMBRANE POTENTIAL (mV)
HIGH [K+]
Na+ INFLUX
K+ EFFLUX
-70
DEPOLARIZATION
Increased permeability allows ions to flow down gradients, changing voltage.

GHK Competing Ions

The Goldman-Hodgkin-Katz Equation: Competing Ions - Real membranes are permeable to multiple ions simultaneously. The Goldman-Hodgkin-Katz (GHK) equation accounts for this by weighting each ion's contribution by its relative permeability: - V_m = 61.5 × log_out + P_Na_out + P_Cl_in) / (P_K_in + P_Na_in + P_Cl_out)] - At rest, P_K : P_Na : P_Cl ≈ 1 : 0.04 : 0.45. Because potassium permeability dominates, the resting potential (−70 mV) sits much closer to E_K (−89 mV) than to E_Na (+60 mV). The small sodium permeability is why neurons rest at −70 mV rather than at the potassium equilibrium potential—sodium's inward leak slightly depolarizes the membrane from where pure potassium selectivity would place it.

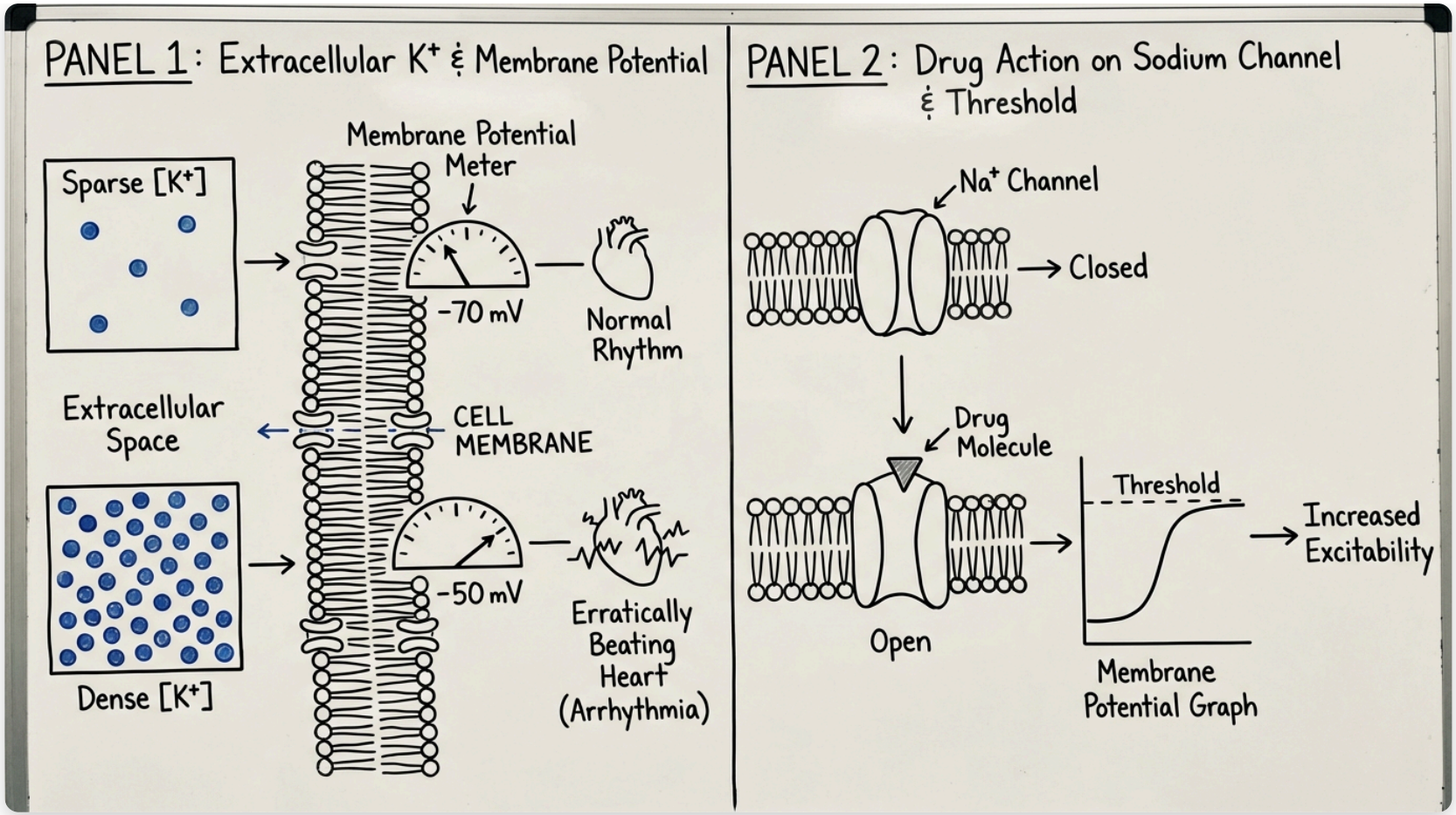
- Here are 3-5 main points from the text:
- Cell membranes allow several different ions to pass through them at once.
- The Goldman-Hodgkin-Katz (GHK) equation calculates membrane potential by considering the permeability of multiple ions.
- At rest, cell membranes are most permeable to potassium ions.
- High potassium permeability makes the resting membrane potential (around -70 mV) very close to the potassium equilibrium potential.
- Small sodium permeability slightly depolarizes the membrane, making the resting potential a bit more positive than the potassium equilibrium potential.


CELL MEMBRANE & ION PERMEABILITY
Extracellular
(Low K+)
PK → Dominant Permeability
Na+
K+ Channels
Cl− Channels
Na+ Channels
Intracellular
(High K+)
GOLDMAN-HODGKIN-KATZ
& RESTING POTENTIAL
$V_m = \frac{RT}{F} \ln\left(\frac{P_K[K^+]_{out} + P_{Na}[Na^+]_{out} + P_{Cl}[Cl^-]_{in}}{P_K[K^+]_{in} + P_{Na}[Na^+]_{in} + P_{Cl}[Cl^-]_{out}}\right)$
-70mV
RESTING POTENTIAL
E_{Na} = +60mV
(Sodium Equilibrium)
0mV
-70mV (Actual V_m)
Na+ Leak Depolarization
E_K = -90mV
(Potassium Equilibrium)

Resting Potential Modulation

- This framework explains why the resting potential isn't fixed but can be modulated. Changing extracellular potassium concentration shifts E_K and therefore V_m—this is why hyperkalemia (high blood potassium) can cause cardiac arrhythmias and why dialysis patients must carefully manage potassium intake. Similarly, drugs that alter sodium permeability shift the resting potential toward E_Na, bringing neurons closer to threshold.

- → Here are 4 main points from the text:
- → The resting potential of a cell is flexible and can be adjusted.
- → Changes in potassium levels outside cells directly affect the resting potential.
- → High blood potassium levels can cause problems with heart rhythm.
- → Drugs that change how easily sodium enters cells shift the resting potential, making neurons more easily activated.

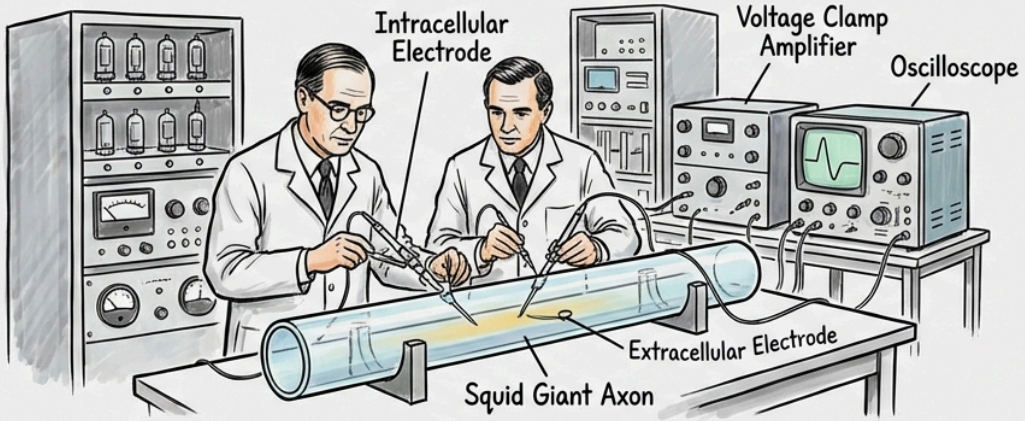

PANEL 1: Extracellular K⁺ & Membrane Potential
Membrane Potential Meter
Sparse [K⁺]
-70 mV
Normal Rhythm
Extracellular Space
CELL MEMBRANE
-50 mV
Erratically Beating Heart (Arrhythmia)
Dense [K⁺]
PANEL 2: Drug Action on Sodium Channel & Threshold
Na⁺ Channel
Closed
Drug Molecule
Open
Threshold
Increased Excitability
Membrane Potential Graph

Action Potential Ionics

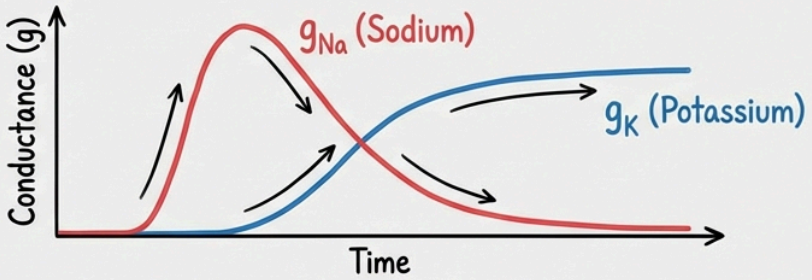
The Action Potential: Ionic Mechanisms - - In 1952, Alan Hodgkin and Andrew Huxley published five papers that explained how action potentials work at the ionic level. They shared the 1963 Nobel Prize for this work—experiments done before anyone knew what an ion channel protein looked like. Hodgkin and Huxley used the squid giant axon (up to 1 mm diameter—visible to the naked eye) and the voltage clamp technique to isolate how membrane conductance changed with voltage. By "clamping" the membrane at a fixed voltage, they could measure the ionic currents flowing across the membrane without the complication of voltage changes. Their key insight: during an action potential, sodium conductance (g_Na) increases first and transiently, then potassium conductance (g_K) increases more slowly and persistently.

- Here are 3 main points from the text:
- Alan Hodgkin and Andrew Huxley explained how action potentials work at an ionic level. They won the Nobel Prize for this important discovery.
- They used a squid giant axon and a voltage clamp technique for their experiments. This method allowed them to measure ionic currents across the membrane.
- During an action potential, sodium conductance increases quickly first. Potassium conductance then increases more slowly and lasts longer.

a) Hodgkin & Huxley (1950s) - Voltage Clamp Setup



b) Ionic Conductance during Action Potential

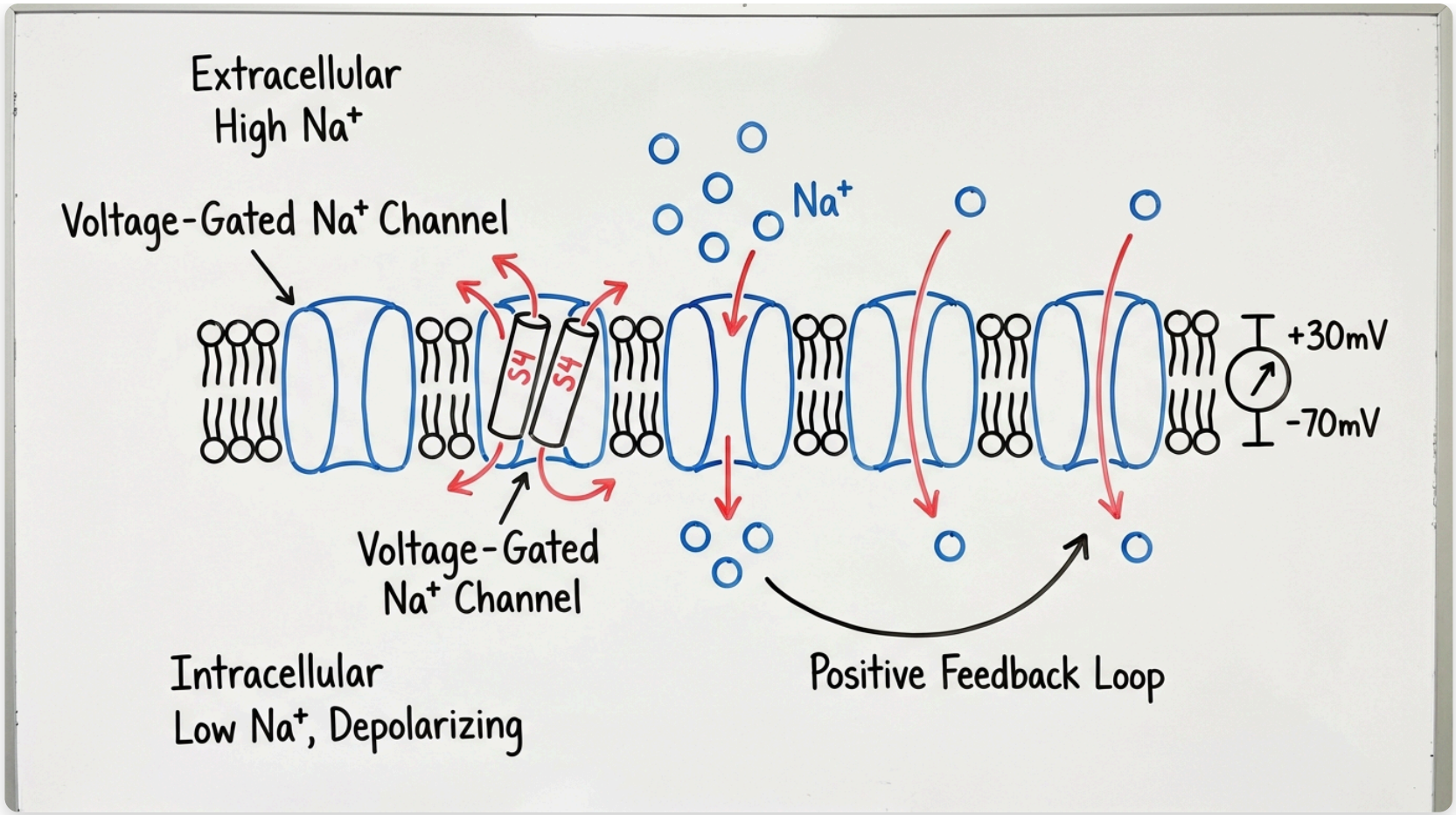


Key Insight: Sequential, transient g_{Na} increase followed by slower, persistent g_K increase underlies the action potential.

Sodium Channel Activation

The Rising Phase: Sodium Channel Activation - When membrane potential reaches threshold (approximately –55 mV), voltage-gated sodium channels undergo a conformational change: their S4 voltage-sensing segments move outward in response to depolarization, opening the channel pore. Sodium rushes in, driven by both its concentration gradient and the electrical gradient—the membrane is negative inside, attracting positive Na^+. This influx further depolarizes the membrane, opening more sodium channels in a positive feedback loop (the Hodgkin cycle). Within a fraction of a millisecond, the membrane potential swings from –70 mV toward +40 mV—approaching E_Na (+60 mV) but never quite reaching it. -

- Here are 3-5 main points from the text:
- Voltage-gated sodium channels open when the membrane potential reaches a threshold of -55 mV.
- Sodium ions then rush into the cell, moved by differences in concentration and electrical charge.
- The incoming sodium makes the membrane more positive and opens more sodium channels in a positive feedback loop.
- The membrane potential quickly changes from -70 mV to about +40 mV.


Extracellular
High Na+
Voltage-Gated Na+ Channel
Na+
S4
S4
+30mV
-70mV
Voltage-Gated
Na+ Channel
Intracellular
Low Na+, Depolarizing
Positive Feedback Loop

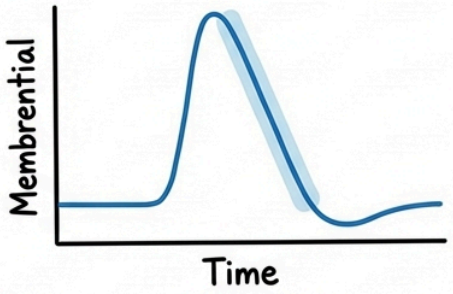
Falling Phase Mechanisms

The Falling Phase: Inactivation and Potassium Channels - Two mechanisms terminate the sodium influx. First, sodium channels inactivate: an intracellular "ball-and-chain" structure swings into the pore, blocking further sodium entry even though the activation gates remain open. This inactivation is distinct from closing—the channel is open but blocked. Second, voltage-gated potassium channels open more slowly (delayed rectifiers). Potassium rushes out, driven by both its concentration gradient (high K^+ inside) and the now-positive membrane potential. This potassium efflux repolarizes the membrane back toward E_K.

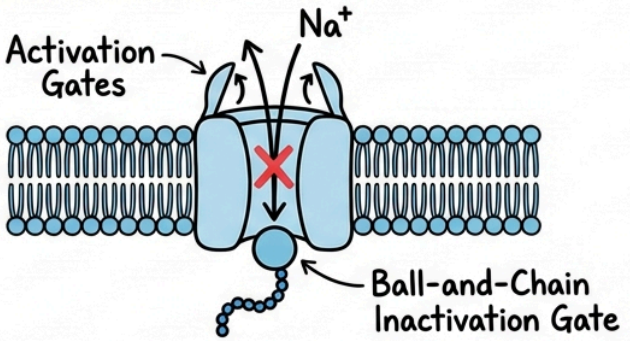
- Main Points:
- Sodium channels inactivate when a "ball-and-chain" part blocks their pore. This stops more sodium from entering the cell.
- Voltage-gated potassium channels open slowly during this phase.
- Potassium rushes out of the cell. Its high concentration inside and the positive membrane potential drive this movement.
- This outflow of potassium repolarizes the cell membrane. It helps the membrane return to its resting potential.

ACTION POTENTIAL PHASE:

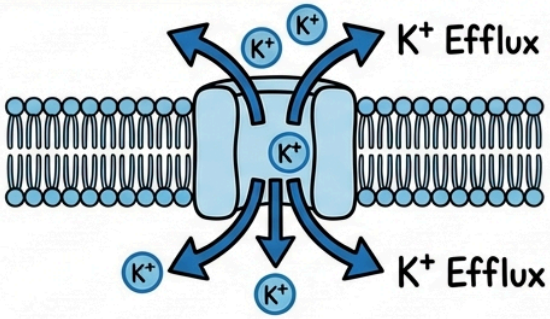
PHASE: FALLING (REPOLARIZATION)



BLOCKED VOLTAGE-GATED Na^+ CHANNEL



OPEN VOLTAGE-GATED K^+ CHANNEL

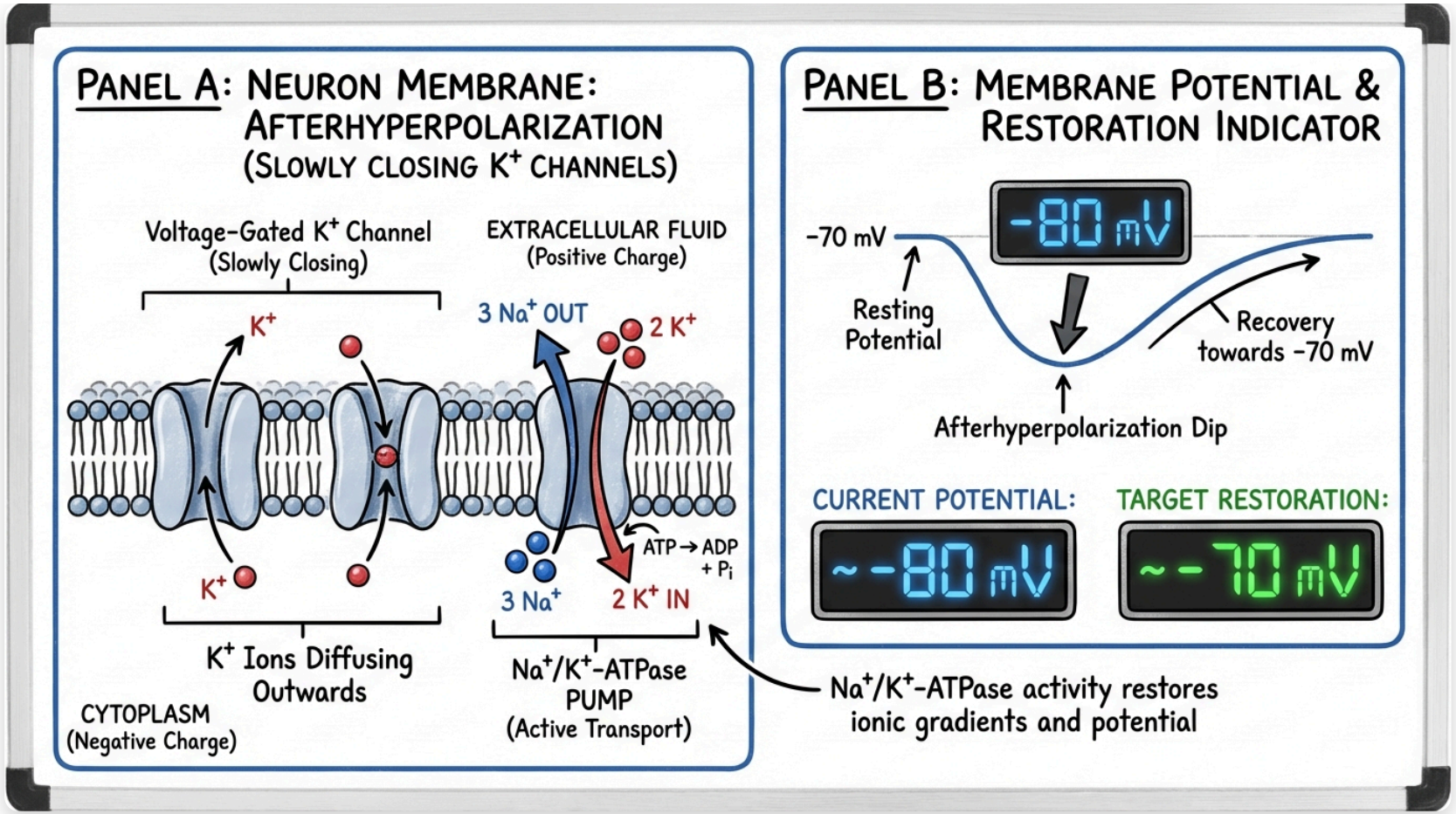


Clear textbook style whiteboard diagram with anatomically accurate physiology and animal images.

Action Potential Recovery

The potassium channels close slowly, causing a brief afterhyperpolarization where the membrane potential dips below the resting level (to approximately –80 mV) before returning to –70 mV as potassium permeability returns to baseline. Meanwhile, the Na^+/K^+-ATPase works continuously in the background, restoring the ion gradients slightly depleted by each action potential. -

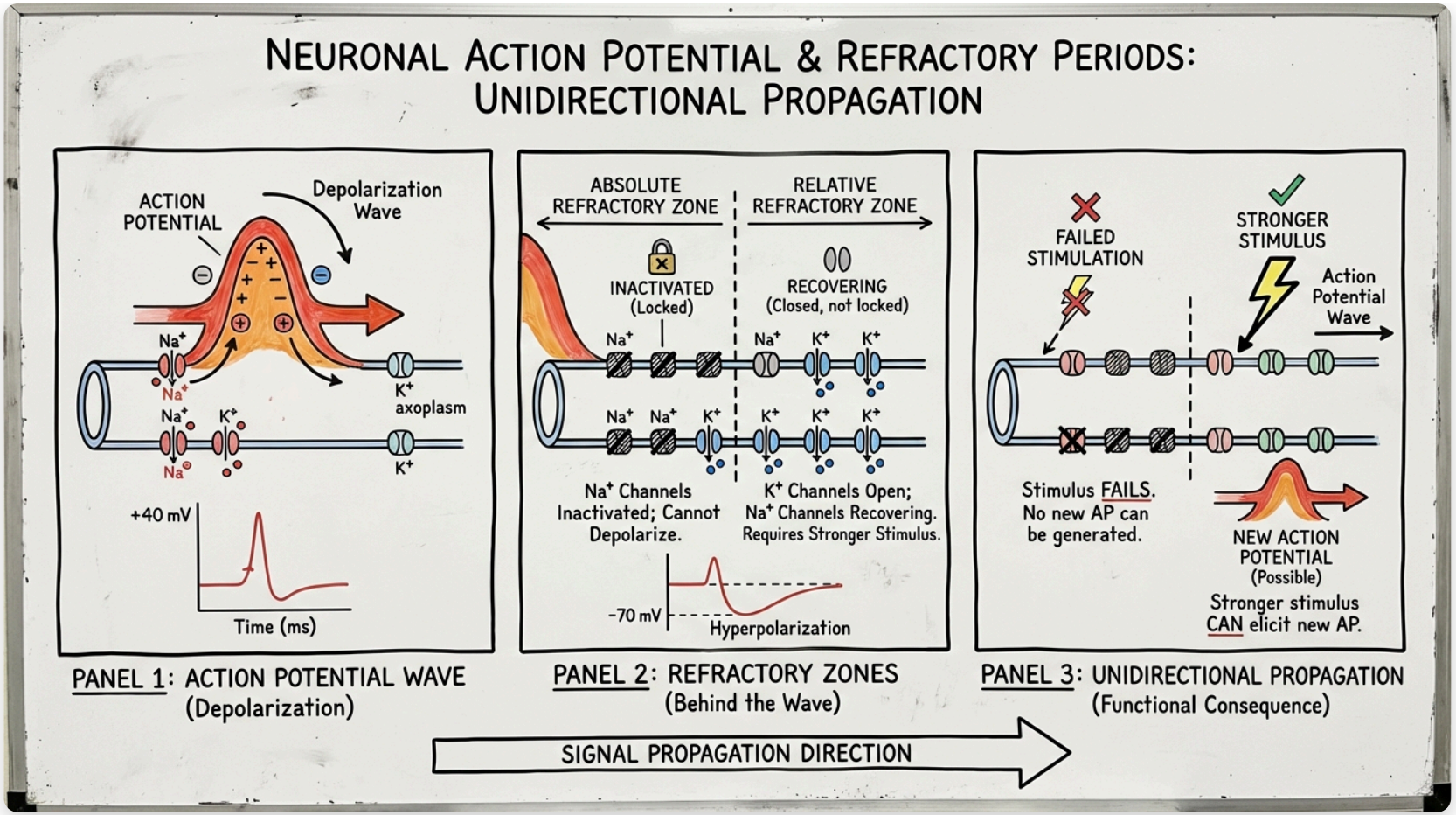
- Here are 3 main points from the text:
- Potassium channels close slowly, causing a brief afterhyperpolarization.
- During afterhyperpolarization, the membrane potential dips below the resting level, to about -80 mV. It then returns to the normal resting potential of -70 mV.
- The Na^+/K^+-ATPase continuously restores ion gradients. These gradients are slightly depleted by each action potential.


PANEL A: NEURON MEMBRANE: AFTERHYPERPOLARIZATION (SLOWLY CLOSING K+ CHANNELS)
Voltage-Gated K+ Channel (Slowly Closing)
EXTRACELLULAR FLUID (Positive Charge)
K+
3 Na+ OUT
2 K+
ATP → ADP + Pi
K+
3 Na+
2 K+ IN
K+ Ions Diffusing Outwards
Na+/K+-ATPase PUMP (Active Transport)
CYTOPLASM (Negative Charge)
PANEL B: MEMBRANE POTENTIAL & RESTORATION INDICATOR
-80 mV
-70 mV
Resting Potential
Recovery towards -70 mV
Afterhyperpolarization Dip
CURRENT POTENTIAL:
~-80 mV
TARGET RESTORATION:
~-70 mV
Na+/K+-ATPase activity restores ionic gradients and potential

Refractory Period Functions

Refractory Periods: Why Signals Travel One Way - The absolute refractory period (approximately 1 ms) occurs while sodium channels are inactivated—no stimulus, however strong, can trigger another action potential. The relative refractory period (several ms) follows, when some sodium channels have recovered but potassium channels remain open; a stronger-than-normal stimulus is required. These refractory periods serve crucial functions: they limit maximum firing frequency (typically 500-1000 Hz), ensure all-or-nothing amplitude by allowing full channel recovery, and enforce unidirectional propagation—the membrane behind an advancing action potential is refractory and cannot be re-excited. -

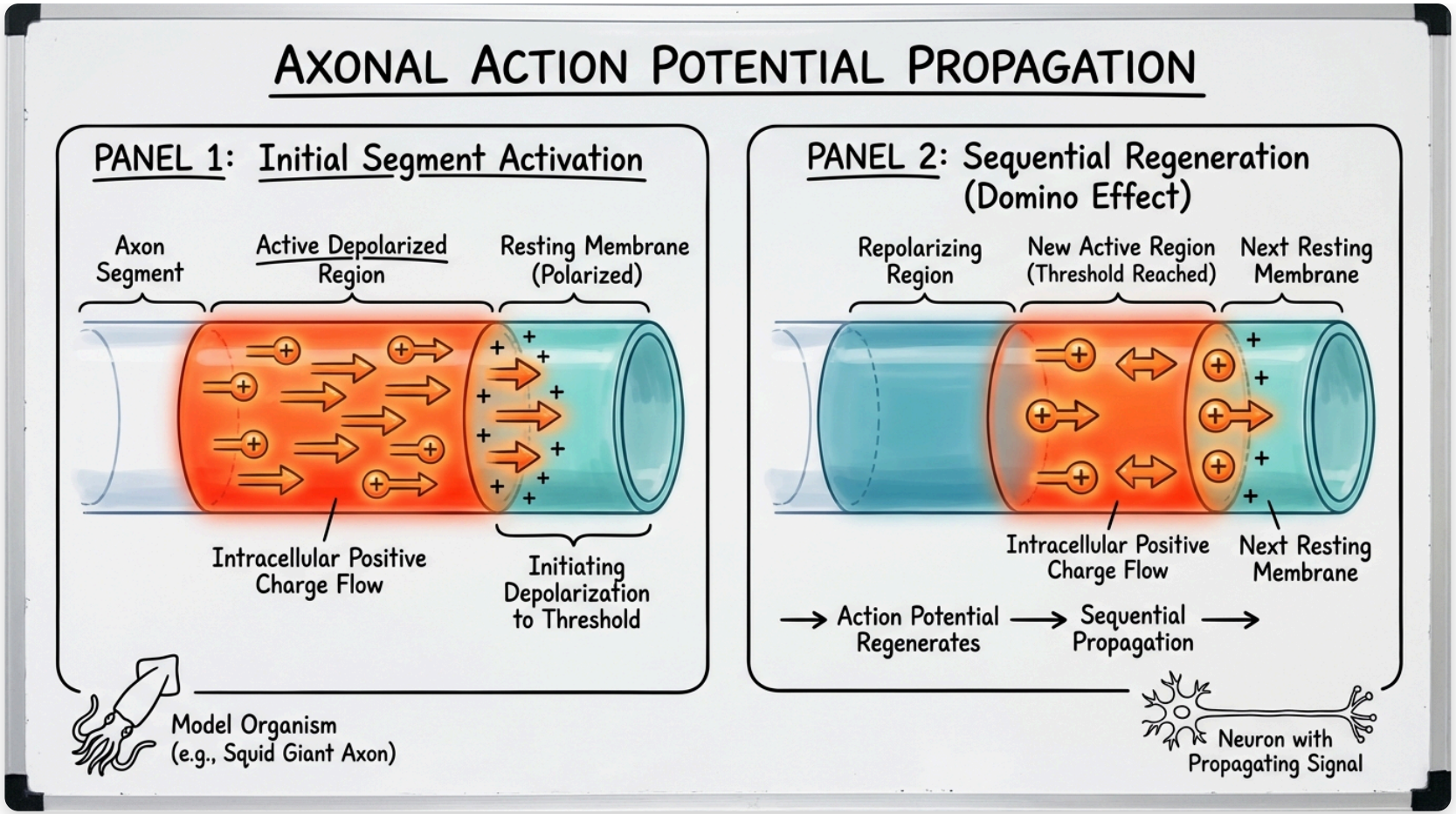
- Main Points:
- The absolute refractory period is a short time when no new nerve signal can be triggered.
- During the relative refractory period, a stronger-than-normal stimulus can trigger a new signal.
- Refractory periods control the maximum rate at which nerve signals can fire.
- They ensure nerve signals maintain a consistent 'all-or-nothing' strength.
- These periods make sure nerve signals travel in only one direction along a neuron.


NEURONAL ACTION POTENTIAL & REFRACTORY PERIODS:
UNIDIRECTIONAL PROPAGATION
ACTION POTENTIAL
Depolarization Wave
Na+
K+
axoplasm
+40 mV
Time (ms)
ABSOLUTE REFRACTORY ZONE
RELATIVE REFRACTORY ZONE
INACTIVATED (Locked)
RECOVERING (Closed, not locked)
Na+ Channels Inactivated; Cannot Depolarize.
K+ Channels Open; Na+ Channels Recovering. Requires Stronger Stimulus.
-70 mV
Hyperpolarization
FAILED STIMULATION
STRONGER STIMULUS
Action Potential Wave
Stimulus FAILS. No new AP can be generated.
NEW ACTION POTENTIAL (Possible)
Stronger stimulus CAN elicit new AP.
PANEL 1: ACTION POTENTIAL WAVE (Depolarization)
PANEL 2: REFRACTORY ZONES (Behind the Wave)
PANEL 3: UNIDIRECTIONAL PROPAGATION (Functional Consequence)
SIGNAL PROPAGATION DIRECTION

Action Potential Propagation

Propagation of the Action Potential - - An action potential at one point on an axon must somehow trigger action potentials further along. This propagation occurs through local circuit currents: the depolarized region becomes a current source, and positive charges flow intracellularly toward adjacent resting membrane, depolarizing it to threshold. The action potential doesn't "travel"—it regenerates sequentially along the axon, like a line of dominoes falling.

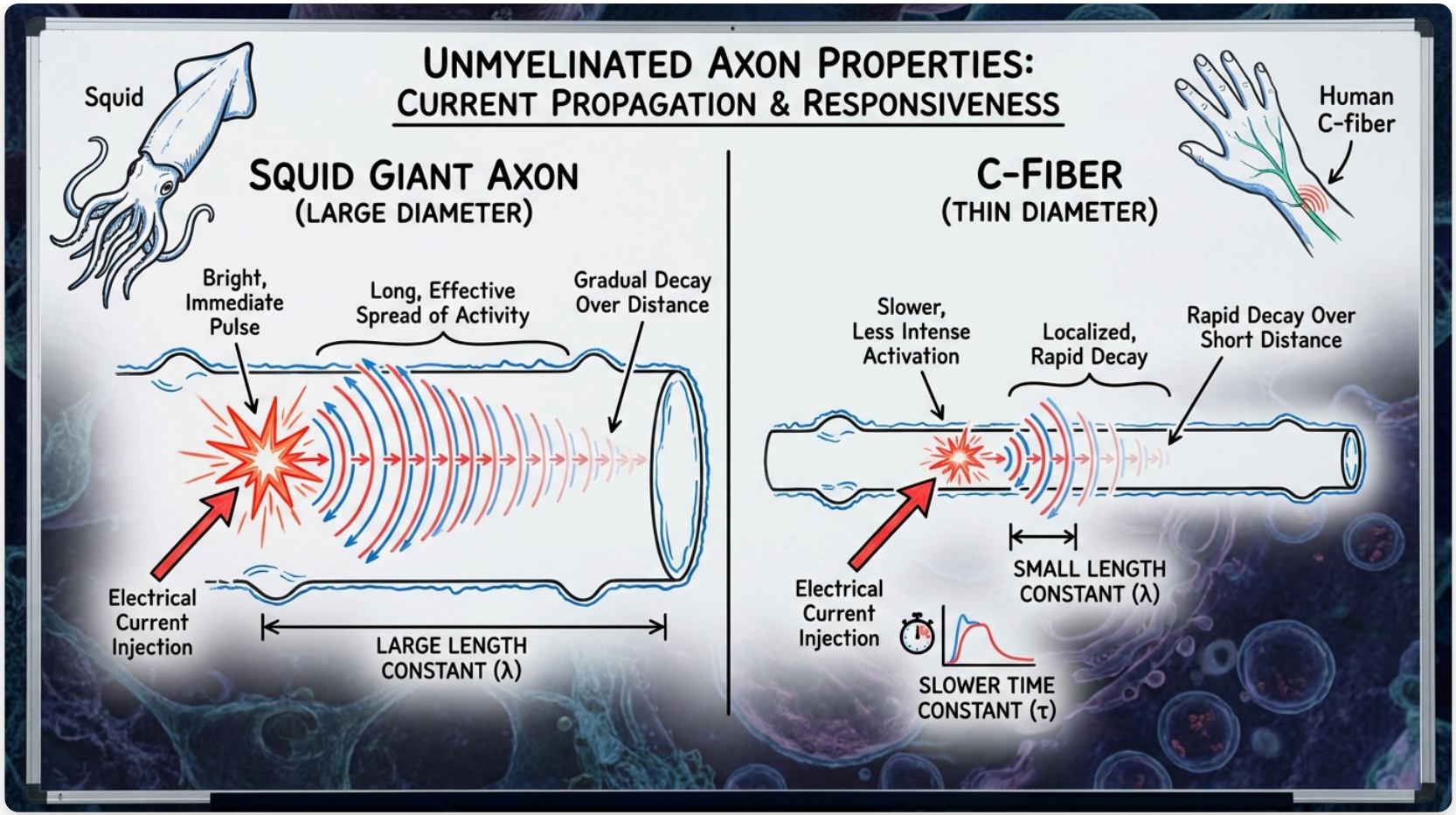
- Here are 3 main points:
- An action potential triggers other action potentials further along an axon.
- Local circuit currents cause this propagation. A depolarized region acts as a current source, sending positive charges to the adjacent membrane.
- The action potential regenerates itself sequentially along the axon.


AXONAL ACTION POTENTIAL PROPAGATION
PANEL 1: Initial Segment Activation
Axon Segment
Active Depolarized Region
Resting Membrane (Polarized)
Intracellular Positive Charge Flow
Initiating Depolarization to Threshold
Model Organism (e.g., Squid Giant Axon)
PANEL 2: Sequential Regeneration (Domino Effect)
Repolarizing Region
New Active Region (Threshold Reached)
Next Resting Membrane
Intracellular Positive Charge Flow
Next Resting Membrane
Action Potential Regenerates
Sequential Propagation
Neuron with Propagating Signal

Cable Length Constant

Cable Properties: Length and Time Constants - The passive electrical properties of axons determine how effectively local currents spread. The cable equation describes this spread using two key parameters: - Length constant (λ) = $\sqrt{}$(r_m/r_i), where r_m is membrane resistance and r_i is internal resistance. This measures how far current spreads before decaying to 37% of its original value—typically 0.1-1 mm in unmyelinated axons. Larger diameter axons have lower r_i and therefore larger λ, which is why the squid giant axon (500 µm) conducts faster than your thin unmyelinated C-fibers (1 µm). - Time constant (τ) = r_m × c_m, where c_m is membrane capacitance. This measures how quickly the membrane potential responds to current injection—typically 1-20 ms. Longer time constants mean slower responses but better temporal integration of inputs. -

- Here are 4 main points from the text:
- The electrical properties of axons determine how effectively local currents spread.
- The cable equation uses two main measurements, the length constant and time constant, to describe this spread.
- The length constant shows how far an electrical signal travels along an axon before it gets much weaker. Larger diameter axons have a bigger length constant, allowing signals to spread farther.
- The time constant measures how quickly an axon's electrical charge responds to an incoming signal. A longer time constant means slower responses but helps the axon combine signals better.

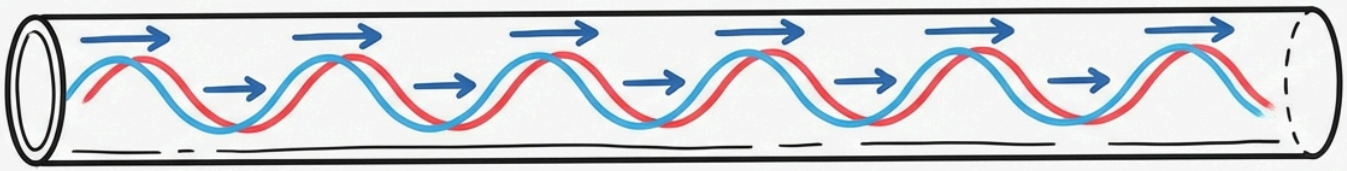

Squid
UNMYELINATED AXON PROPERTIES:
CURRENT PROPAGATION & RESPONSIVENESS
Human
C-fiber
SQUID GIANT AXON
(LARGE DIAMETER)
C-FIBER
(THIN DIAMETER)
Bright,
Immediate
Pulse
Long, Effective
Spread of Activity
Gradual Decay
Over Distance
Slower,
Less Intense
Activation
Localized,
Rapid Decay
Rapid Decay Over
Short Distance
Electrical
Current
Injection
LARGE LENGTH
CONSTANT (λ)
Electrical
Current
Injection
SMALL LENGTH
CONSTANT (λ)
SLOWER TIME
CONSTANT (τ)

Conduction Types

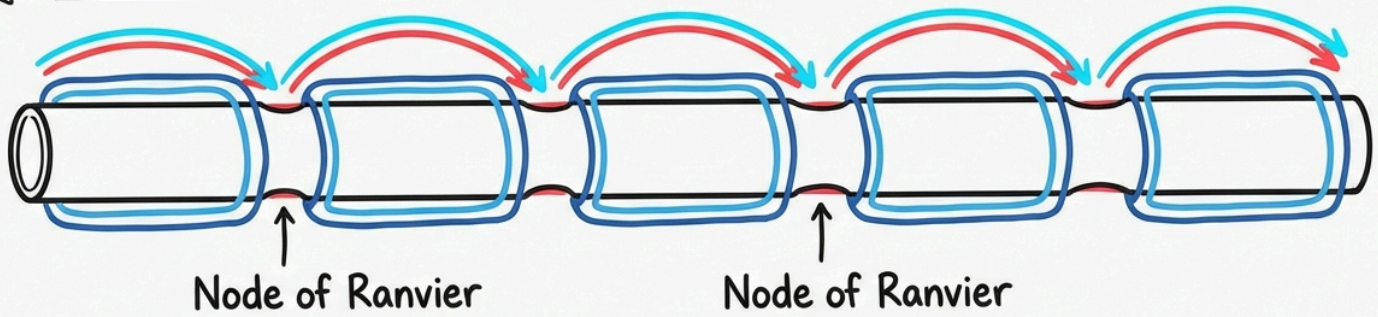
Continuous vs. Saltatory Conduction - In unmyelinated axons, action potentials propagate continuously—each micrometer of membrane must depolarize and fire. Conduction velocity depends on axon diameter (velocity $\propto \sqrt{\text{diameter}}$), reaching about 1 m/s for 1 µm fibers and 25 m/s for the 500 µm squid giant axon. - Myelination revolutionizes propagation. Oligodendrocytes (in the CNS) and Schwann cells (in the PNS) wrap axons in multiple layers of lipid-rich membrane, increasing r_m 5000-fold and decreasing c_m 50-fold. This massively increases the length constant—current spreads much further before decaying. Action potentials occur only at nodes of Ranvier, unmyelinated gaps where sodium channels cluster at extraordinary density (1000-2000/µm²). Current "jumps" from node to node—saltatory conduction (from Latin saltare, "to jump")—achieving velocities up to 120 m/s in 20 µm myelinated fibers while using 100× less energy than continuous conduction would require.

- Main Points:
- Unmyelinated axons conduct nerve signals continuously along their entire length.
- Myelin sheaths, formed by specialized cells, wrap around axons to help nerve signals travel further.
- In myelinated axons, nerve signals jump between unmyelinated gaps called nodes of Ranvier. This process is known as saltatory conduction.
- Saltatory conduction allows nerve signals to travel much faster and use significantly less energy than continuous conduction.

UNMYELINATED AXON: CONTINUOUS PROPAGATION



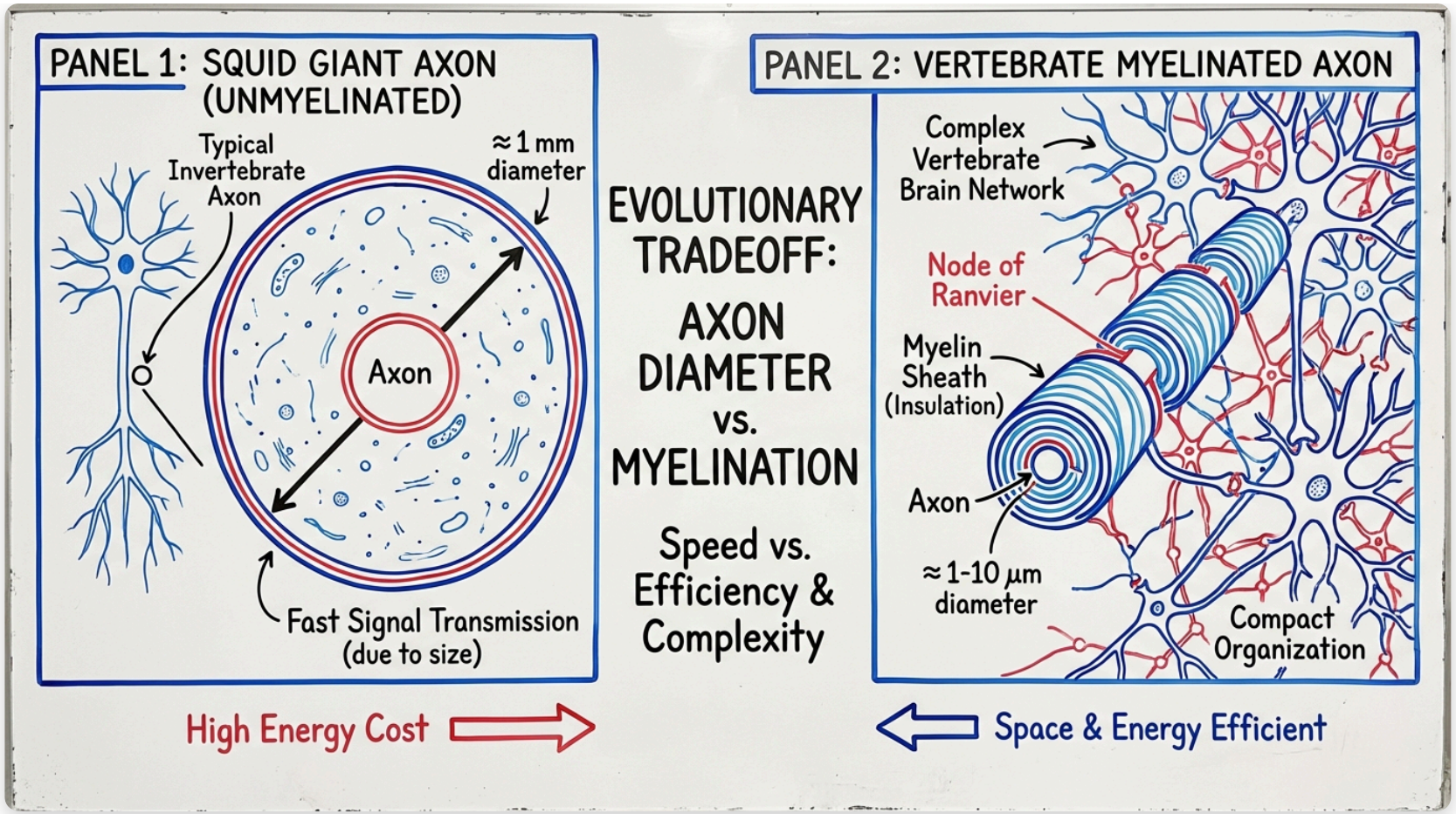
MYELINATED AXON: SALTATORY CONDUCTION



Axon Myelin Tradeoff

- Evolution faced a tradeoff: increase axon diameter (metabolically expensive, takes up space) or evolve myelination (complex developmental program, vulnerable to autoimmune attack). Vertebrates chose myelination, enabling complex brains in compact skulls. Invertebrates chose large axons, which is why the squid giant axon—used for escape responses—reaches 1 mm diameter.

- → Evolution offered two main ways to speed up nerve signals: changing axon diameter or developing myelination.
- → Vertebrates evolved myelination, which allows them to have complex brains within compact skulls.
- → Invertebrates chose to use large-diameter axons to send fast nerve signals.
- → For example, the squid has a giant axon that is 1 mm wide and helps it perform escape responses.


PANEL 1: SQUID GIANT AXON (UNMYELINATED)
Typical Invertebrate Axon
≈1 mm diameter
Axon
Fast Signal Transmission (due to size)
High Energy Cost
EVOLUTIONARY TRADEOFF:
AXON DIAMETER vs. MYELINATION
Speed vs. Efficiency & Complexity
PANEL 2: VERTEBRATE MYELINATED AXON
Complex Vertebrate Brain Network
Node of Ranvier
Myelin Sheath (Insulation)
Axon
≈1-10 µm diameter
Compact Organization
Space & Energy Efficient

When Channels Fail

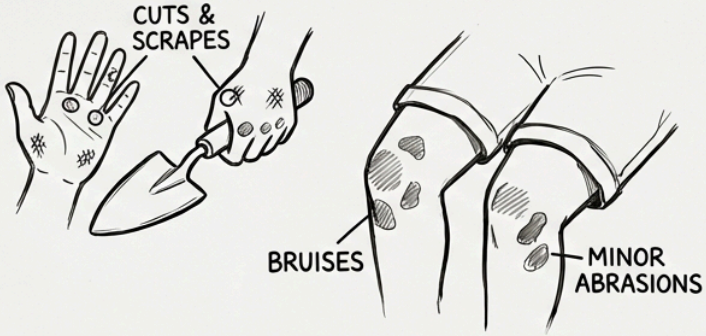
Channel Diversity and Clinical Relevance - Channelopathies: When Channels Fail - - Channelopathies are diseases caused by ion channel mutations. In 2006, Cambridge researchers discovered a Pakistani family where some members felt no pain whatsoever—mutations in SCN9A eliminated functional Nav1.7 sodium channels, specifically expressed in pain-sensing neurons. These individuals could feel touch, temperature, and pressure, but never experienced pain. Tragically, without pain's protective warnings, they suffered repeated injuries. The opposite mutation—Nav1.7 hyperactivity—causes erythromelalgia, where patients experience burning pain from mild warmth.

- Main Points:
- Channelopathies are diseases caused by mutations, or changes, in ion channels.
- A specific gene mutation, like in SCN9A, can remove certain channels and stop people from feeling any pain.
- Without pain's protective warnings, individuals with these mutations often suffer repeated injuries.
- The opposite problem, too much activity in these channels, causes severe burning pain from even mild warmth.

PANEL A: ACTIVITY & EXPRESSION

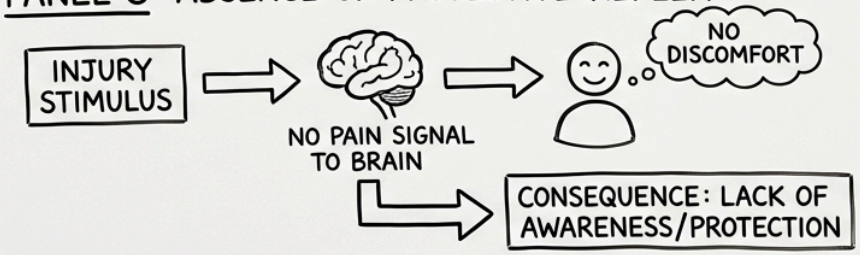
EVERYDAY ACTIVITY: GARDENING.
FACIAL EXPRESSION: UNFAZED, SERENE.

PANEL B: VISIBLE INJURIES (HANDS & KNEES)



PHYSICAL EVIDENCE: MINOR WOUNDS PRESENT.

PANEL C: ABSENCE OF PROTECTIVE REFLEX

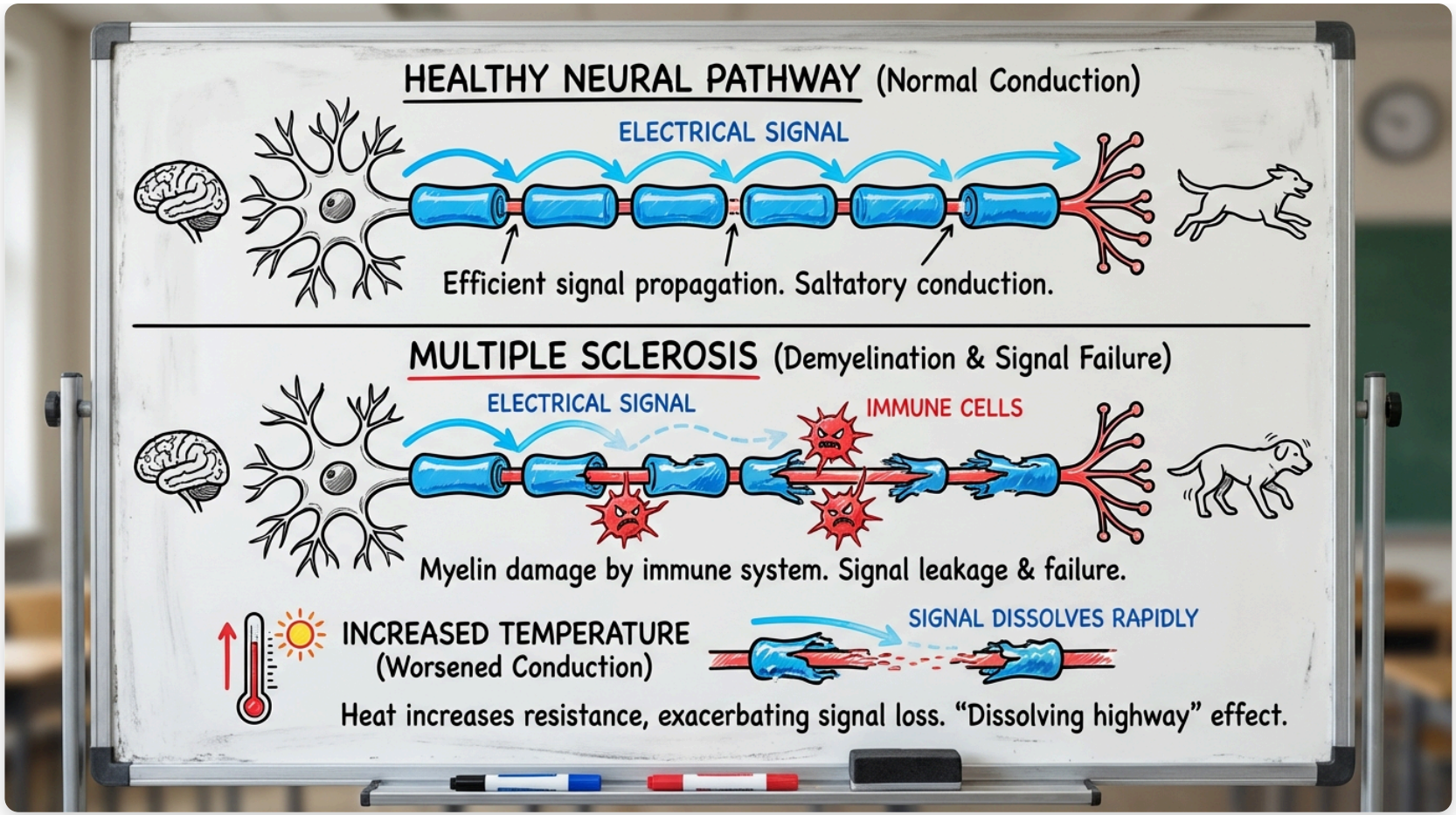


CONDITION: CONGENITAL INSENSITIVITY TO PAIN (CIP)

MS Demyelination

Multiple Sclerosis and Demyelination - Multiple sclerosis is an autoimmune disease where immune cells attack myelin. As myelin degrades, the length constant shrinks—current no longer reaches the next node, and conduction fails. Patients experience progressive paralysis, sensory loss, and cognitive decline as white matter highways dissolve. The temperature sensitivity of MS symptoms (worsening with heat) reflects how membrane capacitance and channel kinetics change with temperature, further degrading already-marginal conduction. -

- Here are 4 main points from the text:
- Multiple sclerosis (MS) is an autoimmune disease where immune cells attack myelin.
- As myelin degrades, nerve signals fail to transmit properly.
- Patients experience progressive paralysis, sensory loss, and cognitive decline.
- MS symptoms often worsen in warmer temperatures.


HEALTHY NEURAL PATHWAY (Normal Conduction)
ELECTRICAL SIGNAL
Efficient signal propagation. Saltatory conduction.
MULTIPLE SCLEROSIS (Demyelination & Signal Failure)
ELECTRICAL SIGNAL
IMMUNE CELLS
Myelin damage by immune system. Signal leakage & failure.
INCREASED TEMPERATURE
(Worsened Conduction)
SIGNAL DISSOLVES RAPIDLY
Heat increases resistance, exacerbating signal loss. "Dissolving highway" effect.

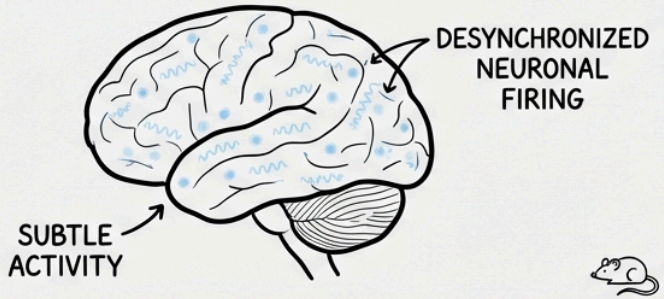
Brain Electrical Storms

Epilepsy: Electrical Storms - Epilepsy represents network-level electrical failure. Dravet syndrome, caused by SCN1A mutations, illustrates the exquisite balance required: the mutation affects inhibitory interneurons more than excitatory neurons, shifting the network toward hyperexcitability. During seizures, millions of neurons fire synchronously—the opposite of normal desynchronized activity. Antiepileptic drugs typically work by enhancing inhibition (benzodiazepines enhance GABA receptors) or reducing sodium channel activity (phenytoin, carbamazepine). -

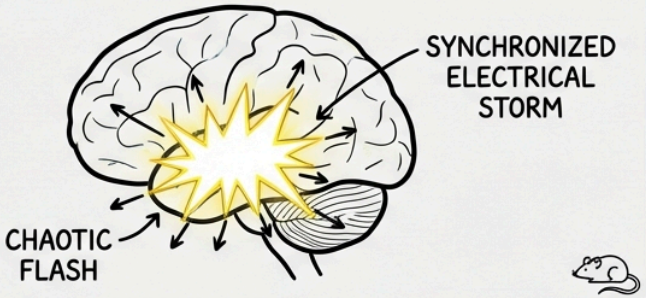
- Main Points:
- Epilepsy is an electrical problem within the brain's networks.
- During a seizure, many brain cells fire at the same time. This activity is abnormal for the brain.
- Epilepsy can happen when brain signals become unbalanced. This makes the brain's networks too active.
- Antiepileptic drugs work by calming brain activity. They do this by increasing inhibition or reducing nerve signals.

EPILEPTIC SEIZURE PHYSIOLOGY & INTERVENTION

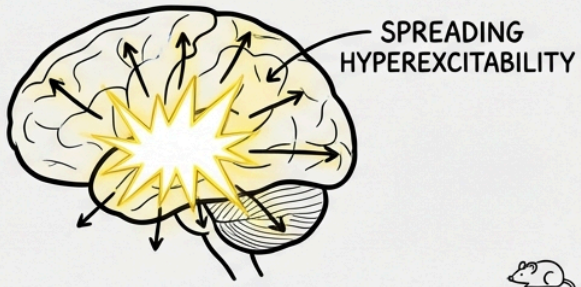
1. NORMAL BRAIN ACTIVITY



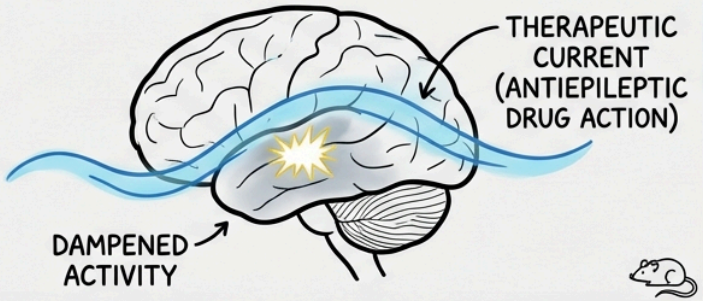
2. SEIZURE ONSET (HYPEREXCITABILITY)



3. SEIZURE PROPAGATION



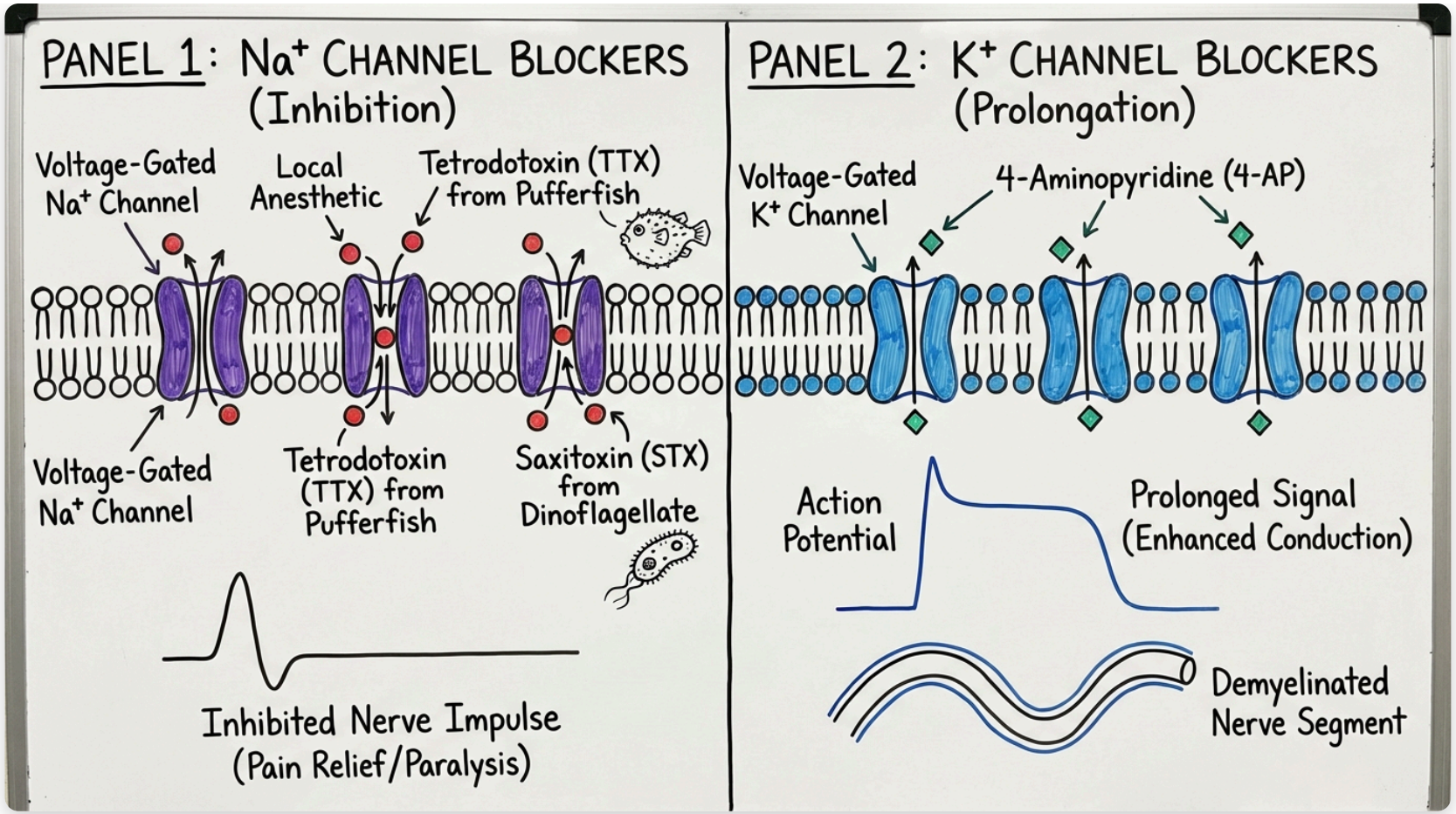
4. THERAPEUTIC INTERVENTION



Channel Pharmacology

Channel Pharmacology - Ion channels are major drug targets. Local anesthetics (lidocaine, novocaine) block voltage-gated sodium channels, preventing action potentials in pain fibers. Tetrodotoxin (from pufferfish) and saxitoxin (from dinoflagellates) are exquisitely potent sodium channel blockers—nanomolar concentrations cause paralysis and death. TEA (tetraethylammonium) and 4-aminopyridine block potassium channels, prolonging action potentials—4-AP is used therapeutically in multiple sclerosis to enhance conduction through demyelinated segments.

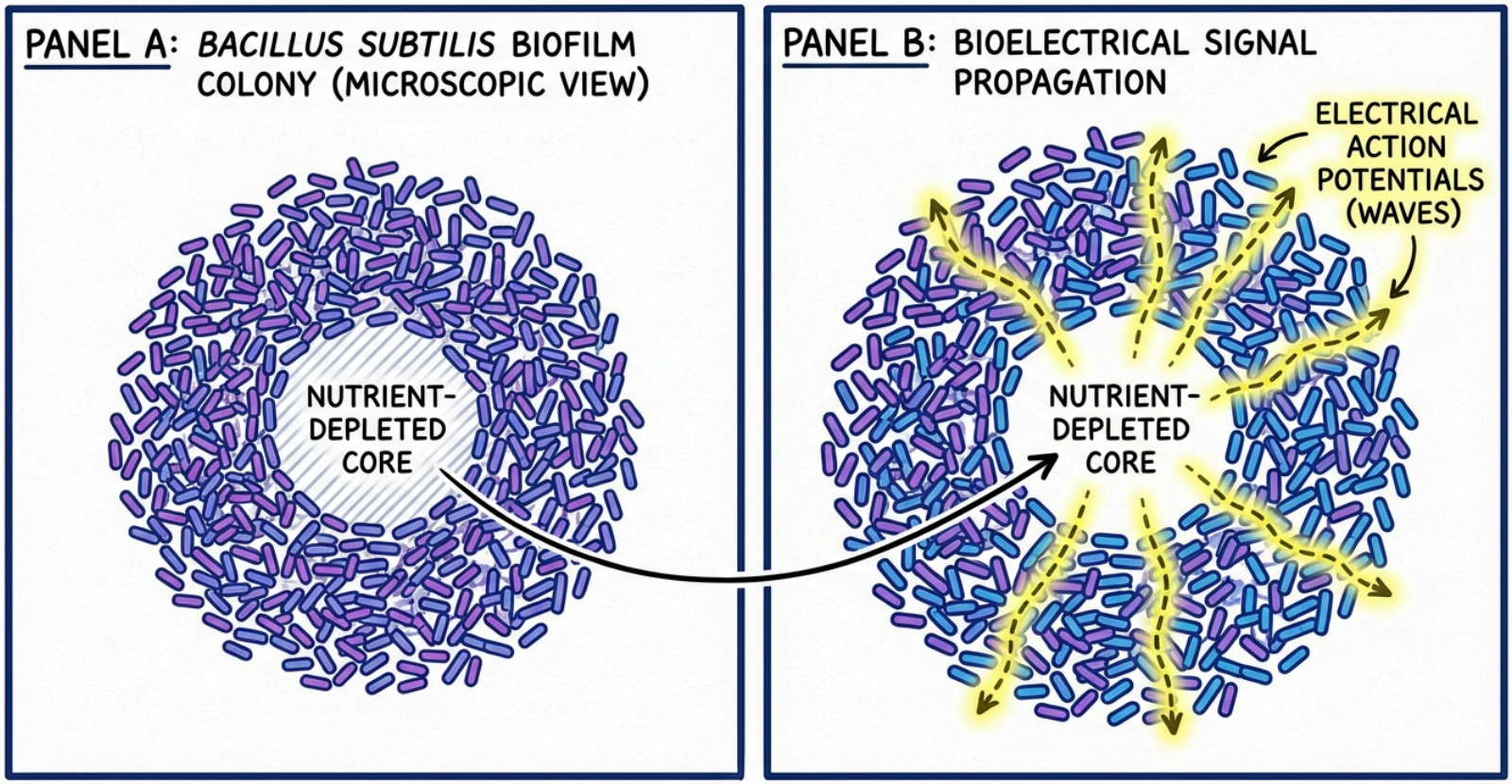
- Here are 4 main points from the text:
- Ion channels serve as key targets for many medications.
- Local anesthetics like lidocaine block sodium channels to prevent pain signals.
- Powerful natural toxins, such as tetrodotoxin, also block sodium channels and can cause paralysis or death.
- Some drugs block potassium channels, which can help improve nerve signaling in conditions like multiple sclerosis.


PANEL 1: Na+ CHANNEL BLOCKERS (Inhibition)
Voltage-Gated Na+ Channel
Local Anesthetic
Tetrodotoxin (TTX) from Pufferfish
Voltage-Gated Na+ Channel
Tetrodotoxin (TTX) from Pufferfish
Saxitoxin (STX) from Dinoflagellate
Inhibited Nerve Impulse (Pain Relief/Paralysis)
PANEL 2: K+ CHANNEL BLOCKERS (Prolongation)
Voltage-Gated K+ Channel
4-Aminopyridine (4-AP)
Action Potential
Prolonged Signal (Enhanced Conduction)
Demyelinated Nerve Segment

Ancient Bioelectricity

Evolutionary Origins: The Ancient Voltage of Life - - Electrical signaling is ancient. Gürol Süel's lab discovered that Bacillus subtilis bacteria generate action potentials using potassium channels structurally similar to yours. When nutrients run low in a biofilm's center, bacteria fire electrical signals that propagate outward, coordinating colony behavior. These bacterial channels follow Hodgkin-Huxley dynamics—the same equations govern bacterial and human electrical signaling. The molecular machinery for bioelectricity evolved once, billions of years ago, and has been conserved ever since.

- Main Points:
- Electrical signaling in life began billions of years ago.
- Specific bacteria, like Bacillus subtilis, create electrical signals called action potentials.
- Bacteria use potassium channels and electrical signaling methods similar to humans.
- Bacteria use these electrical signals to coordinate their colony's behavior, especially when food is scarce.

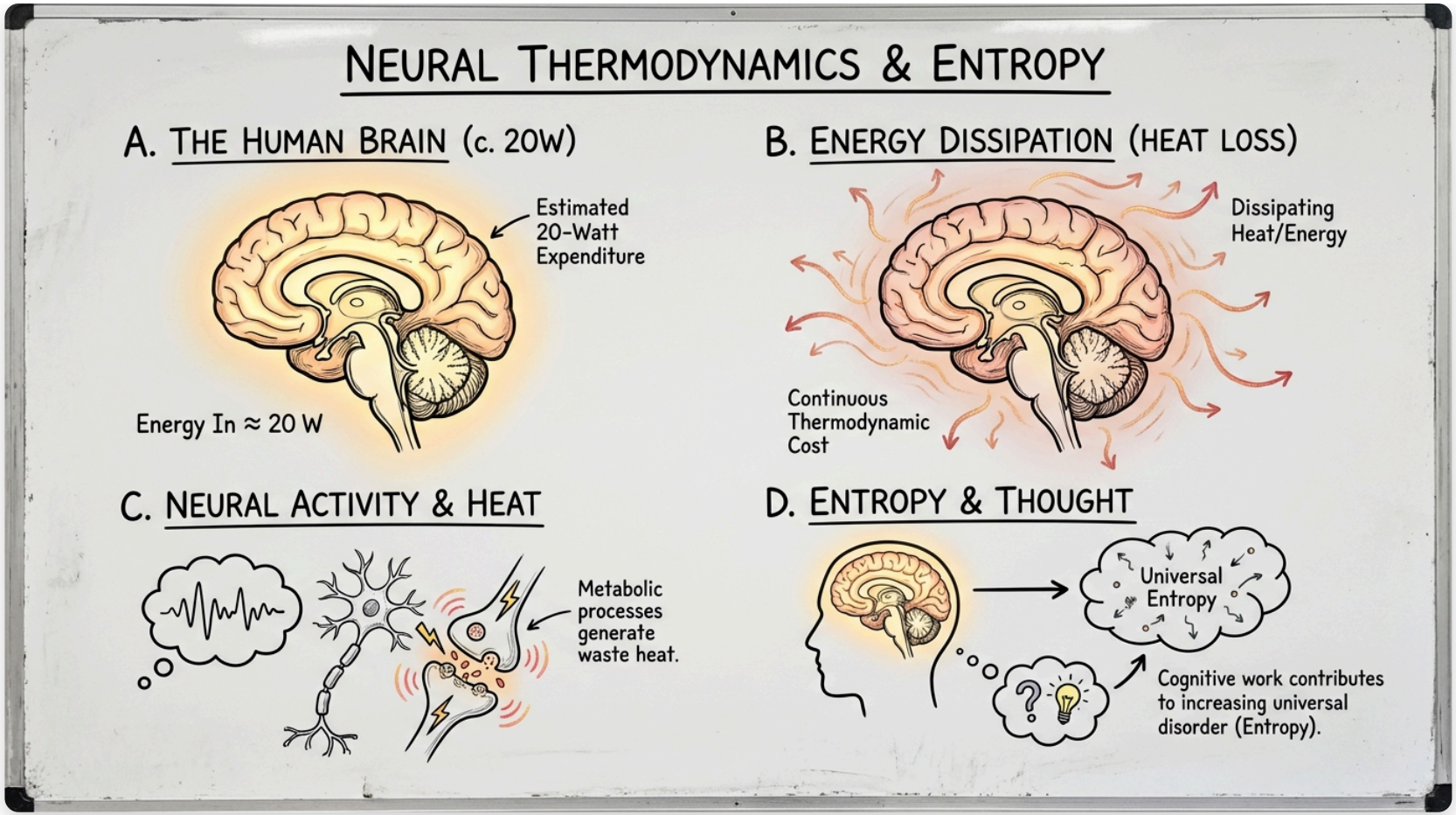


EVOLUTIONARY CONSERVED BIOELECTRICITY IN BACTERIAL COMMUNITIES

Thought Energy Cost

The Thermodynamic Cost of Thought - David Attwell and Simon Laughlin calculated that 50% of the brain's energy budget goes to reversing ion movements from action potentials and synaptic transmission. Your brain consumes 20 watts—enough to power a dim light bulb—with 86 billion neurons, each firing action potentials that cost hundreds of millions of ATP molecules. This is why your brain, just 2% of body weight, uses 20% of your oxygen and glucose. The price of consciousness is thermodynamic—every thought increases universal entropy. -

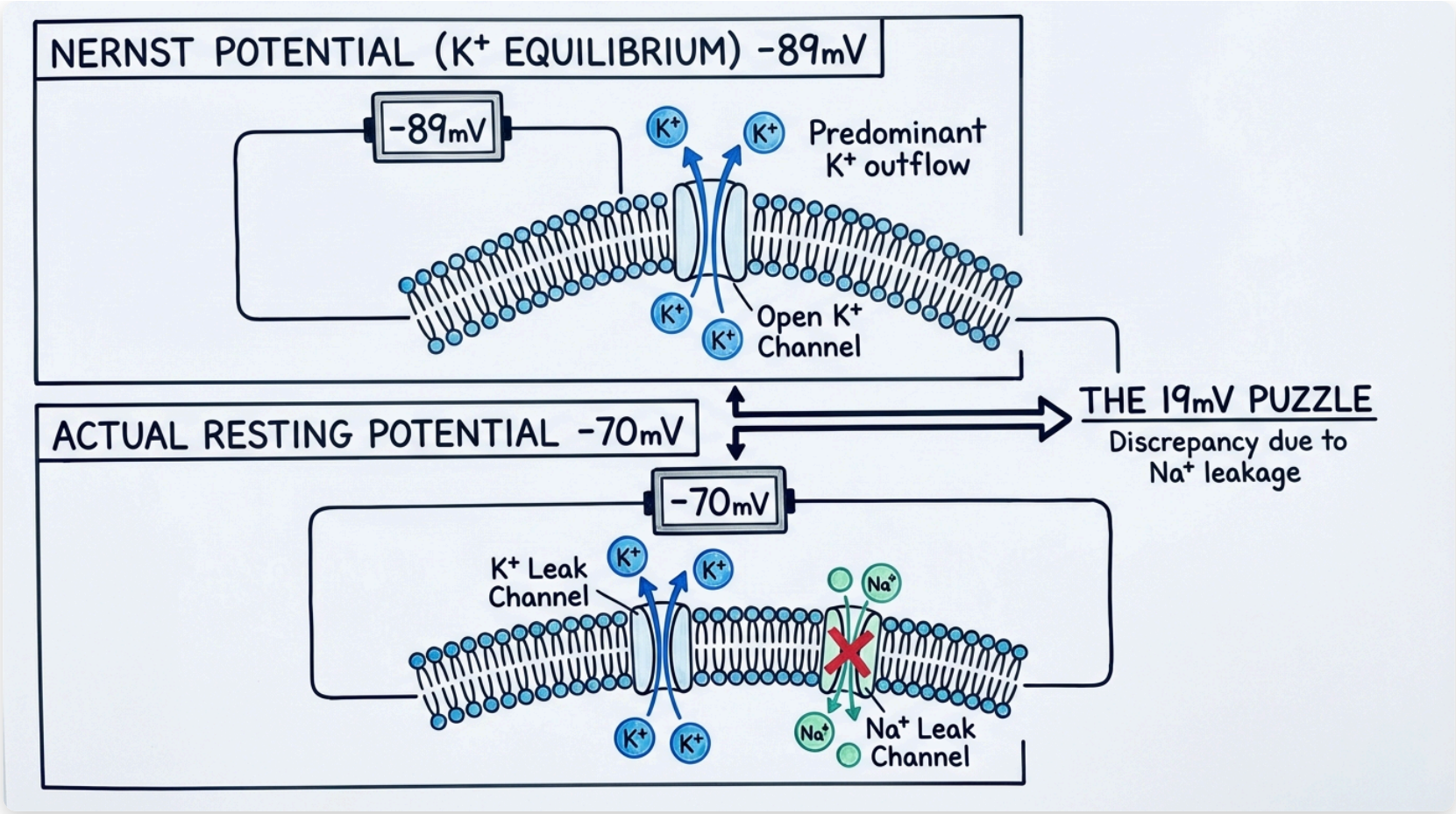
- Here are 4 main points from the text:
- Half of the brain's energy is used to reset ion movements after nerve signals.
- The brain uses about 20 watts of power, similar to a dim light bulb.
- The brain, though only 2% of body weight, uses 20% of the body's oxygen and glucose.
- Every thought consumes energy and contributes to universal entropy.


NEURAL THERMODYNAMICS & ENTROPY
A. THE HUMAN BRAIN (c. 20W)
Estimated 20-Watt Expenditure
Energy In ≈ 20 W
B. ENERGY DISSIPATION (HEAT LOSS)
Dissipating Heat/Energy
Continuous Thermodynamic Cost
C. NEURAL ACTIVITY & HEAT
Metabolic processes generate waste heat.
D. ENTROPY & THOUGHT
Universal Entropy
Cognitive work contributes to increasing universal disorder (Entropy).

Resting Potential Factors

Thought Questions for Discussion - Three questions to spark discussion before your next class: - The Nernst vs. Reality Puzzle: The Nernst equation predicts $E_K = -89$ mV for potassium, yet neurons rest at −70 mV. Why the 19 mV difference? Consider what happens if you experimentally block all sodium channels—does the resting potential shift toward E_K? What does this tell you about the molecular basis of the resting potential, and how might pharmacological manipulation of sodium leak channels affect neuronal excitability?

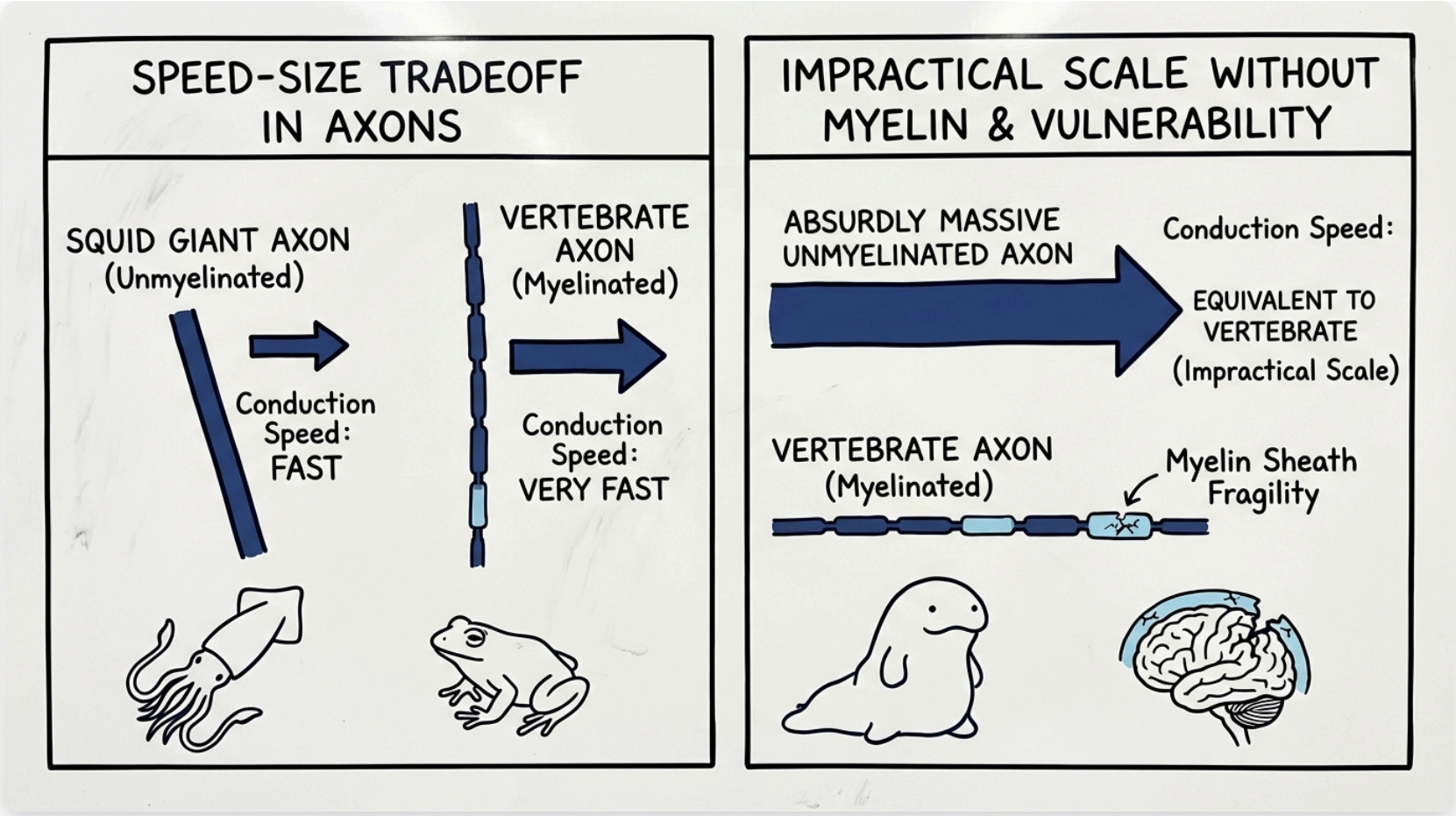
- The Nernst equation predicts potassium's equilibrium potential at -89 mV.
- However, neurons actually rest at a different potential, typically -70 mV.
- Sodium channels influence a neuron's resting potential and its excitability.


NERNST POTENTIAL (K+ EQUILIBRIUM) -89mV
-89mV
K+
K+
Predominant K+ outflow
K+
K+
Open K+ Channel
THE 19mV PUZZLE
Discrepancy due to Na+ leakage
ACTUAL RESTING POTENTIAL -70mV
-70mV
K+ Leak Channel
K+
K+
Na+
Na+
Na+ Leak Channel
K+
K+

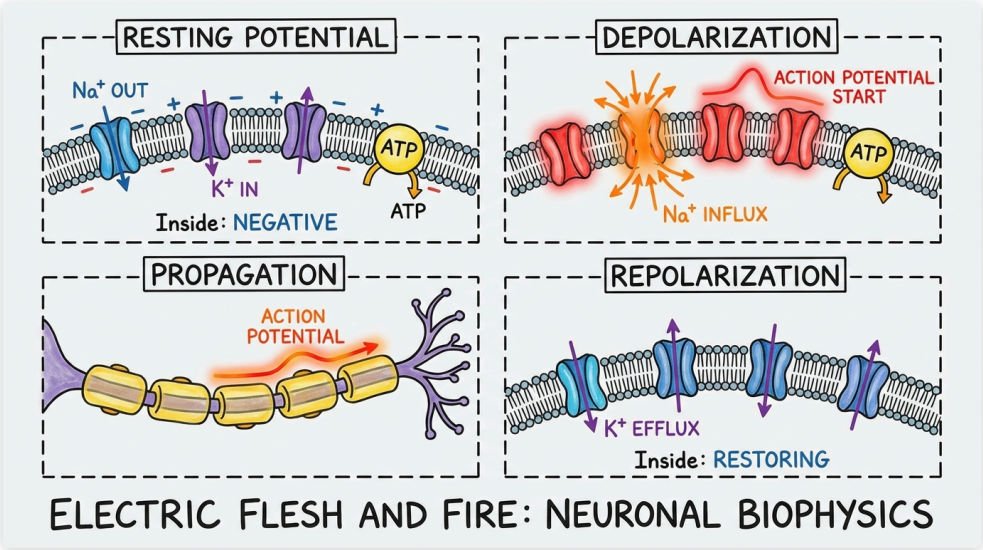
Speed Size Tradeoff

The Speed-Size Tradeoff: Evolution produced two solutions for fast conduction: giant axons (squid) and myelinated axons (vertebrates). The squid giant axon is 500 µm diameter and conducts at 25 m/s. Your myelinated motor neurons are 20 µm diameter and conduct at 120 m/s. Calculate how large an unmyelinated axon would need to be to conduct at 120 m/s. (Hint: velocity scales with $\sqrt{}$diameter for unmyelinated axons.) Why was this solution not viable for vertebrate nervous systems? The Vulnerability Question: Myelination increases conduction velocity 100-fold and appeared 425 million years ago, enabling complex vertebrate nervous systems. Yet myelin is uniquely vulnerable—multiple sclerosis, Guillain-Barré syndrome, and leukodystrophies all attack it. Why didn't evolution produce a more robust insulation? What does myelin's vulnerability reveal about biological tradeoffs between performance and resilience?

- Here are 4 main points from the text:
- Evolution developed two main ways for nerves to send fast signals: very large axons or myelinated axons.
- Myelination lets vertebrates have small nerve fibers that send signals very quickly, unlike giant, unmyelinated axons.
- Myelination significantly increases nerve signal speed and allowed complex nervous systems to develop in vertebrates.
- Despite its benefits, myelin is fragile and can be attacked by serious diseases such as multiple sclerosis.


SPEED-SIZE TRADEOFF IN AXONS
SQUID GIANT AXON (Unmyelinated)
Conduction Speed: FAST
VERTEBRATE AXON (Myelinated)
Conduction Speed: VERY FAST
IMPRACTICAL SCALE WITHOUT MYELIN & VULNERABILITY
ABSURDLY MASSIVE UNMYELINATED AXON
Conduction Speed:
EQUIVALENT TO VERTEBRATE
(Impractical Scale)
VERTEBRATE AXON (Myelinated)
Myelin Sheath Fragility

Electrical Neural Activity

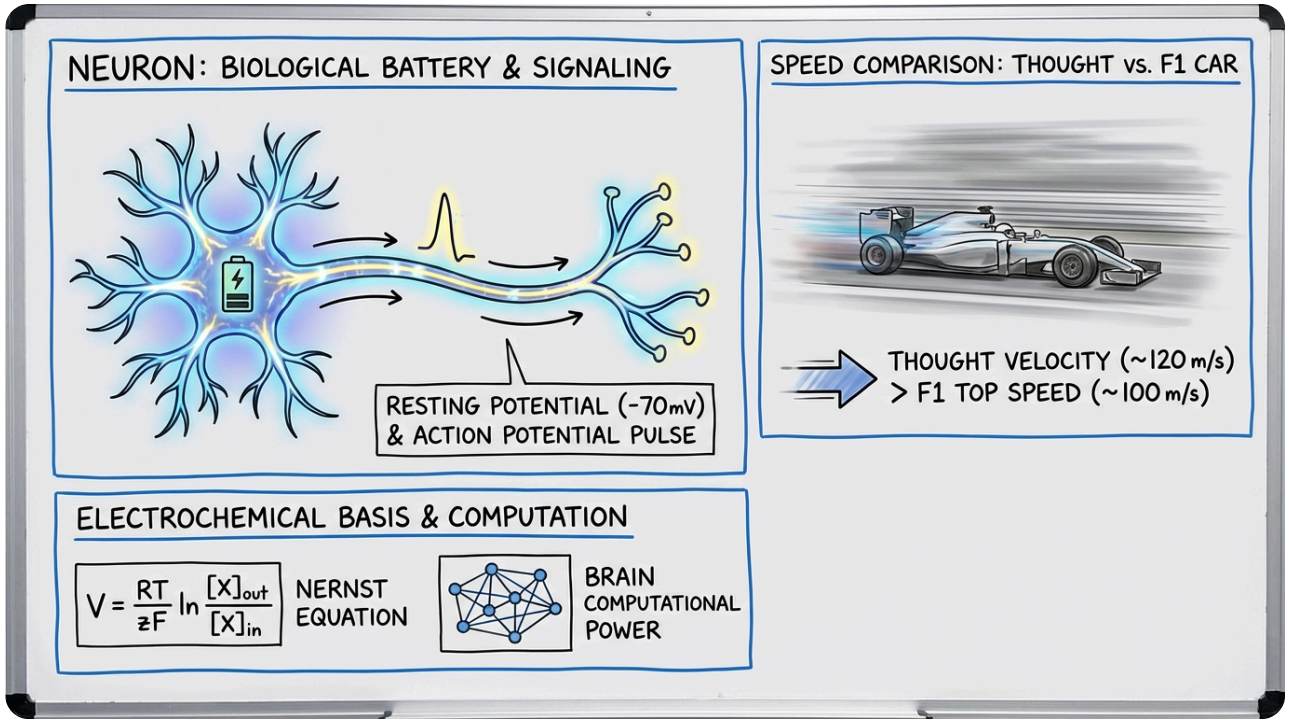


- Here are 4 main points from the text:
- Neurons maintain a resting electrical charge across t membrane, typically at -70 mV, due to the movement distribution of ions.
- An action potential is an electrical signal generated b neurons through the rapid opening and closing of vo gated sodium and potassium channels.
- Action potentials travel along the neuron, and myelin significantly increases their speed and efficiency.
- Disorders of ion channels, called channelopathies, ca various diseases like multiple sclerosis and epilepsy.

Full Text

Electric Flesh and Fire: The Biophysics of Thought Electrical Neur Visual Summary LECTURE OUTLINE (80 minutes) I. The Resting M Potential (20 min) • Ion distributions and the Na⁺/K⁺-ATPase • The equation: equilibrium potentials for single ions • The Goldman-Ho Katz equation: multiple ion contributions • Why neurons rest at –7 at E_K II. The Action Potential: Ionic Mechanisms (20 min) • Hodg Huxley's voltage clamp experiments • Voltage-gated Na⁺ channel activation and inactivation • Voltage-gated K⁺ channels: delayed rectification • The absolute and relative refractory periods III. Pro of the Action Potential (15 min) • Local circuit currents and the ca equation • Length constant and time constant • Continuous vs. sa conduction • Myelination and conduction velocity IV. Channel Div Clinical Relevtic (15 min) • Channelopathies: from painlessness to • Multiple sclerosis and demyelination • Epilepsy as electrical stor Pharmacology of ion channels V. Evolutionary Origins (10 min) • E action potentials and ancient ion channels • The thermodynamic thought

Brain's Battery

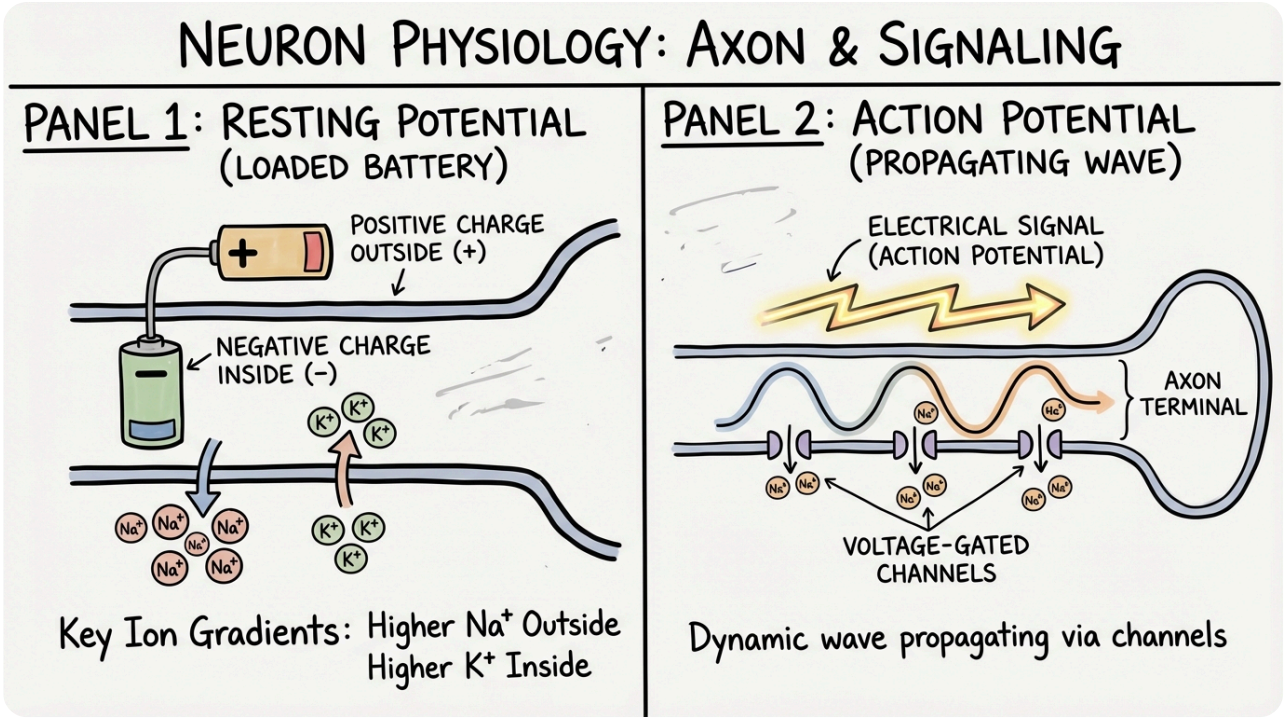


- Main Points:
- Thoughts travel at 120 meters per second within the This biological electricity is much slower than electri wires.
- The brain uses tiny electrical signals as the foundatic consciousness.
- Your brain uses 20% of your body's calories to maint electrical readiness.
- Neurons send electrical signals using a process with "resting potential" and an "action potential."

Full Text

Your thoughts move at 120 meters per second—the speed of a Fo car—yet this biological lightning is a million times slower than elec copper wire. Today we decode the most elegant hack in evolution history: how life transforms a 70-millivolt battery smaller than a v the computational foundation of consciousness. We'll discover wl brain burns 20% of your calories just maintaining electrical readir two equations—the Nernst and Goldman—predict the voltage of e neuron on Earth, and how Hodgkin and Huxley's squid experimen the molecular machinery underlying every thought. From the resti potential that sets the stage to the action potential that carries th we'll trace the complete electrical journey within a single neuron– the chemical synapse for next time.

Electrical Signals

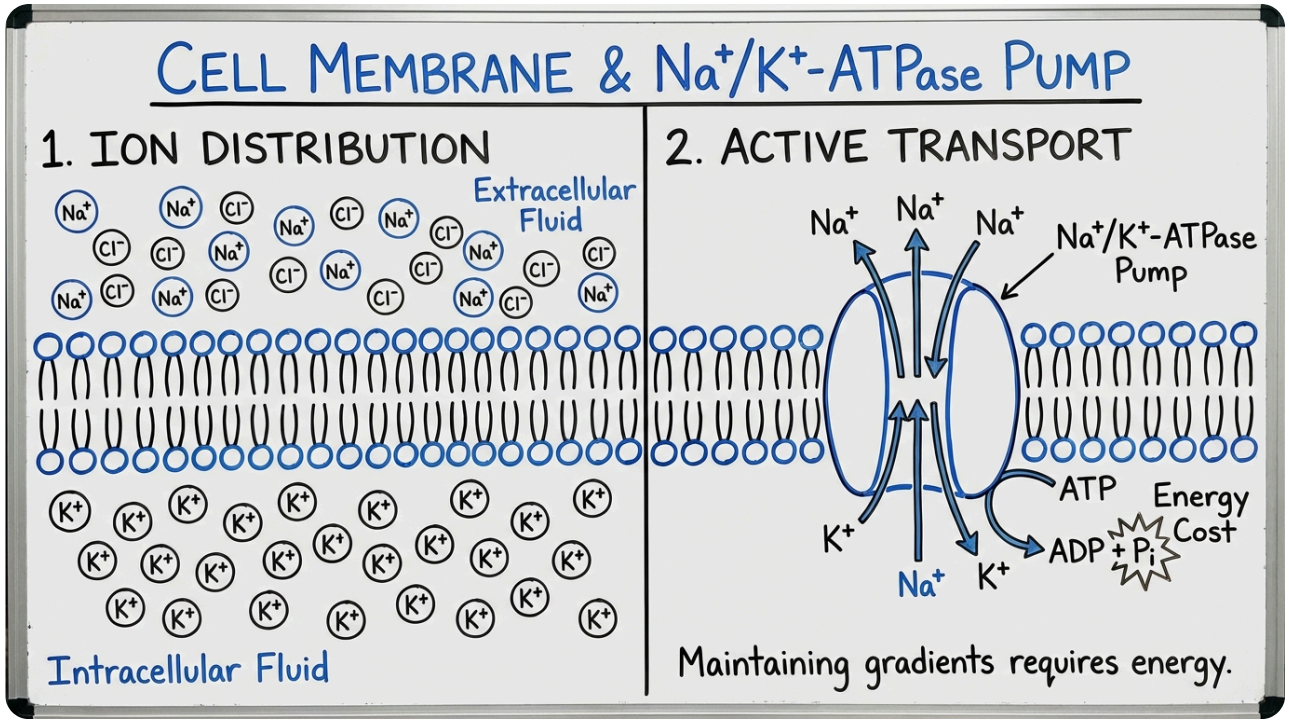


- Main Points:
- The resting membrane potential is the voltage differe across a neuron's membrane when it is not actively s
- This voltage typically measures around -70 mV, mea cell's inside is negative compared to its outside.
- It functions like a loaded battery, an energetic reserv allows for rapid electrical signaling.
- Ion distributions and the forces acting on them creat voltage difference.

Full Text

Today's journey: From the ion gradients that create the resting pc through the voltage-gated channels that generate action potentia cable properties that propagate signals along axons. We stop at t terminal—next class, we'll see what happens when electricity mee chemistry. The Resting Membrane Potential: A Battery Waiting to resting membrane potential is the voltage difference across the n membrane when the cell is not actively signaling—typically aroun (inside negative relative to outside). This isn't just a baseline; it's battery, an energetic reservoir that enables rapid electrical signal Understanding where this voltage comes from requires understan distributions and the forces that create them.

Ion Gradients

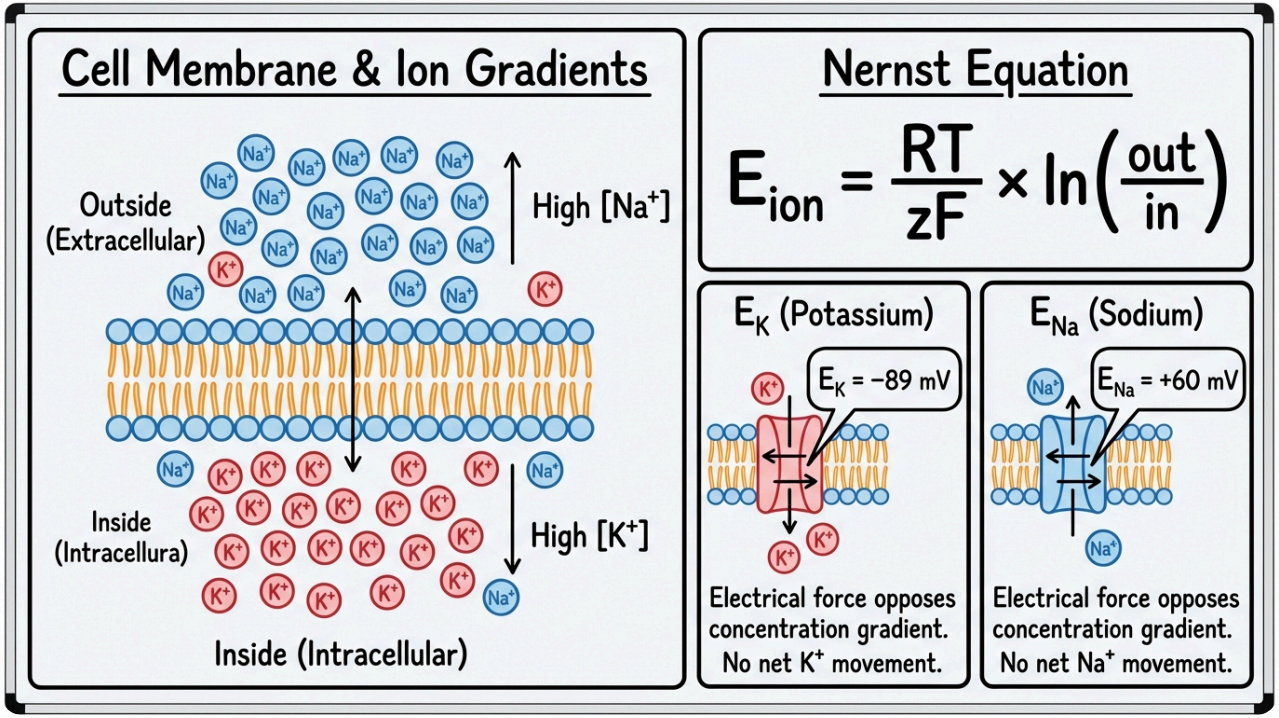


- Here are 5 main points from the text:
- Intracellular and extracellular fluids have very differe compositions.
- Potassium (K^+) is concentrated inside cells, while soc (Na^+) and chloride (Cl^-) are concentrated outside cel
- The Na^+/K^+-ATPase, a molecular pump, actively main these ion differences.
- This pump uses one ATP molecule to move 3 sodium of the cell and 2 potassium ions into the cell.
- The Na^+/K^+-ATPase consumes about 25% of all ATP i neurons, which is essential for electrical readiness.

Full Text

Ion Distributions: The Unequal Players - The intracellular and extr fluids have dramatically different ion compositions. Potassium (K^+ concentrated inside cells (~140 mM intracellular vs. ~5 mM extrac 28:1 ratio). Sodium (Na^+) shows the opposite pattern (~15 mM ins ~145 mM outside—a 1:10 ratio). Chloride (Cl^-) is concentrated out mM vs. ~10 mM inside). These gradients don't exist by accident— actively maintained by the Na^+/K^+-ATPase, a molecular pump that ATP molecule to export 3 Na^+ and import 2 K^+. This pump consum 25% of all ATP in neurons—the energetic price of electrical readir

Nernst Equilibrium Potentials

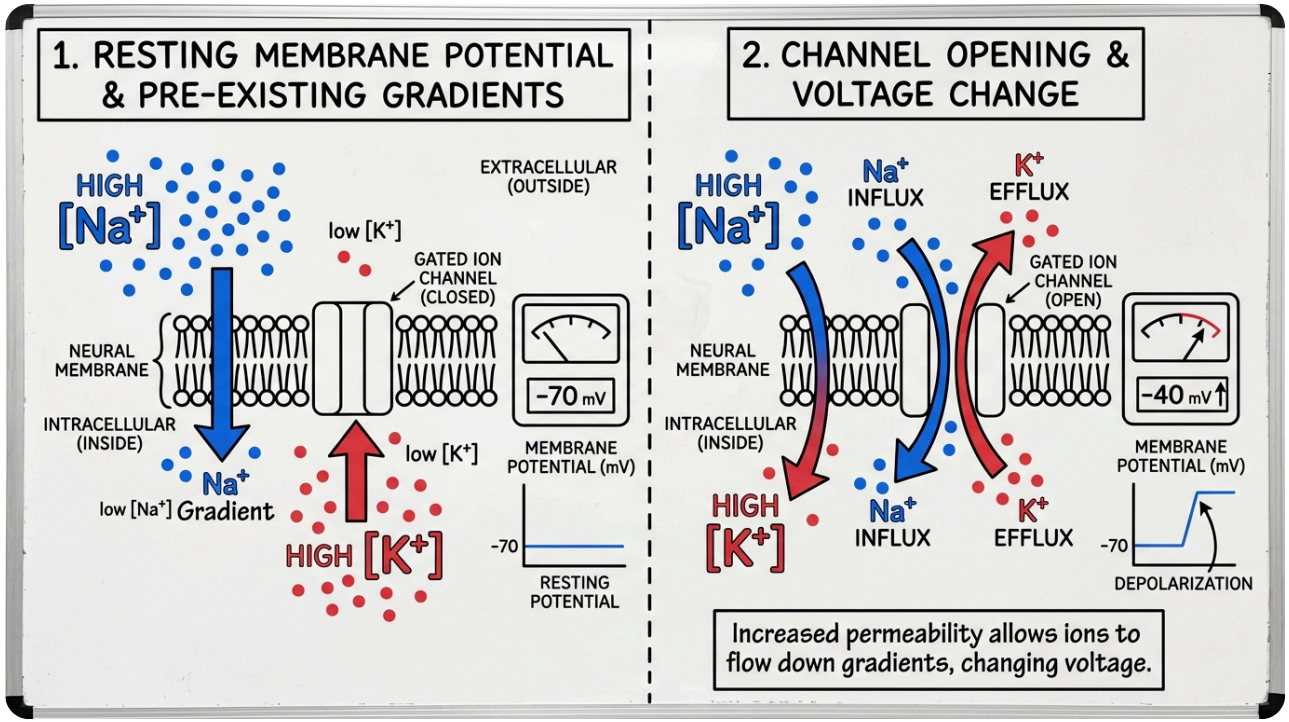


- Here are 4 main points from the text:
- Walther Nernst developed an equation to predict the voltage across a membrane permeable to only one ty ion.
- The Nernst equation calculates an "equilibrium poter each specific ion.
- The equilibrium potential is the voltage where an ion' electrical force perfectly balances its concentration g causing no net movement.
- For example, the Nernst equation predicts potassium equilibrium potential at -89 mV and sodium's at +60

Full Text

The Nernst Equation: Predicting Equilibrium Potentials - If a mem permeable only to potassium, what voltage would result? Walther answered this in 1889 with his equation: E_ion = (RT/zF) × ln(_out body temperature: E_ion = 61.5/z × $\log_{10}$(_out/_in) mV. For potass its 28:1 inside-to-outside ratio: E_K = 61.5 × log(5/140) = −89 mV sodium: E_Na = 61.5 × log(145/15) = +60 mV. These equilibrium p represent the voltage at which the electrical force on an ion exact balances its concentration gradient—no net flow occurs. -

Nernst Voltage Principle

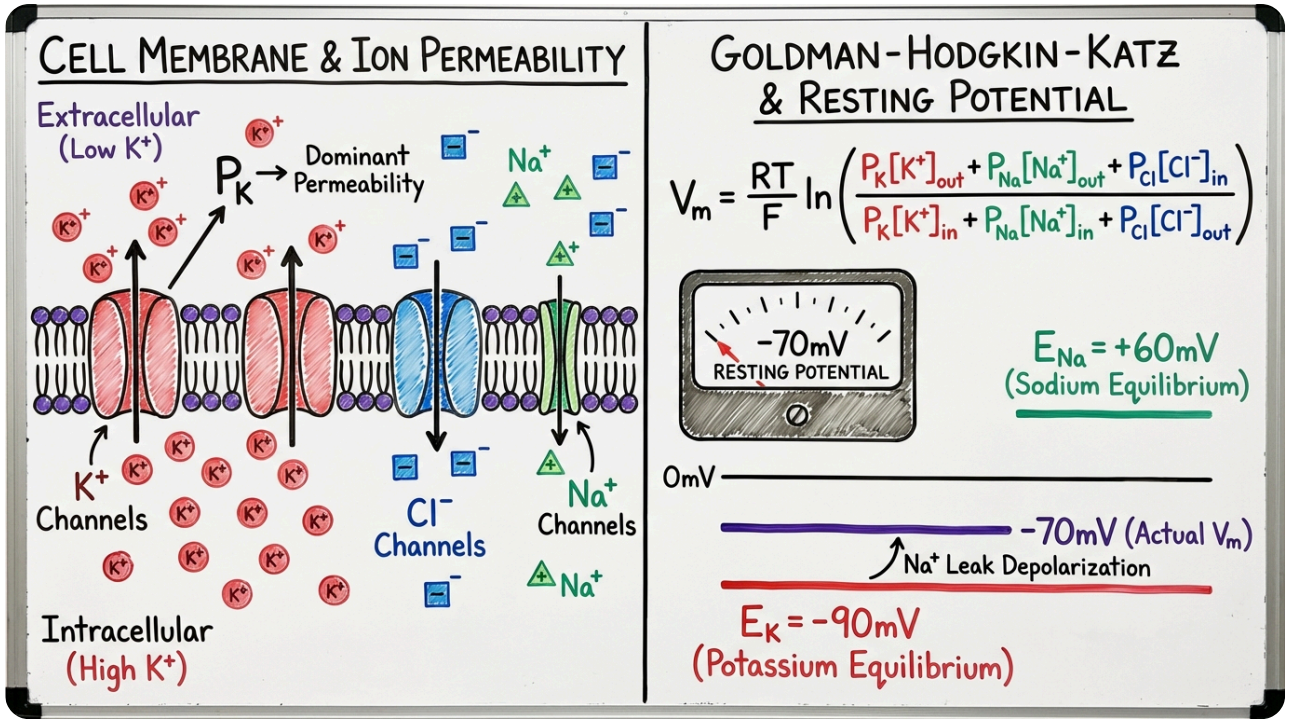


- Membrane voltage is determined by ion concentratio membrane permeability.
- Changing ion concentrations or membrane permeabi the voltage.
- Neurons change their membrane voltage during sign altering permeability.
- Neurons open and close channels to change membra permeability.
- Pre-existing ion gradients drive these voltage chang neurons.

Full Text

The Nernst equation reveals a profound truth: the voltage across membrane is determined by ion concentrations and membrane permeability. Change either, and you change the voltage. Neurons this principle continuously—they don't create new ions during sig they simply open and close channels that change permeability, al pre-existing gradients to drive voltage changes.

GHK Competing Ions

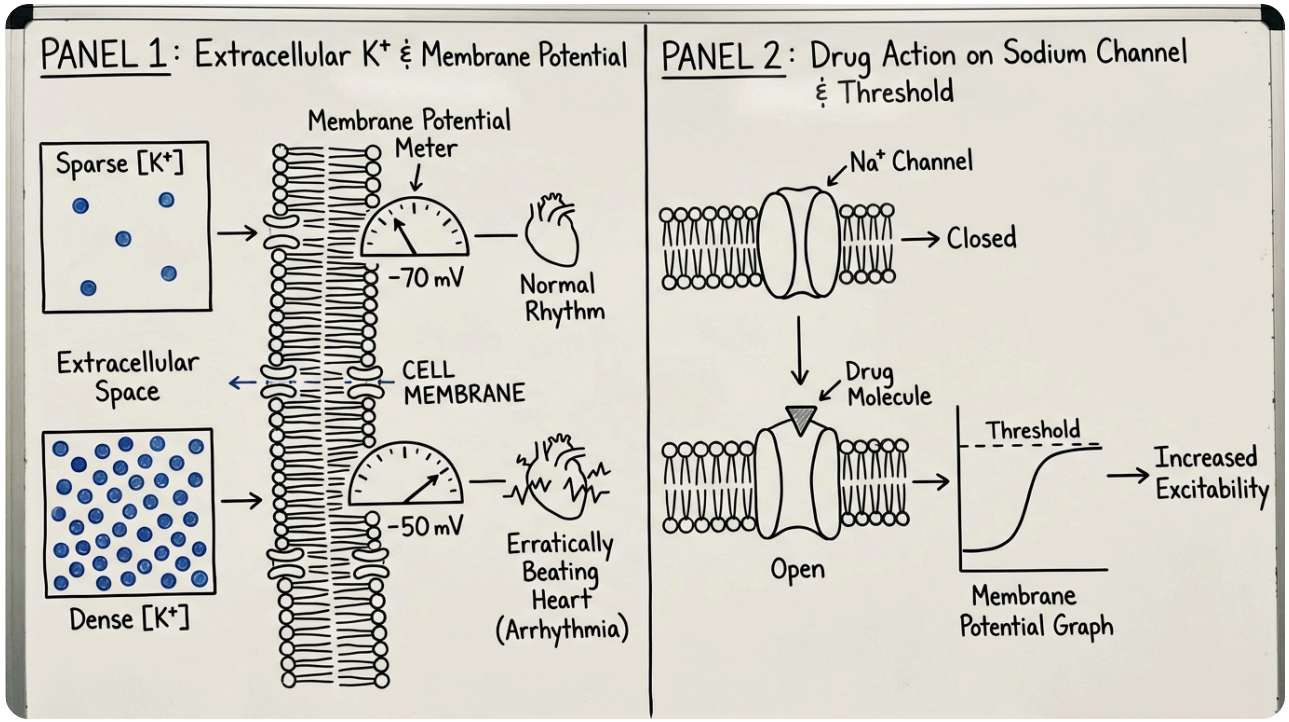


- Here are 3-5 main points from the text:
- Cell membranes allow several different ions to pass t them at once.
- The Goldman-Hodgkin-Katz (GHK) equation calculat membrane potential by considering the permeability multiple ions.
- At rest, cell membranes are most permeable to potas ions.
- High potassium permeability makes the resting mem potential (around -70 mV) very close to the potassiu equilibrium potential.
- Small sodium permeability slightly depolarizes the m making the resting potential a bit more positive than potassium equilibrium potential.

Full Text

The Goldman-Hodgkin-Katz Equation: Competing Ions - Real mer are permeable to multiple ions simultaneously. The Goldman-Hod (GHK) equation accounts for this by weighting each ion's contribu relative permeability: - V_m = 61.5 × log_out + P_Na_out + P_Cl_i (P_K_in + P_Na_in + P_Cl_out)] - At rest, P_K : P_Na : P_Cl ≈ 1 : 0. Because potassium permeability dominates, the resting potential sits much closer to E_K (−89 mV) than to E_Na (+60 mV). The sm permeability is why neurons rest at −70 mV rather than at the pot equilibrium potential—sodium's inward leak slightly depolarizes th membrane from where pure potassium selectivity would place it.

Resting Potential Modulation

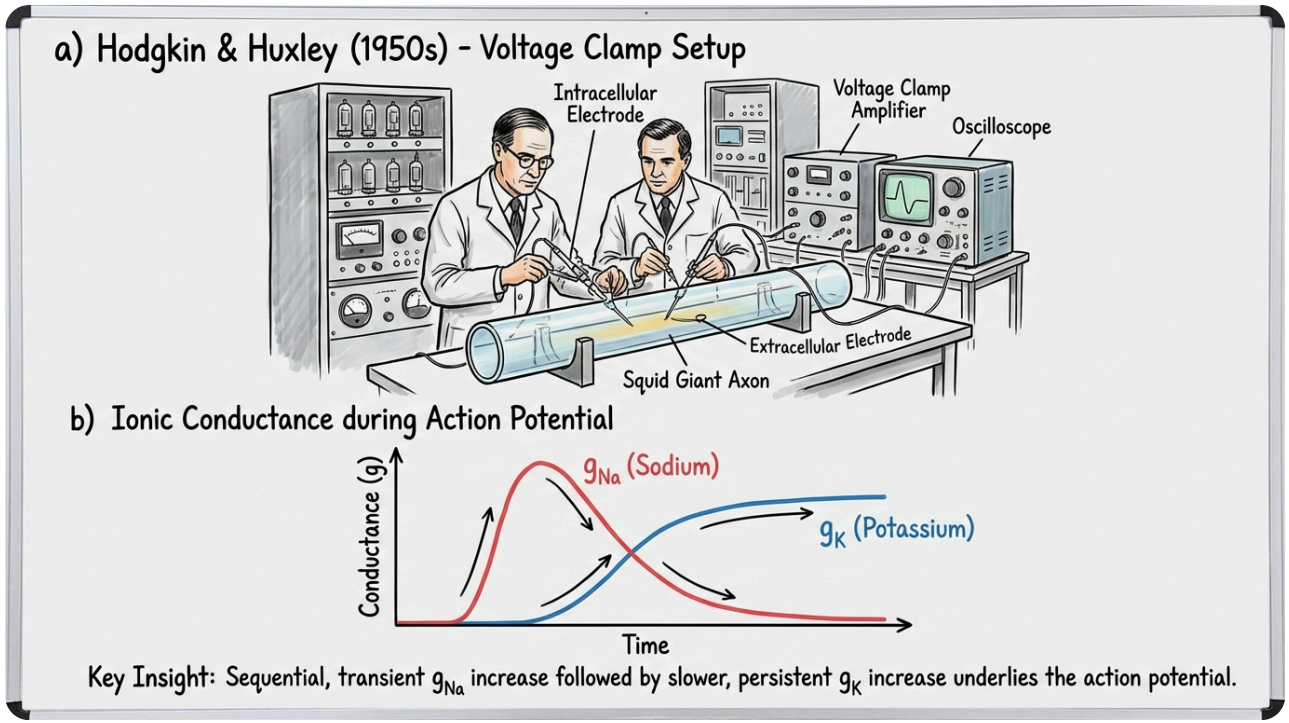


- Here are 4 main points from the text:
- The resting potential of a cell is flexible and can be a
- Changes in potassium levels outside cells directly aff resting potential.
- High blood potassium levels can cause problems wit rhythm.
- Drugs that change how easily sodium enters cells sh resting potential, making neurons more easily activat

Full Text

- This framework explains why the resting potential isn't fixed but modulated. Changing extracellular potassium concentration shifts therefore V_m—this is why hyperkalemia (high blood potassium) c cardiac arrhythmias and why dialysis patients must carefully mana potassium intake. Similarly, drugs that alter sodium permeability s resting potential toward E_Na, bringing neurons closer to thresho

Action Potential Ionics

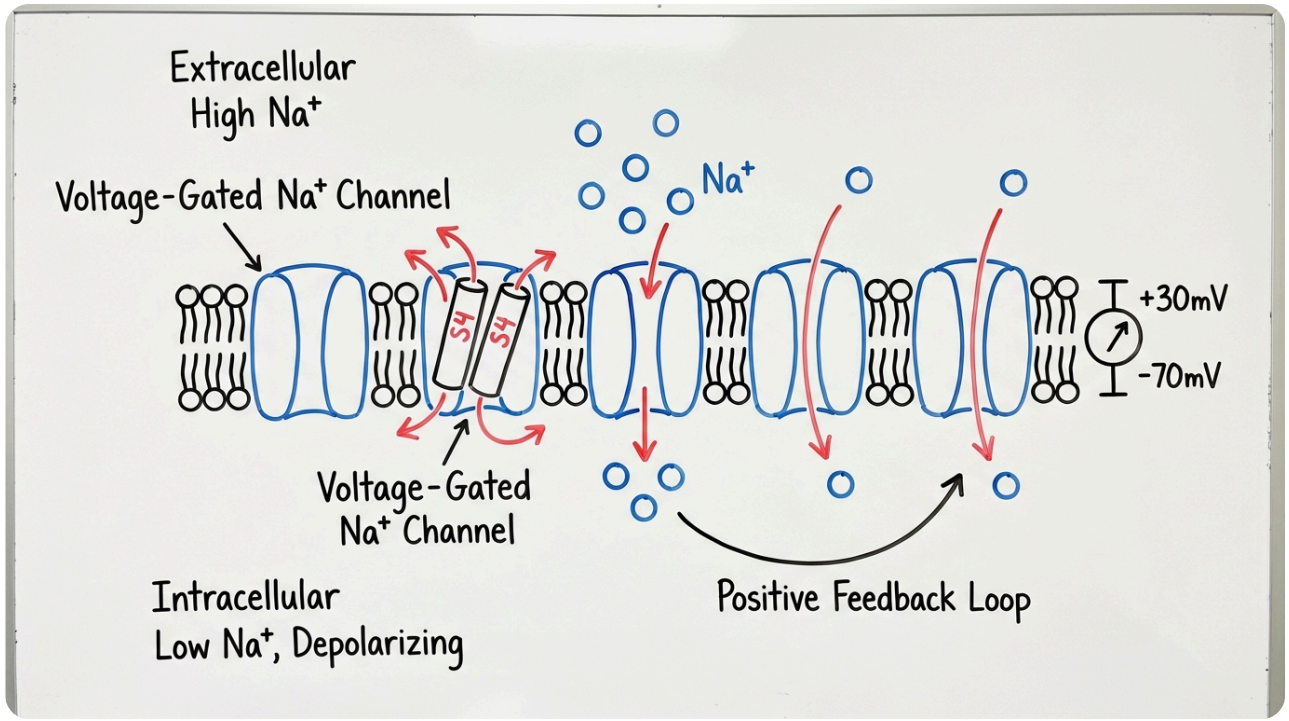


- Here are 3 main points from the text:
- Alan Hodgkin and Andrew Huxley explained how acti potentials work at an ionic level. They won the Nobel this important discovery.
- They used a squid giant axon and a voltage clamp te for their experiments. This method allowed them to r ionic currents across the membrane.
- During an action potential, sodium conductance incr quickly first. Potassium conductance then increases slowly and lasts longer.

Full Text

The Action Potential: Ionic Mechanisms - - In 1952, Alan Hodgkin Andrew Huxley published five papers that explained how action p work at the ionic level. They shared the 1963 Nobel Prize for this experiments done before anyone knew what an ion channel prote like. Hodgkin and Huxley used the squid giant axon (up to 1 mm d visible to the naked eye) and the voltage clamp technique to isola membrane conductance changed with voltage. By "clamping" the membrane at a fixed voltage, they could measure the ionic curren across the membrane without the complication of voltage change key insight: during an action potential, sodium conductance (g_N increases first and transiently, then potassium conductance (g_K more slowly and persistently.

Sodium Channel Activation

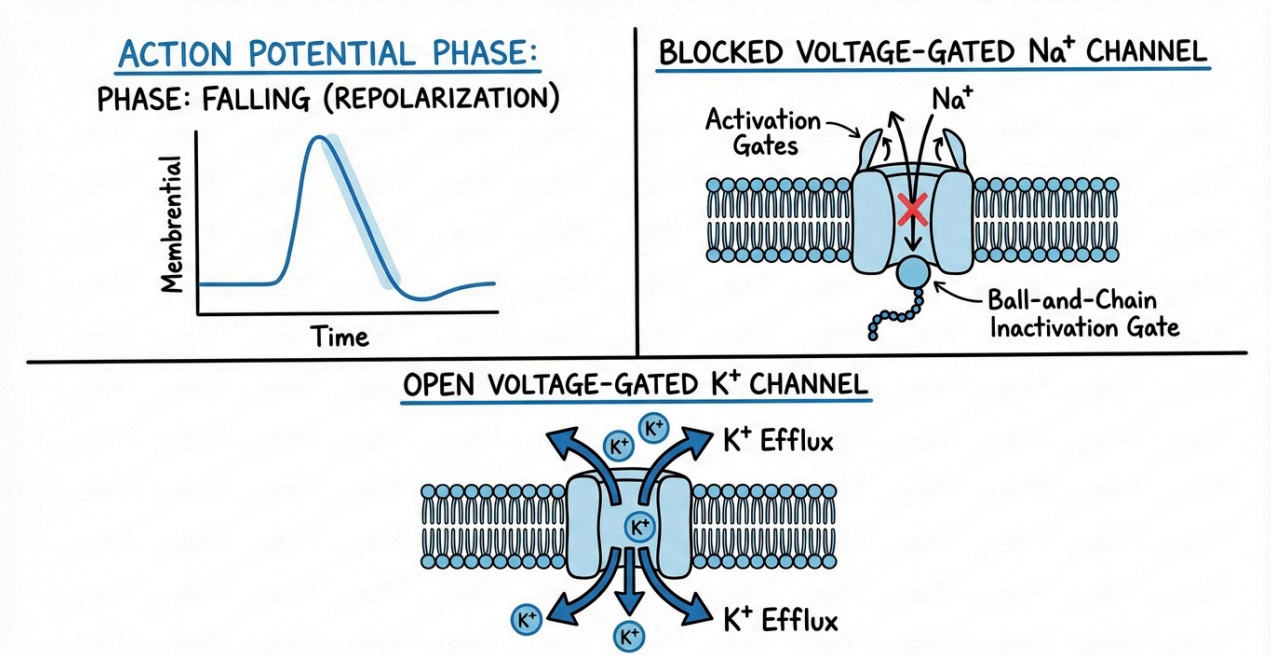


- Here are 3-5 main points from the text:
- Voltage-gated sodium channels open when the mem potential reaches a threshold of -55 mV.
- Sodium ions then rush into the cell, moved by differe concentration and electrical charge.
- The incoming sodium makes the membrane more po opens more sodium channels in a positive feedback
- The membrane potential quickly changes from -70 m about +40 mV.

Full Text

The Rising Phase: Sodium Channel Activation - When membrane reaches threshold (approximately –55 mV), voltage-gated sodium undergo a conformational change: their S4 voltage-sensing segm outward in response to depolarization, opening the channel pore. rushes in, driven by both its concentration gradient and the electr gradient—the membrane is negative inside, attracting positive Na influx further depolarizes the membrane, opening more sodium cl a positive feedback loop (the Hodgkin cycle). Within a fraction of millisecond, the membrane potential swings from –70 mV toward approaching E_Na (+60 mV) but never quite reaching it. -

Falling Phase Mechanisms



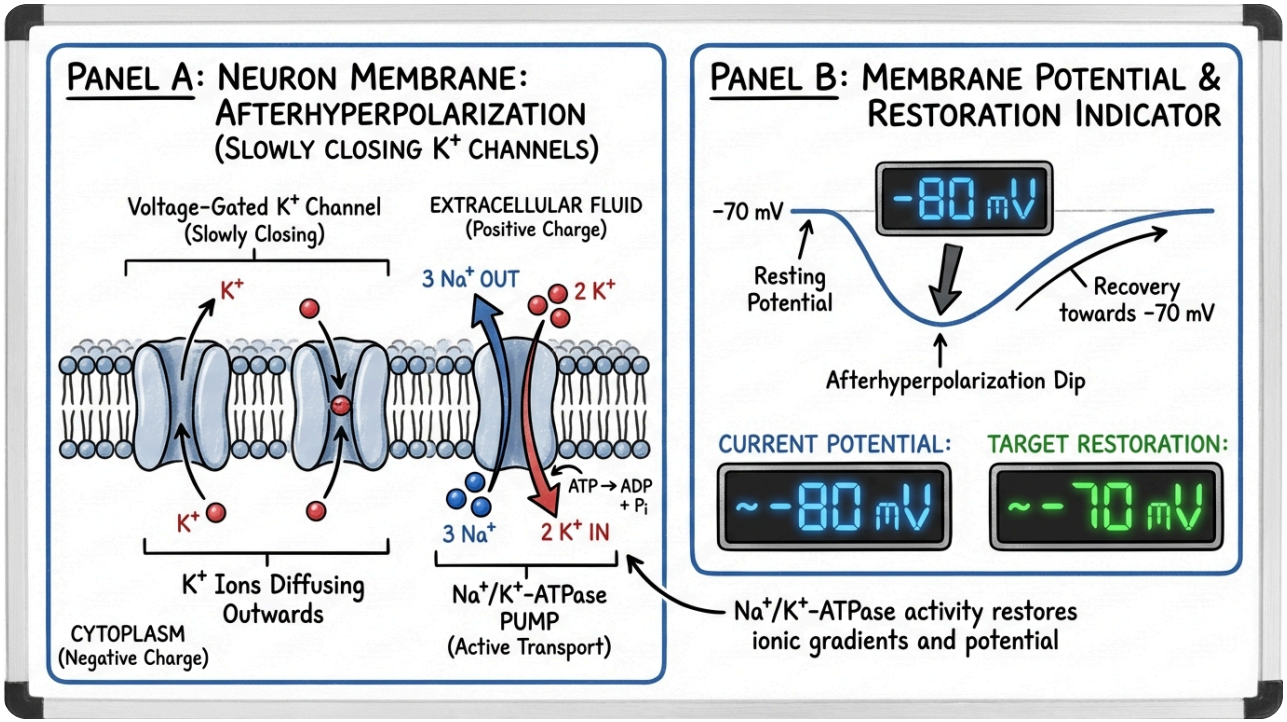
Clear textbook style whiteboard diagram with anatomically accurate physiology and animal images.

- Main Points:
- Sodium channels inactivate when a "ball-and-chain" blocks their pore. This stops more sodium from ente cell.
- Voltage-gated potassium channels open slowly durir phase.
- Potassium rushes out of the cell. Its high concentrati and the positive membrane potential drive this move
- This outflow of potassium repolarizes the cell membı helps the membrane return to its resting potential.

Full Text

The Falling Phase: Inactivation and Potassium Channels - Two me terminate the sodium influx. First, sodium channels inactivate: an intracellular "ball-and-chain" structure swings into the pore, bloc further sodium entry even though the activation gates remain ope inactivation is distinct from closing—the channel is open but bloc Second, voltage-gated potassium channels open more slowly (de rectifiers). Potassium rushes out, driven by both its concentration (high K^+ inside) and the now-positive membrane potential. This po efflux repolarizes the membrane back toward E_K.

Action Potential Recovery

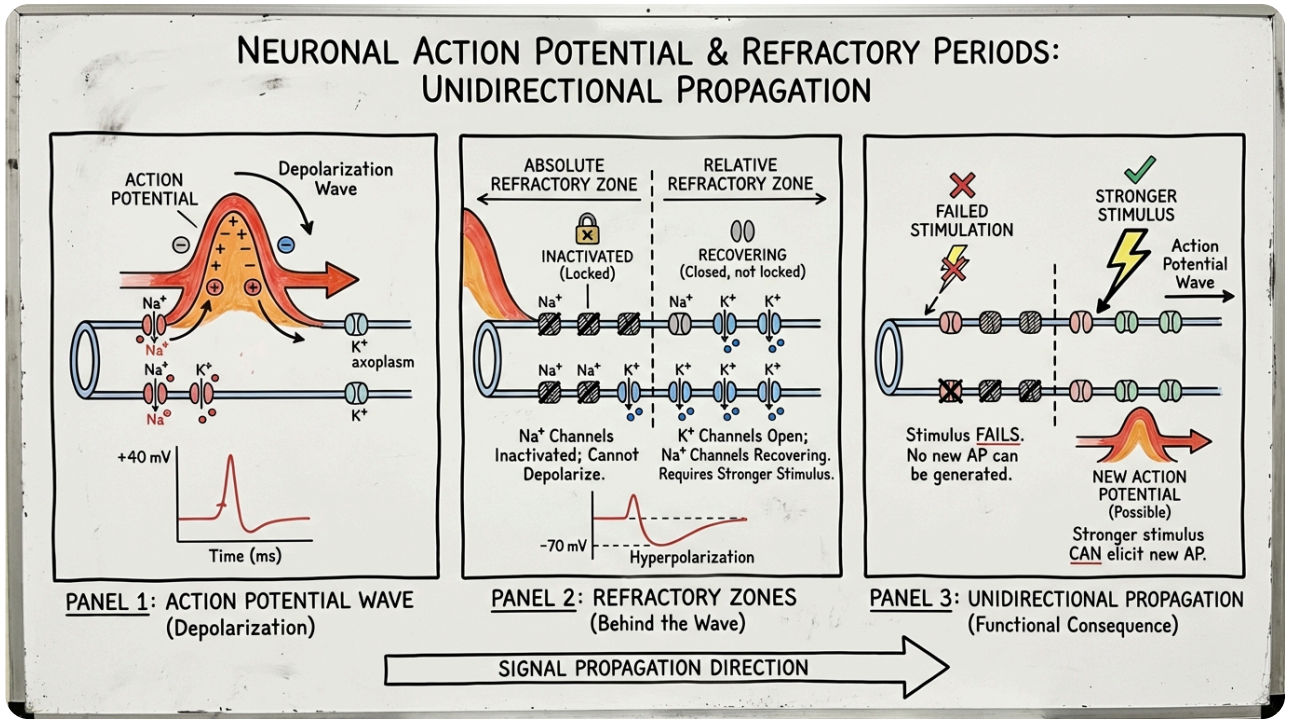


- Here are 3 main points from the text:
- Potassium channels close slowly, causing a brief afterhyperpolarization.
- During afterhyperpolarization, the membrane potenti below the resting level, to about -80 mV. It then retu normal resting potential of -70 mV.
- The Na⁺/K⁺-ATPase continuously restores ion gradier gradients are slightly depleted by each action potent

Full Text

The potassium channels close slowly, causing a brief afterhyperp where the membrane potential dips below the resting level (to approximately –80 mV) before returning to –70 mV as potassium permeability returns to baseline. Meanwhile, the Na⁺/K⁺-ATPase w continuously in the background, restoring the ion gradients slight depleted by each action potential. -

Refractory Period Functions

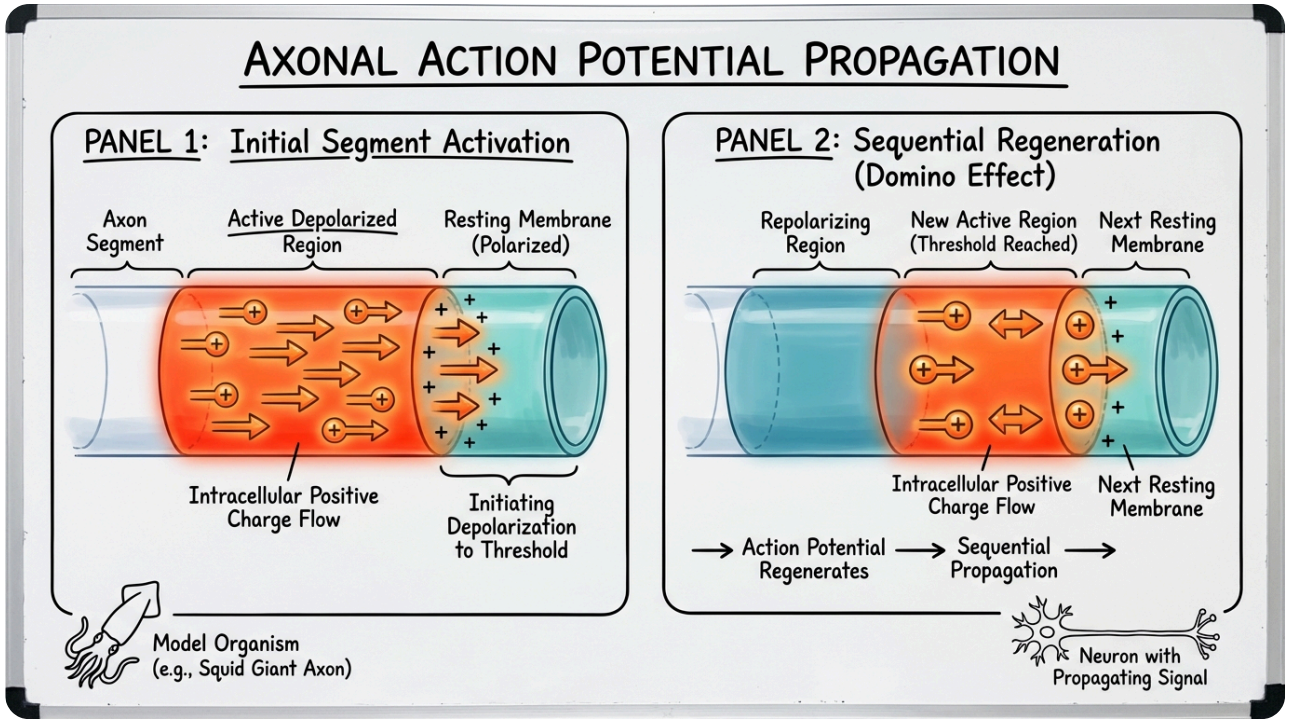


- Main Points:
- The absolute refractory period is a short time when r nerve signal can be triggered.
- During the relative refractory period, a stronger-than stimulus can trigger a new signal.
- Refractory periods control the maximum rate at whic signals can fire.
- They ensure nerve signals maintain a consistent 'all- nothing' strength.
- These periods make sure nerve signals travel in only direction along a neuron.

Full Text

Refractory Periods: Why Signals Travel One Way - The absolute re period (approximately 1 ms) occurs while sodium channels are ina no stimulus, however strong, can trigger another action potential. relative refractory period (several ms) follows, when some sodium have recovered but potassium channels remain open; a stronger- normal stimulus is required. These refractory periods serve crucia functions: they limit maximum firing frequency (typically 500-100 ensure all-or-nothing amplitude by allowing full channel recovery, enforce unidirectional propagation—the membrane behind an adv action potential is refractory and cannot be re-excited. -

Action Potential Propagation

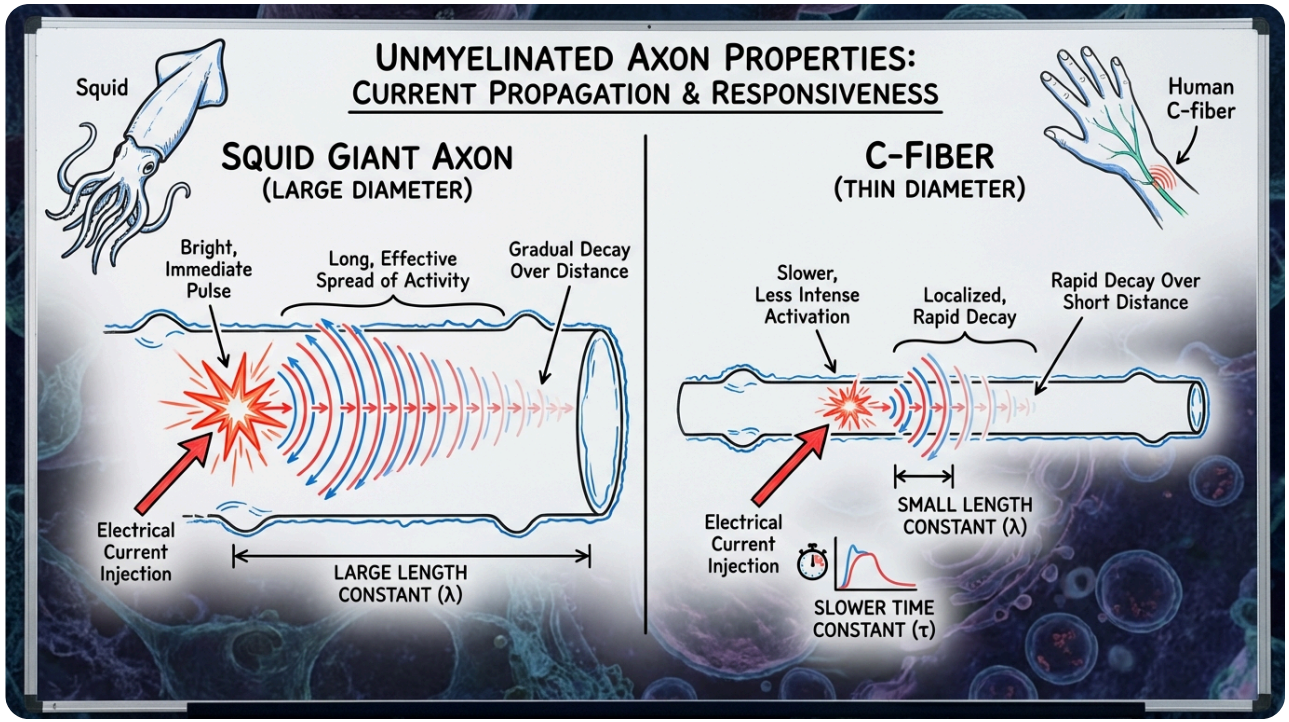


- Here are 3 main points:
- An action potential triggers other action potentials fu along an axon.
- Local circuit currents cause this propagation. A depo region acts as a current source, sending positive cha the adjacent membrane.
- The action potential regenerates itself sequentially a axon.

Full Text

Propagation of the Action Potential - - An action potential at one an axon must somehow trigger action potentials further along. Th propagation occurs through local circuit currents: the depolarized becomes a current source, and positive charges flow intracellular adjacent resting membrane, depolarizing it to threshold. The acti potential doesn't "travel"—it regenerates sequentially along the a line of dominoes falling.

Cable Length Constant

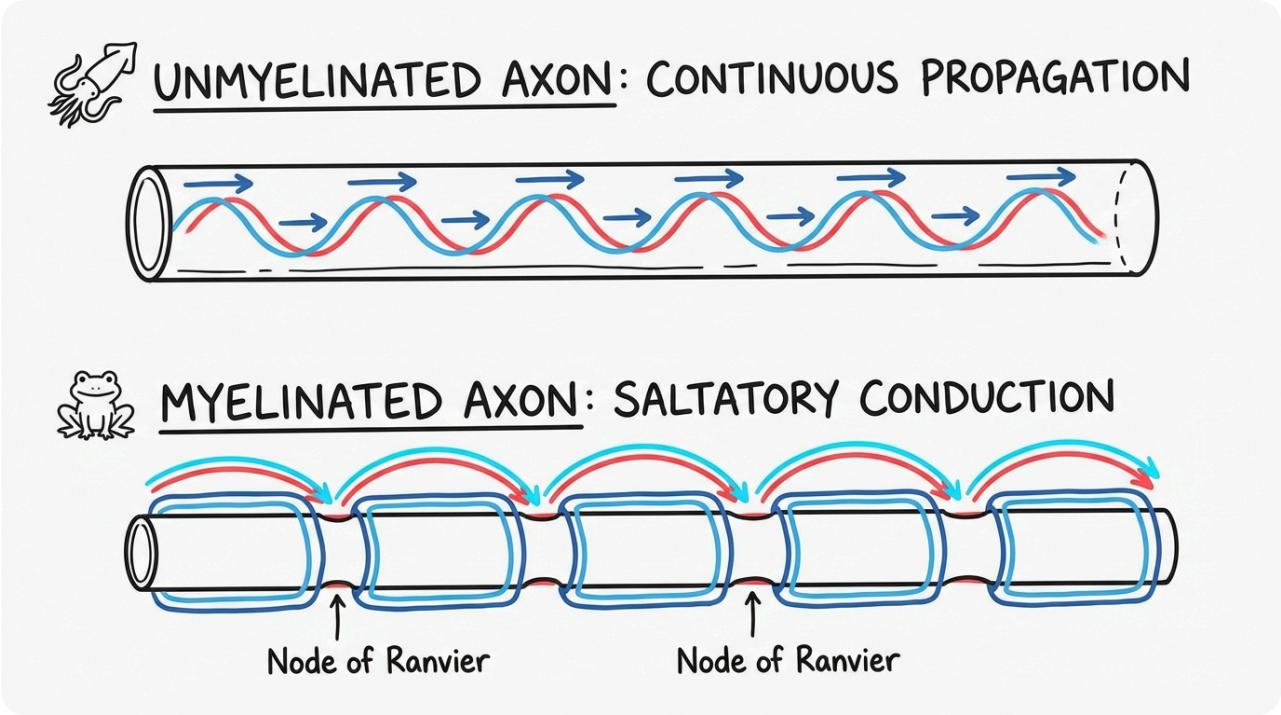


- Here are 4 main points from the text:
- The electrical properties of axons determine how eff local currents spread.
- The cable equation uses two main measurements, th constant and time constant, to describe this spread.
- The length constant shows how far an electrical sign along an axon before it gets much weaker. Larger dia axons have a bigger length constant, allowing signals spread farther.
- The time constant measures how quickly an axon's e charge responds to an incoming signal. A longer time constant means slower responses but helps the axon signals better.

Full Text

Cable Properties: Length and Time Constants - The passive elect properties of axons determine how effectively local currents spre cable equation describes this spread using two key parameters: - constant (λ) = √(r_m/r_i), where r_m is membrane resistance and internal resistance. This measures how far current spreads before to 37% of its original value—typically 0.1-1 mm in unmyelinated ax Larger diameter axons have lower r_i and therefore larger λ, whicl the squid giant axon (500 µm) conducts faster than your thin unm C-fibers (1 µm). - Time constant (τ) = r_m × c_m, where c_m is m capacitance. This measures how quickly the membrane potential to current injection—typically 1-20 ms. Longer time constants me responses but better temporal integration of inputs. -

Conduction Types

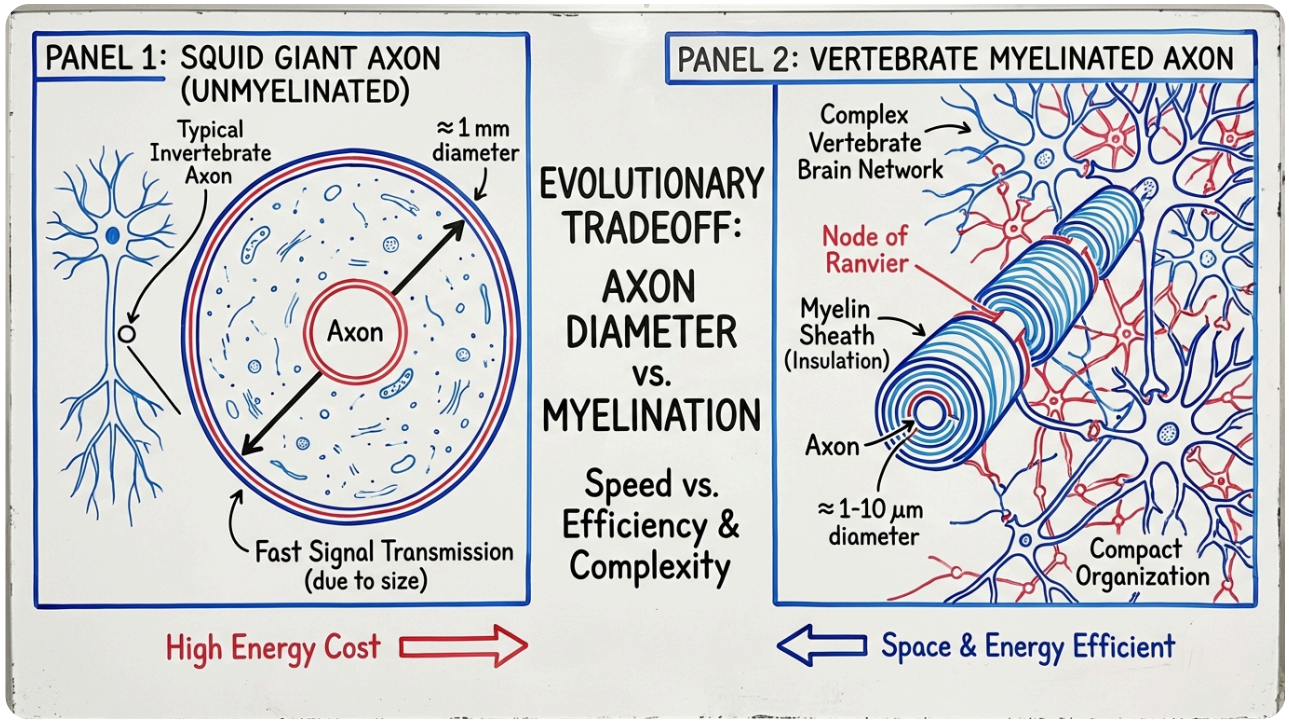


- Main Points:
- Unmyelinated axons conduct nerve signals continuou their entire length.
- Myelin sheaths, formed by specialized cells, wrap arc axons to help nerve signals travel further.
- In myelinated axons, nerve signals jump between unmyelinated gaps called nodes of Ranvier. This proc known as saltatory conduction.
- Saltatory conduction allows nerve signals to travel m faster and use significantly less energy than continuc conduction.

Full Text

Continuous vs. Saltatory Conduction - In unmyelinated axons, act potentials propagate continuously—each micrometer of membran depolarize and fire. Conduction velocity depends on axon diamet ∝ √diameter), reaching about 1 m/s for 1 µm fibers and 25 m/s for µm squid giant axon. - Myelination revolutionizes propagation. Oligodendrocytes (in the CNS) and Schwann cells (in the PNS) wr in multiple layers of lipid-rich membrane, increasing r_m 5000-fo decreasing c_m 50-fold. This massively increases the length cons current spreads much further before decaying. Action potentials at nodes of Ranvier, unmyelinated gaps where sodium channels c extraordinary density (1000-2000/µm²). Current "jumps" from no —saltatory conduction (from Latin saltare, "to jump")—achieving up to 120 m/s in 20 µm myelinated fibers while using 100× less er continuous conduction would require.

Axon Myelin Tradeoff

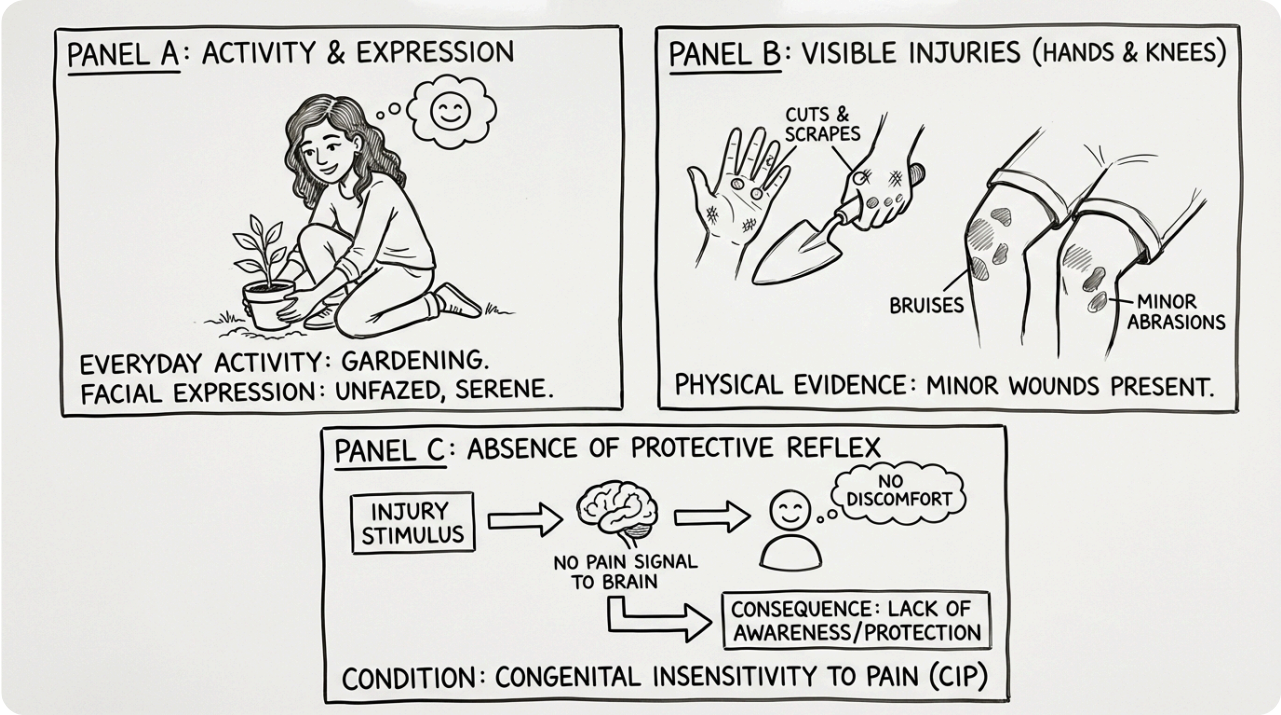


- Evolution offered two main ways to speed up nerve s changing axon diameter or developing myelination.
- Vertebrates evolved myelination, which allows them t complex brains within compact skulls.
- Invertebrates chose to use large-diameter axons to s nerve signals.
- For example, the squid has a giant axon that is 1 mm helps it perform escape responses.

Full Text

- Evolution faced a tradeoff: increase axon diameter (metabolicall expensive, takes up space) or evolve myelination (complex develo program, vulnerable to autoimmune attack). Vertebrates chose m enabling complex brains in compact skulls. Invertebrates chose la which is why the squid giant axon—used for escape responses—r mm diameter.

When Channels Fail

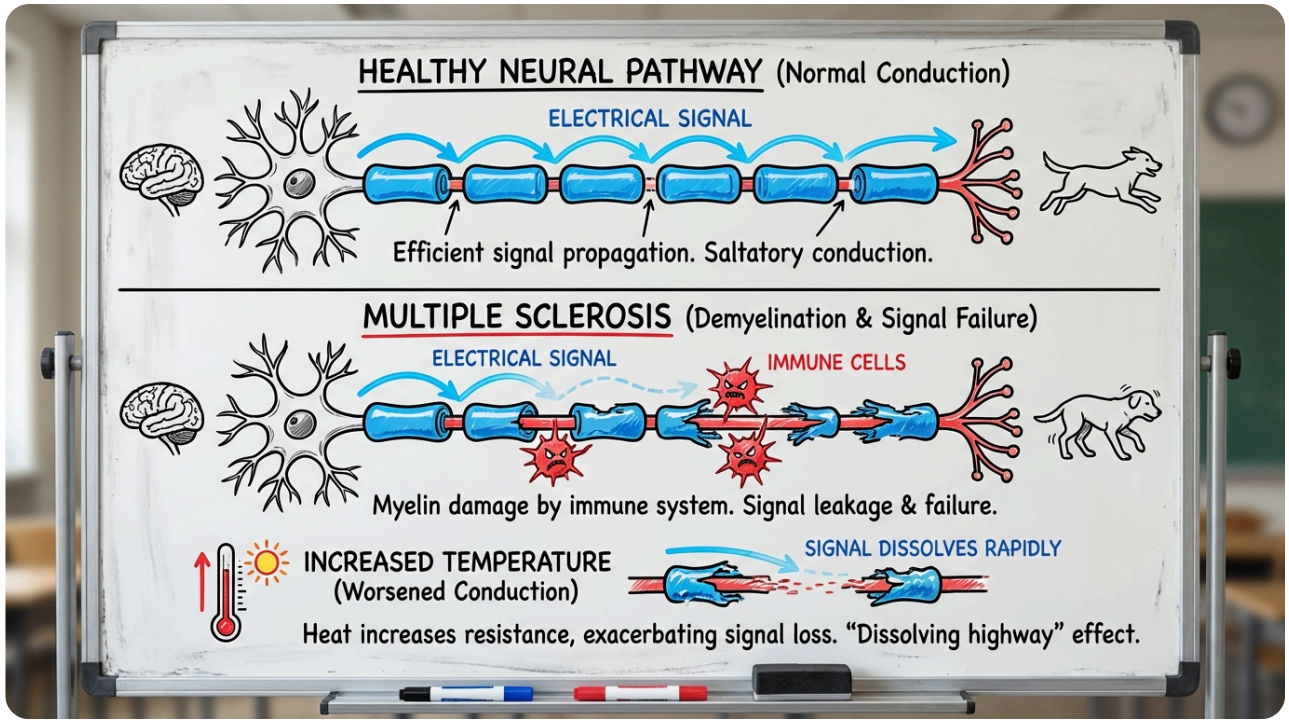


- Main Points:
- Channelopathies are diseases caused by mutations, changes, in ion channels.
- A specific gene mutation, like in SCN9A, can remove channels and stop people from feeling any pain.
- Without pain's protective warnings, individuals with t mutations often suffer repeated injuries.
- The opposite problem, too much activity in these cha causes severe burning pain from even mild warmth.

Full Text

Channel Diversity and Clinical Relevance - Channelopathies: Whe Channels Fail - - Channelopathies are diseases caused by ion cha mutations. In 2006, Cambridge researchers discovered a Pakistar where some members felt no pain whatsoever—mutations in SCN eliminated functional Nav1.7 sodium channels, specifically expres pain-sensing neurons. These individuals could feel touch, temper pressure, but never experienced pain. Tragically, without pain's p warnings, they suffered repeated injuries. The opposite mutation- hyperactivity—causes erythromelalgia, where patients experience pain from mild warmth.

MS Demyelination

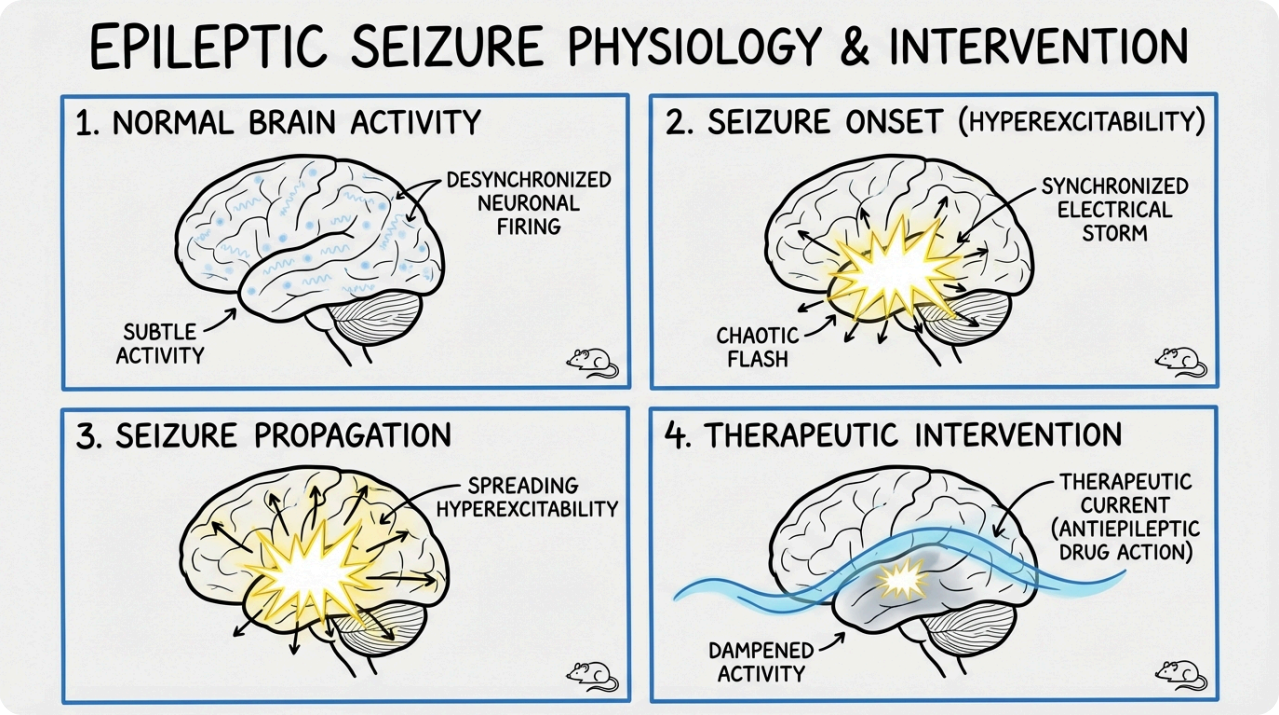


- Here are 4 main points from the text:
- Multiple sclerosis (MS) is an autoimmune disease wh immune cells attack myelin.
- As myelin degrades, nerve signals fail to transmit pro
- Patients experience progressive paralysis, sensory lo cognitive decline.
- MS symptoms often worsen in warmer temperatures

Full Text

Multiple Sclerosis and Demyelination - Multiple sclerosis is an aut disease where immune cells attack myelin. As myelin degrades, th constant shrinks—current no longer reaches the next node, and c fails. Patients experience progressive paralysis, sensory loss, and decline as white matter highways dissolve. The temperature sens MS symptoms (worsening with heat) reflects how membrane capa and channel kinetics change with temperature, further degrading marginal conduction. -

Brain Electrical Storms

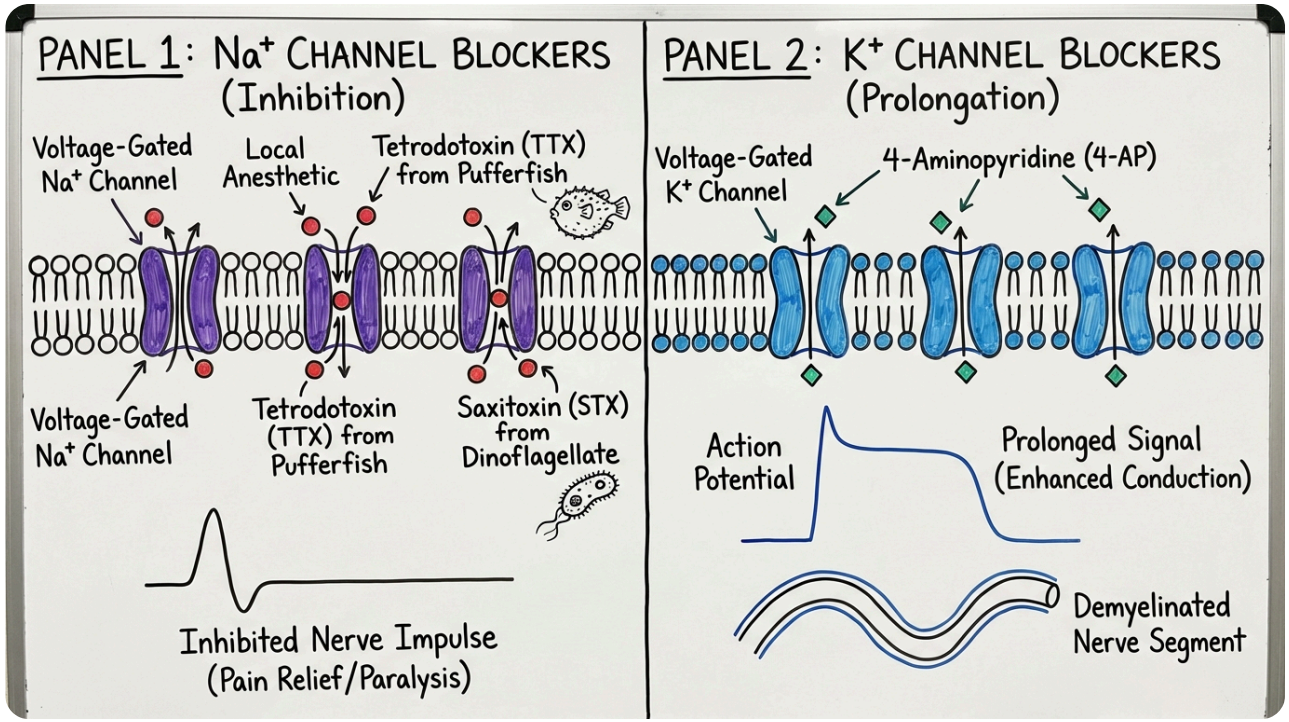


- Main Points:
- Epilepsy is an electrical problem within the brain's ne
- During a seizure, many brain cells fire at the same tir activity is abnormal for the brain.
- Epilepsy can happen when brain signals become unb This makes the brain's networks too active.
- Antiepileptic drugs work by calming brain activity. Th this by increasing inhibition or reducing nerve signals

Full Text

Epilepsy: Electrical Storms - Epilepsy represents network-level el failure. Dravet syndrome, caused by SCN1A mutations, illustrates exquisite balance required: the mutation affects inhibitory interne more than excitatory neurons, shifting the network toward hypere During seizures, millions of neurons fire synchronously—the oppo normal desynchronized activity. Antiepileptic drugs typically work enhancing inhibition (benzodiazepines enhance GABA receptors) reducing sodium channel activity (phenytoin, carbamazepine). -

Channel Pharmacology

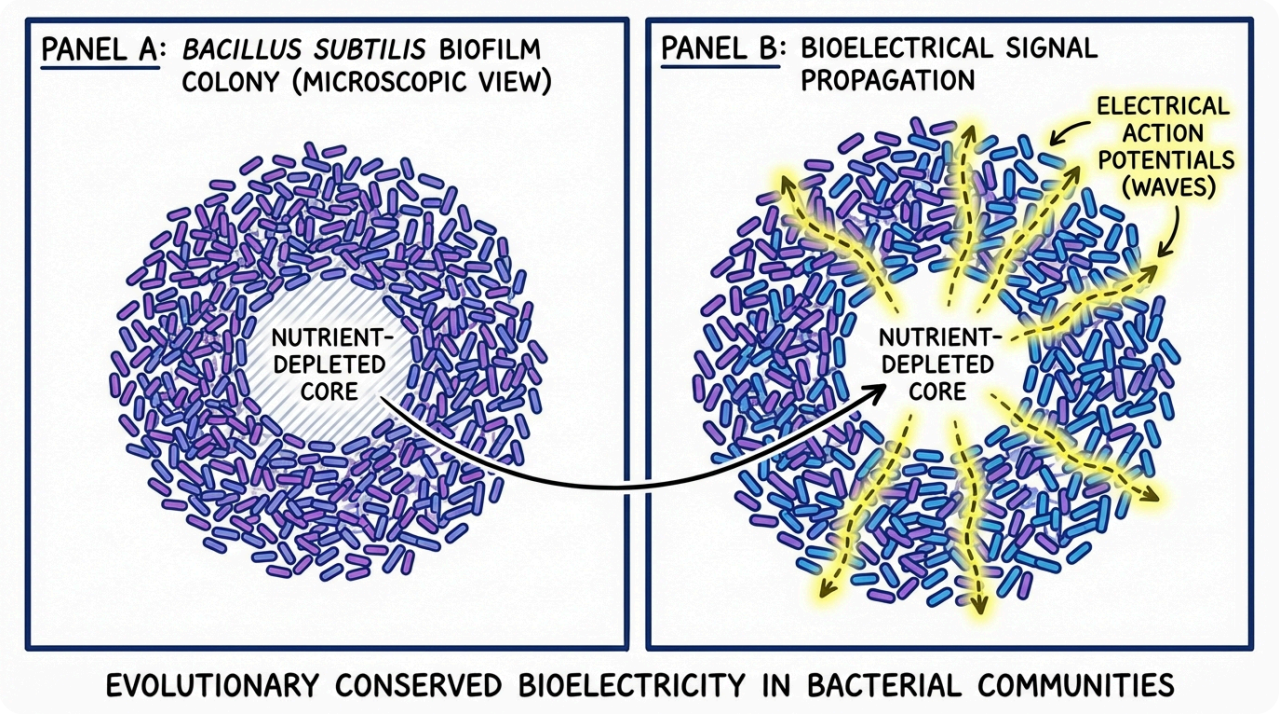


- Here are 4 main points from the text:
- Ion channels serve as key targets for many medicatio
- Local anesthetics like lidocaine block sodium channe prevent pain signals.
- Powerful natural toxins, such as tetrodotoxin, also bl sodium channels and can cause paralysis or death.
- Some drugs block potassium channels, which can he improve nerve signaling in conditions like multiple sc

Full Text

Channel Pharmacology - Ion channels are major drug targets. Loc anesthetics (lidocaine, novocaine) block voltage-gated sodium ch preventing action potentials in pain fibers. Tetrodotoxin (from puf and saxitoxin (from dinoflagellates) are exquisitely potent sodium blockers—nanomolar concentrations cause paralysis and death. T (tetraethylammonium) and 4-aminopyridine block potassium char prolonging action potentials—4-AP is used therapeutically in mult sclerosis to enhance conduction through demyelinated segments

Ancient Bioelectricity

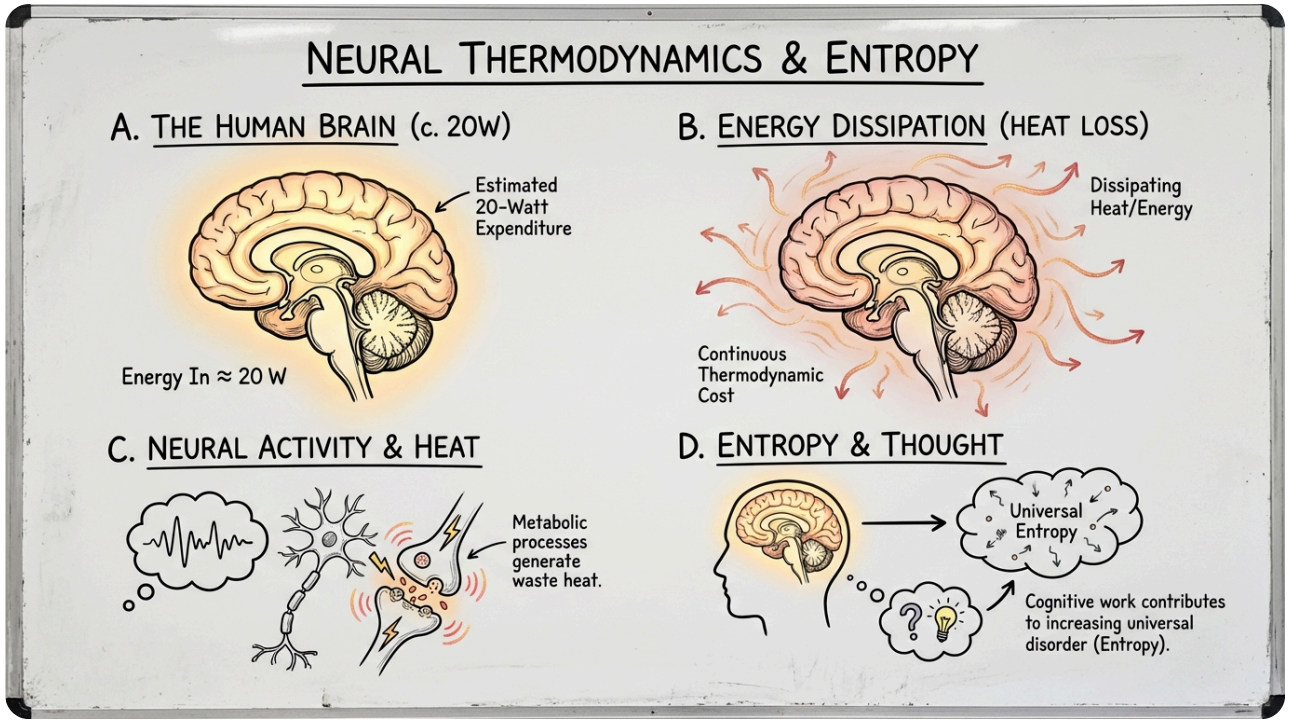


- Main Points:
- Electrical signaling in life began billions of years ago.
- Specific bacteria, like Bacillus subtilis, create electric called action potentials.
- Bacteria use potassium channels and electrical signa methods similar to humans.
- Bacteria use these electrical signals to coordinate th colony's behavior, especially when food is scarce.

Full Text

Evolutionary Origins: The Ancient Voltage of Life - - Electrical sig ancient. Gürol Süel's lab discovered that Bacillus subtilis bacteria action potentials using potassium channels structurally similar to When nutrients run low in a biofilm's center, bacteria fire electrica that propagate outward, coordinating colony behavior. These bac channels follow Hodgkin-Huxley dynamics—the same equations g bacterial and human electrical signaling. The molecular machiner bioelectricity evolved once, billions of years ago, and has been co ever since.

Thought Energy Cost

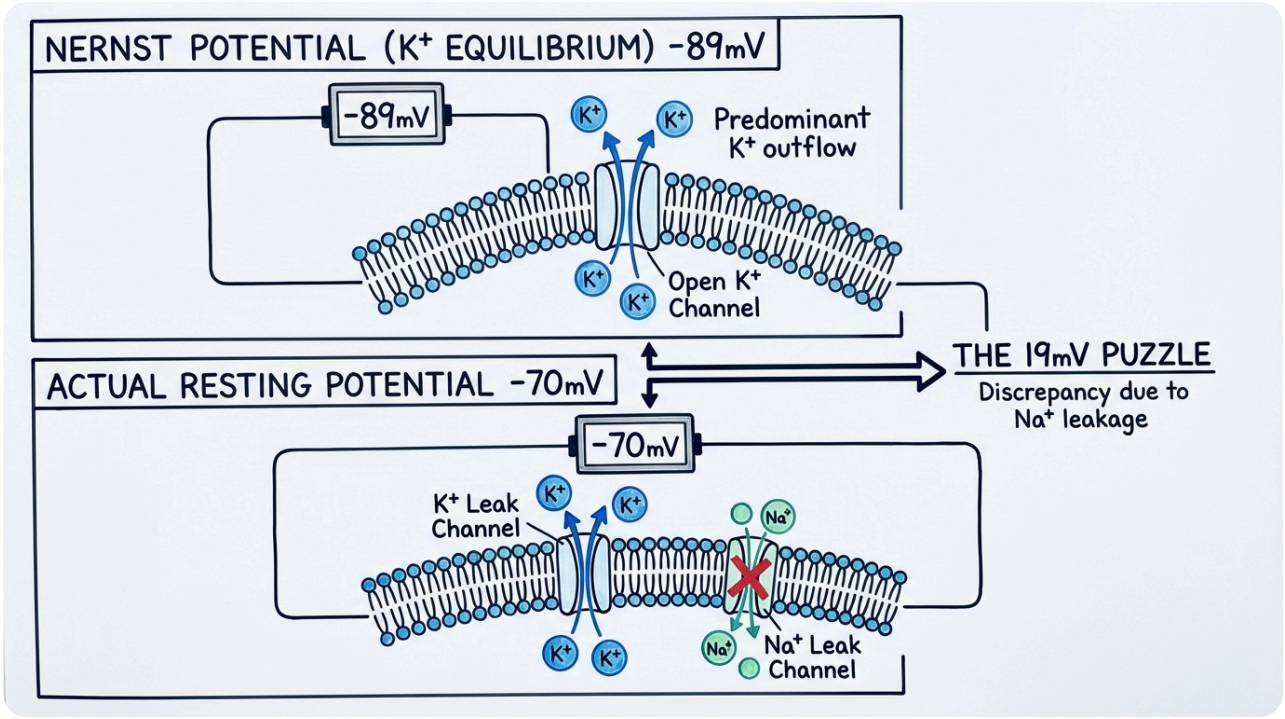


- Here are 4 main points from the text:
- Half of the brain's energy is used to reset ion movem after nerve signals.
- The brain uses about 20 watts of power, similar to a bulb.
- The brain, though only 2% of body weight, uses 20% body's oxygen and glucose.
- Every thought consumes energy and contributes to u entropy.

Full Text

The Thermodynamic Cost of Thought - David Attwell and Simon L calculated that 50% of the brain's energy budget goes to reversir movements from action potentials and synaptic transmission. You consumes 20 watts—enough to power a dim light bulb—with 86 b neurons, each firing action potentials that cost hundreds of millio molecules. This is why your brain, just 2% of body weight, uses 2 oxygen and glucose. The price of consciousness is thermodynam thought increases universal entropy. -

Resting Potential Factors

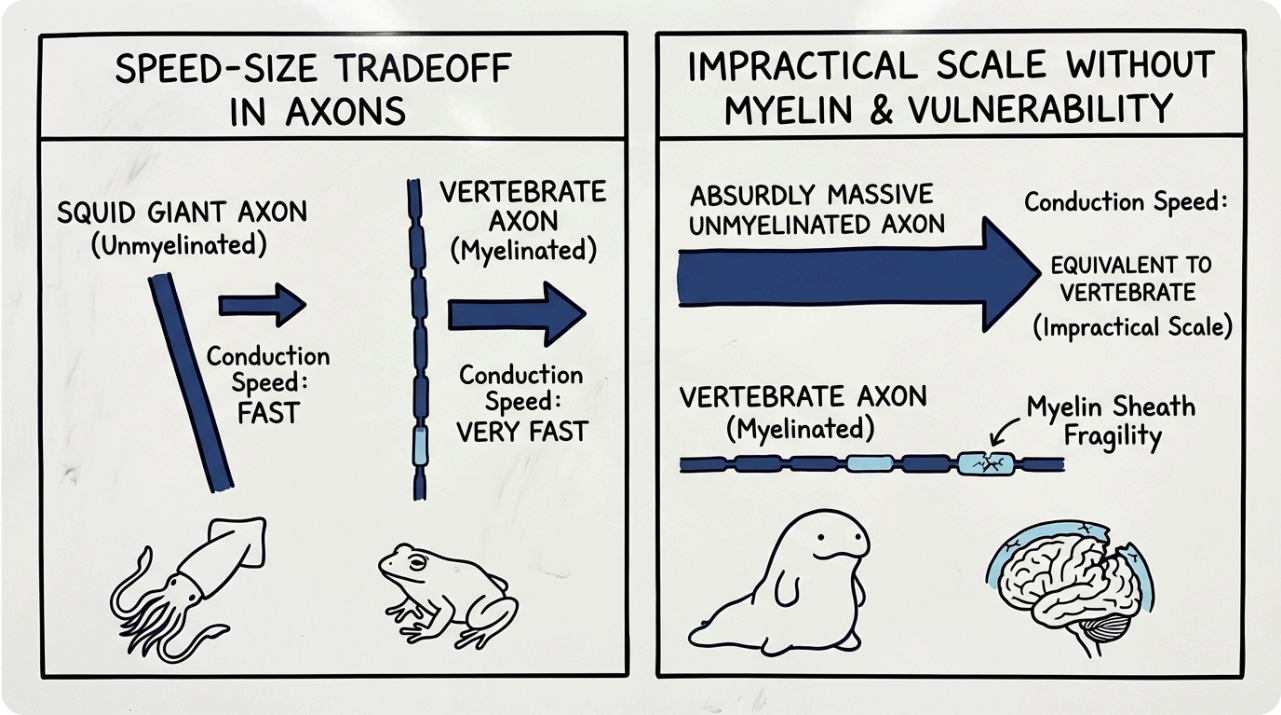


- The Nernst equation predicts potassium's equilibriur potential at -89 mV.
- However, neurons actually rest at a different potentia typically -70 mV.
- Sodium channels influence a neuron's resting potent excitability.

Full Text

Thought Questions for Discussion - Three questions to spark disc before your next class: - The Nernst vs. Reality Puzzle: The Nerns predicts E_K = −89 mV for potassium, yet neurons rest at −70 mV 19 mV difference? Consider what happens if you experimentally b sodium channels—does the resting potential shift toward E_K? W this tell you about the molecular basis of the resting potential, an might pharmacological manipulation of sodium leak channels affe neuronal excitability?

Speed Size Tradeoff



- Here are 4 main points from the text:
- Evolution developed two main ways for nerves to ser signals: very large axons or myelinated axons.
- Myelination lets vertebrates have small nerve fibers t signals very quickly, unlike giant, unmyelinated axons
- Myelination significantly increases nerve signal spee allowed complex nervous systems to develop in verte
- Despite its benefits, myelin is fragile and can be atta serious diseases such as multiple sclerosis.

Full Text

The Speed-Size Tradeoff: Evolution produced two solutions for fa conduction: giant axons (squid) and myelinated axons (vertebrate squid giant axon is 500 µm diameter and conducts at 25 m/s. You myelinated motor neurons are 20 µm diameter and conduct at 12(Calculate how large an unmyelinated axon would need to be to co 120 m/s. (Hint: velocity scales with √diameter for unmyelinated ax was this solution not viable for vertebrate nervous systems? The Vulnerability Question: Myelination increases conduction velocity and appeared 425 million years ago, enabling complex vertebrate systems. Yet myelin is uniquely vulnerable—multiple sclerosis, Gu Barré syndrome, and leukodystrophies all attack it. Why didn't ev produce a more robust insulation? What does myelin's vulnerabili about biological tradeoffs between performance and resilience?