511-2018-09-21-neurophys-II

Rick Gilmore

Ease on down, ease on down

Propagation is the way…

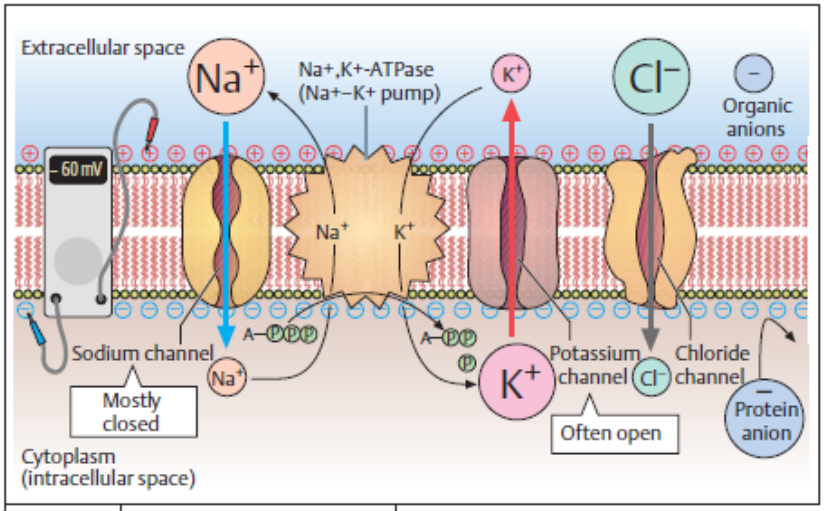
Today's Topics

- Equilibrium potential and driving forces
- The action potential
- Synaptic communication

Party On

- Annie (A-) was having a party.
  - Used to date Nate (Na^+), but now sees Karl (K^+)
- Hired bouncers called
  - "The Channels"
  - Let Karl and friends in or out, keep Nate out
- Annie's friends (A-) and Karl's (K^+) mostly inside
- Nate and friends (Na^+) mostly outside
- Claudia (Cl-) tagging along

Party On



Ion	Concentration	
	Cytoplasm (mM)	Extracellular space (mM)
K^+	139	4
Na^+	12	145
Cl^-	4	116
Organic anions	138	134

Fig. 1.13 **Membrane potential of a cell.** (After Koolman and Röhm)

The K^+ story

- Na^+/K^+ pump pulls K^+ **in**
- $[K^+]_{in}$ (~150 mM) >> $[K^+]_{out}$ (~4 mM)
- Outward flow of K^+ through passive/leak channels
- Outflow stops when , V_m = for K^+

Equilibrium potential

- Voltage (V_K) that keeps system in equilibrium
  - $[K^+]_{in}$ >> $[K^+]_{out}$
- Nernst equation
  - $V_K = \frac{RT}{(+1)F} ln(\frac{[K^+]_{out}}{[K^+]_{in}})$
  - V_K = ~ -90 mV
  - Negative in/positive out keeps in/out concentration gradient

Equilibrium potential

- K^+ flows out through passive/leak channels; most remains near membrane
- Separation from A^- creates charge $\frac{K+K+K+K+K+}{A-A-A-A-A-}$ along capacitor-like membrane
- V_m –> V_K

Equilibrium potentials calculated under typical conditions

Ion	[inside]	[outside]	Voltage
K^+	~150 mM	~4 mM	~ -90 mV
Na^+	~10 mM	~140 mM	~ +55-60 mV
Cl-	~10 mM	~110 mM	~ - 65-80 mV

$$V_{\mathrm{K}} = \frac{RT}{(+1)F} \ln \frac{[\mathrm{K}^+]_o}{[\mathrm{K}^+]_i}$$

The Na^+ story

- Na^+/K^+ pump pushes Na^+ **out**
- $[Na^+]_{in}$ (~10 mM) << $[Na^+]_{out}$ (~140 mM)
- Equilibrium potential for Na^+, V_{Na} = ~ +55 mV
  - Inside positive/outside negative to maintain outside > inside concentration gradient
- If Na^+ alone, V_m –> V_{Na} (~ +55 mV)

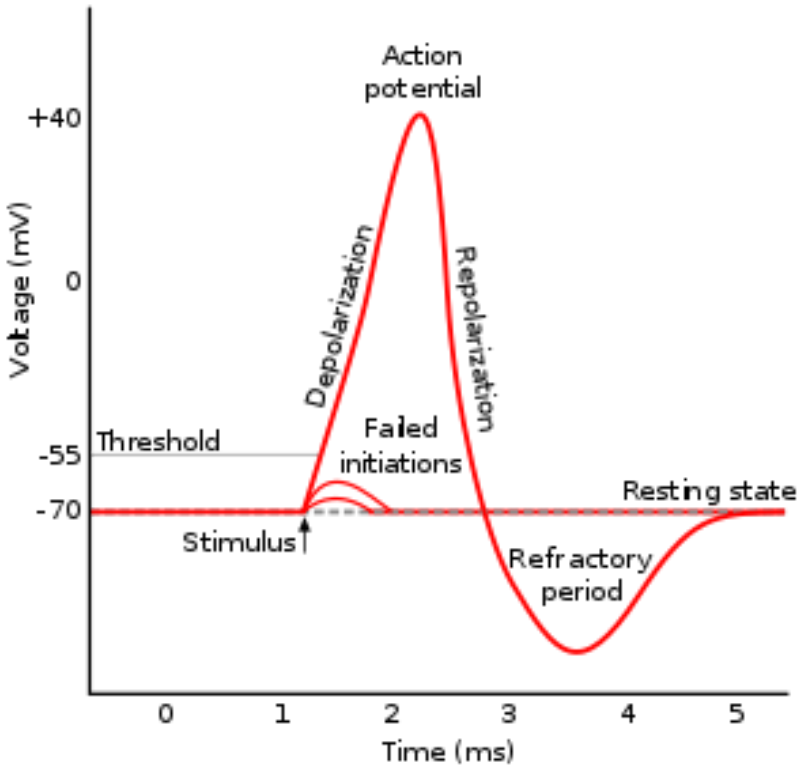
"Resting" potential

- Sum of outward K^+ and inward Na^+
  - Membrane more permeable to K^+ than Na^+, p_{K+}>p_{Na+}$
  - Outward flow of K^+ > inward flow of Na^+
  - Resting potential (~-70 mV) closer to V_K (-90 mV) than V_{Na} (+55 mV)
- Goldman-Hodgkin-Katz equation
  - $V_m = \frac{RT}{F} ln(\frac{p_{K+}[K^+]_{out} + p_{Na+}[Na^+]_{out}}{p_{K+}[K^+]_{in} + p_{Na+}[Na^+]_{in}})$

"Driving force" and equilibrium potential

- "Driving Force" on a given ion depends on difference between
  - Equilibrium potential for given ion
  - Membrane potential = effects of all ions
- Anthropomorphic metaphor
  - K^+ "wants" to flow out (pull neuron toward V_K)
  - Na^+ "wants" to flow in (pull neuron toward V_{Na})
  - Strength of that "desire" depends on distance from equilibrium potential

Action potential



https://upload.wikimedia.org/wikipedia/commons/thumb/4/4a/Action_potential.svg/300px-Action_potential.svg.png

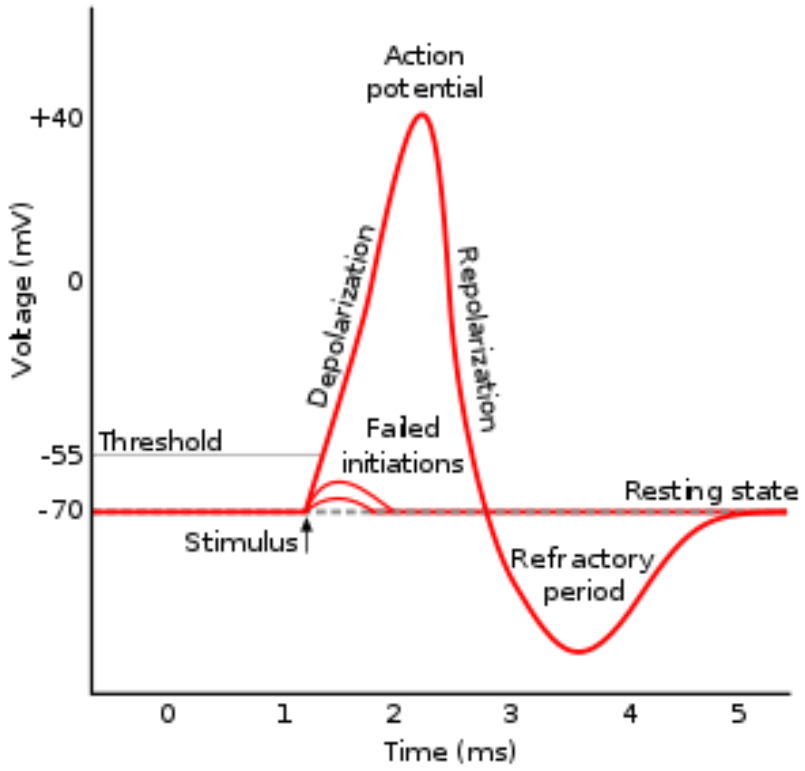
Action potential

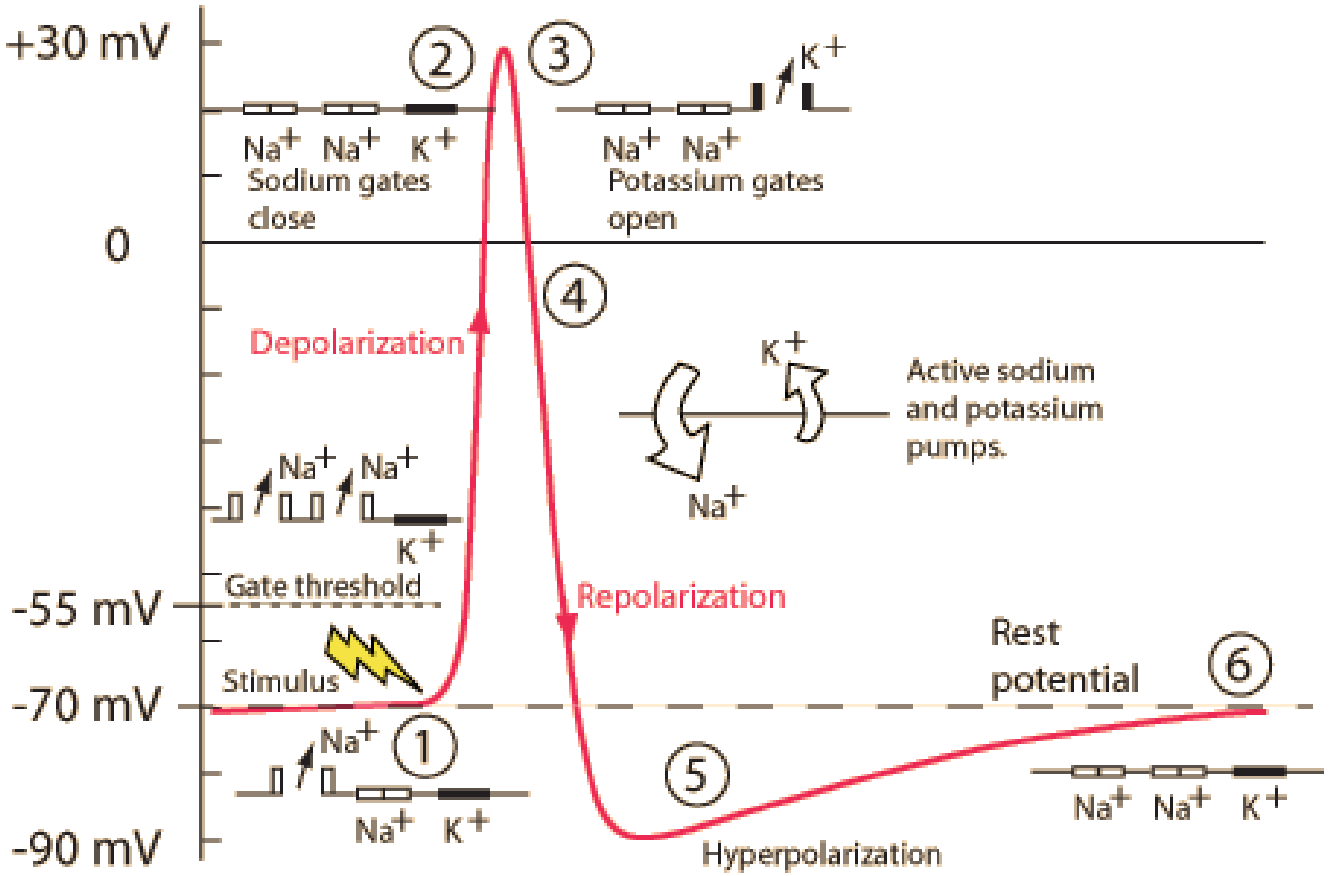
- Rapid rise, fall of membrane potential
- Threshold of excitation
- Increase (rising phase/depolarization)
- Peak
    - at positive voltage
- Decline (falling phase/repolarization)
- Return to resting potential (refractory period)

Action potential components

Phase	Neuron State
Rise to threshold	+ input makes membrane potential more +
Rising phase	Voltage-gated Na^+ channels open, Na^+ enters
Peak	Voltage-gated Na^+ channels close and deactivate; voltage-gated K^+ channels open
Falling phase	K^+ exits
Refractory period	Na^+/K^+ pump restores [Na^+], [K^+]; voltage-gated K^+ channels close

Action potentials and driving forces

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Stimulus
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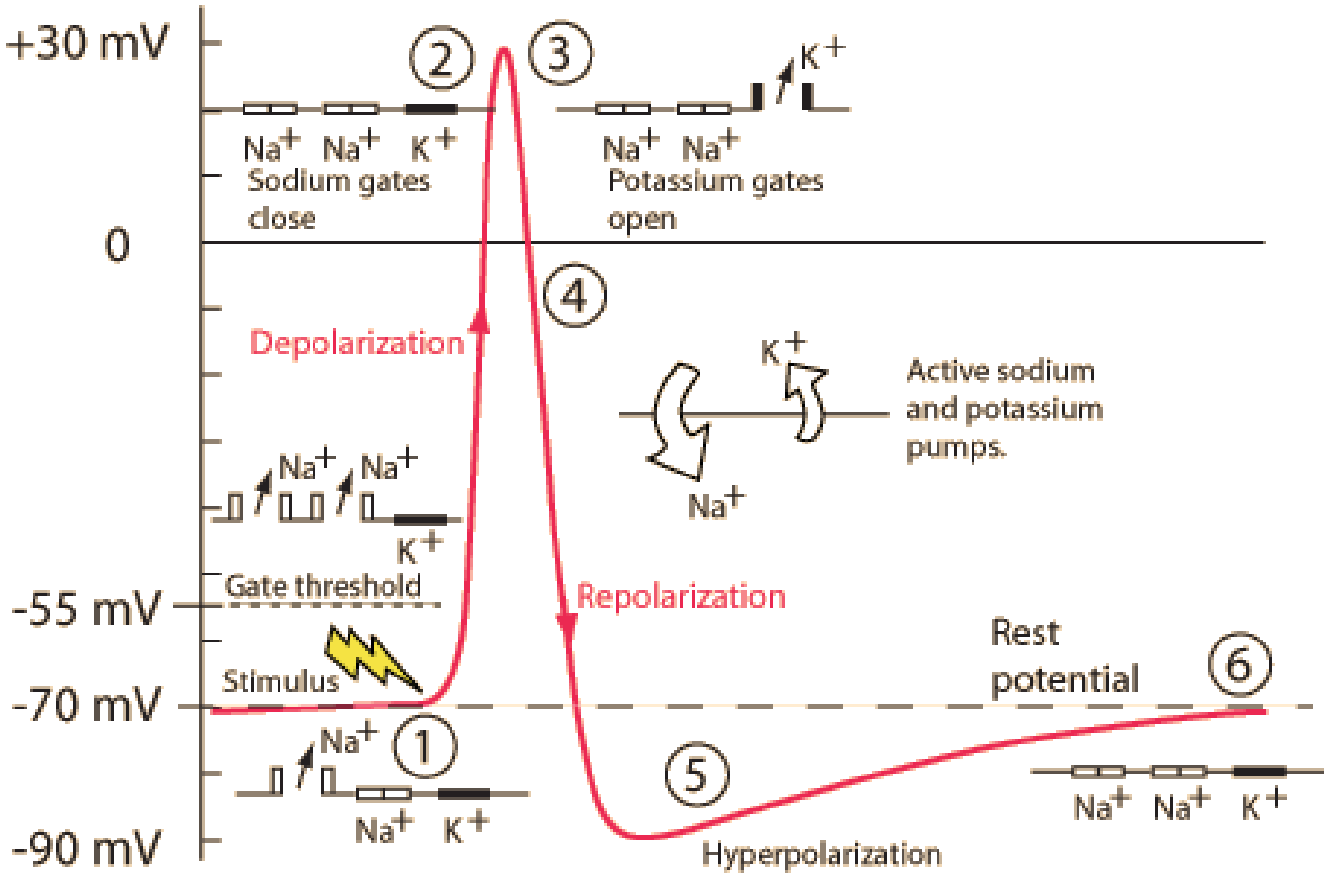
Hyperpolarization
Na+ Na+ K+

Neuron at rest

- Driving force on K^+ weakly out
  - -70 mV - (-90 mV) = +20 mV
- Driving force on Na^+ strongly in
  - -70 mV - (+55 mV) = -125 mV
- Na^+/K^+ pump maintains concentrations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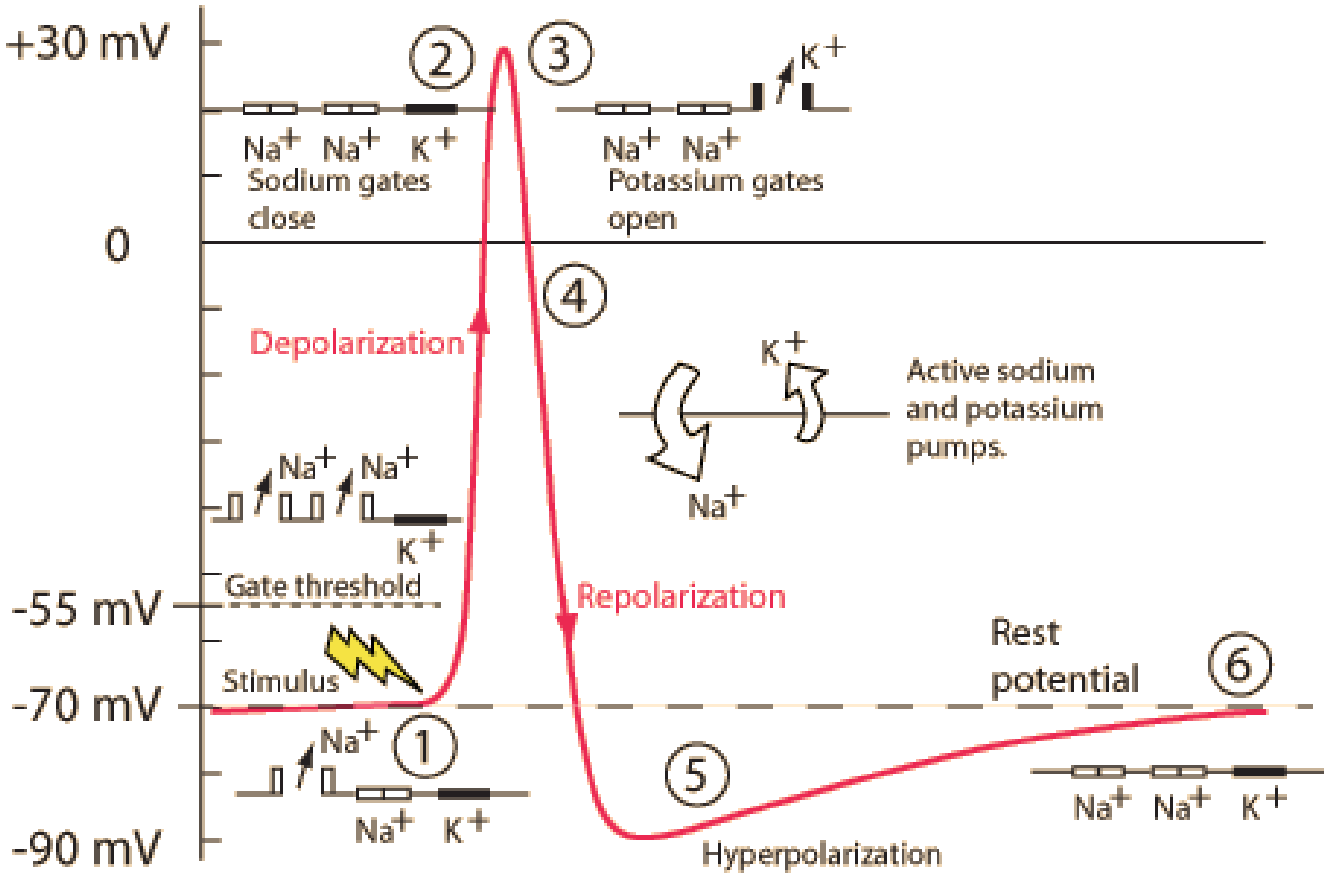
Action potential rising phase

- Voltage-gated Na^+ channels open
- Membrane permeability to Na^+ increases
  - Na^+ inflow through passive + voltage-gated channels
  - continued K^+ outflow through passive channels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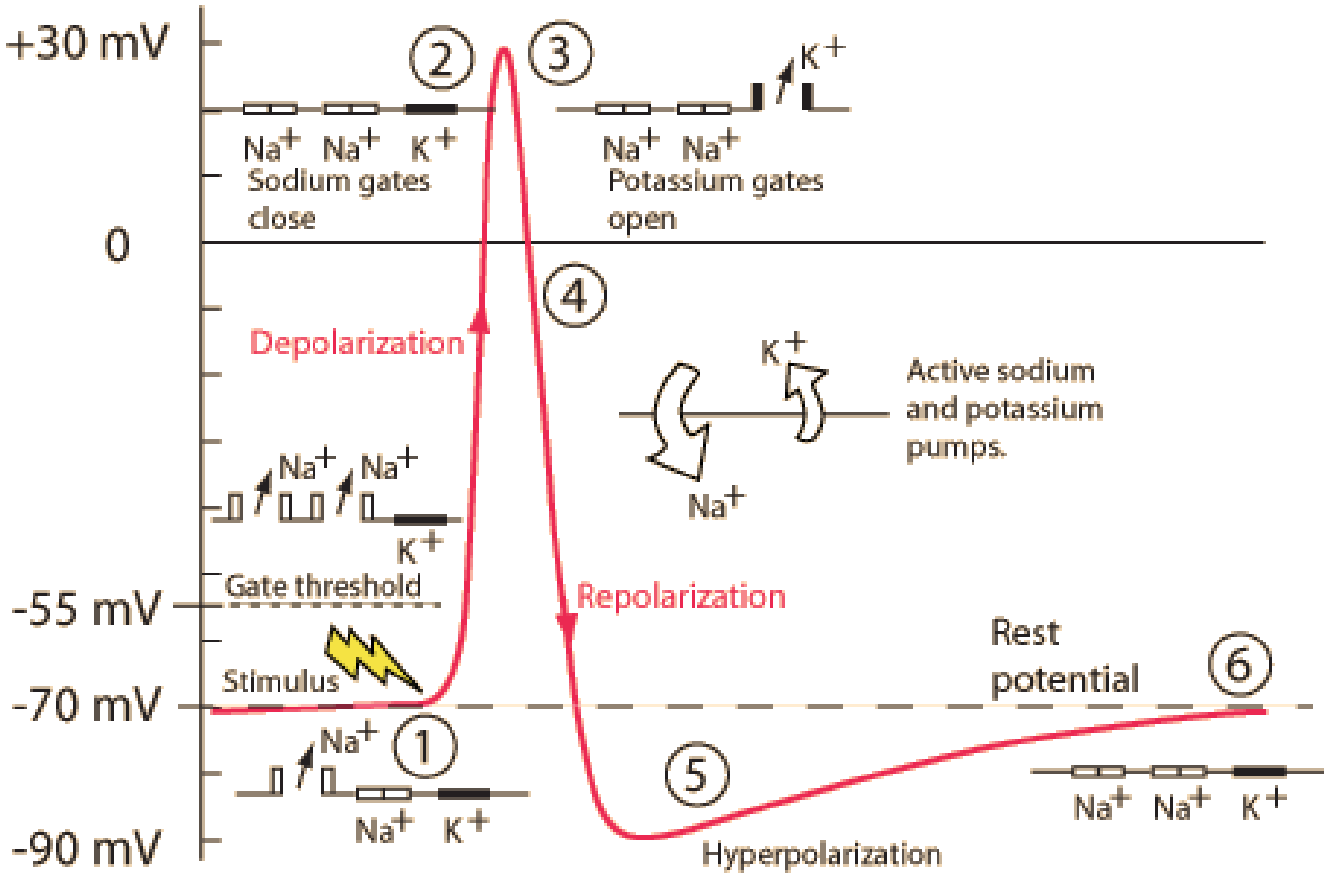
Peak

- Membrane permeability to Na^+ reverts to resting state
  - Voltage-gated Na^+ channels close & inactivate
  - Slow inflow due to small driving force (+30 mV - 55mV = -25 mv)

Peak

- Membrane permeability to K^+ increases
  - Voltage-gated K^+ channels open
  - Fast outflow due to strong driving force (+30 mv - (-90 mv) = +120 mV)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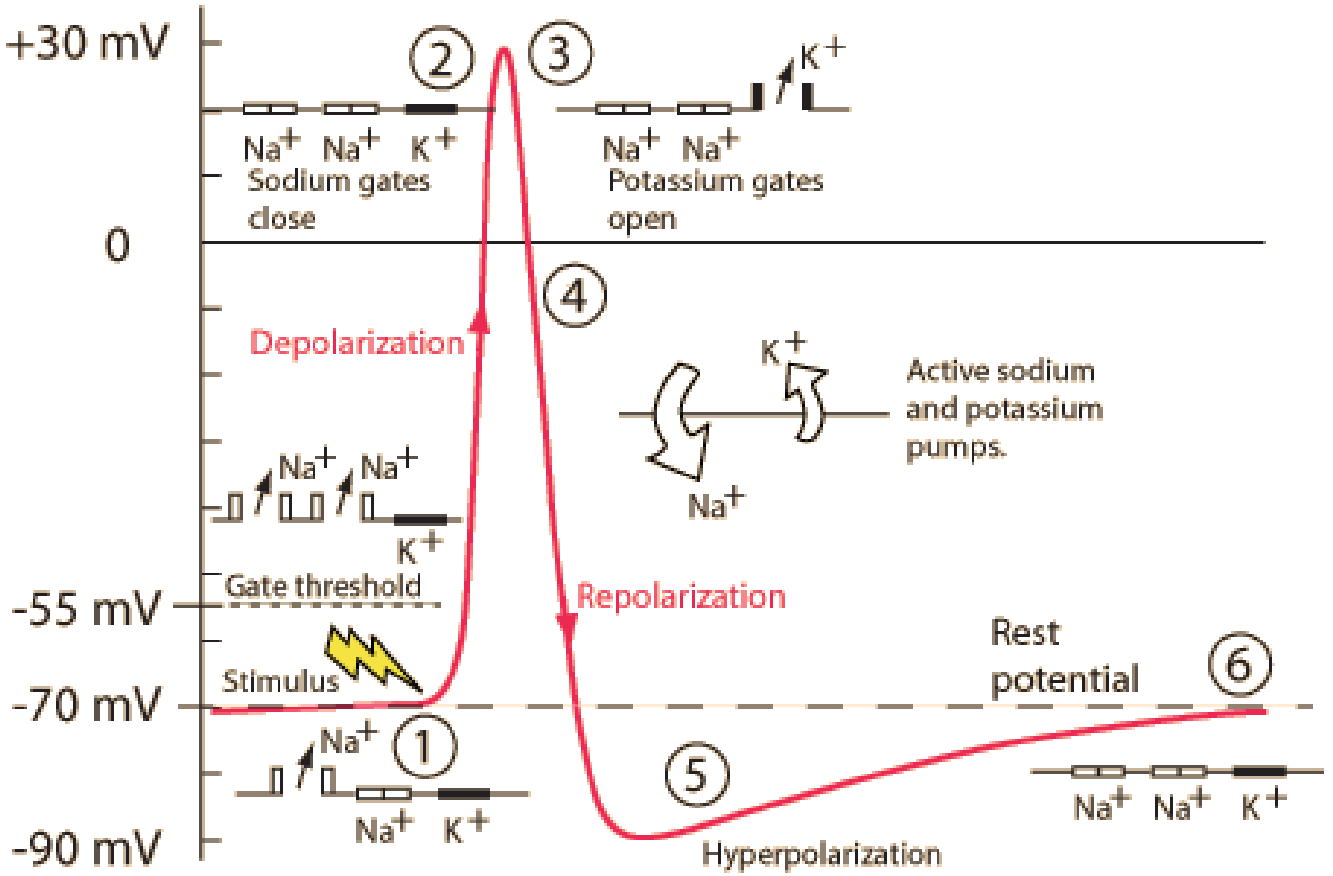
Falling phase

- K^+ outflow
  - Through voltage-gated K^+ and passive K^+ channels
- Na^+ inflow
  - Through passive channels only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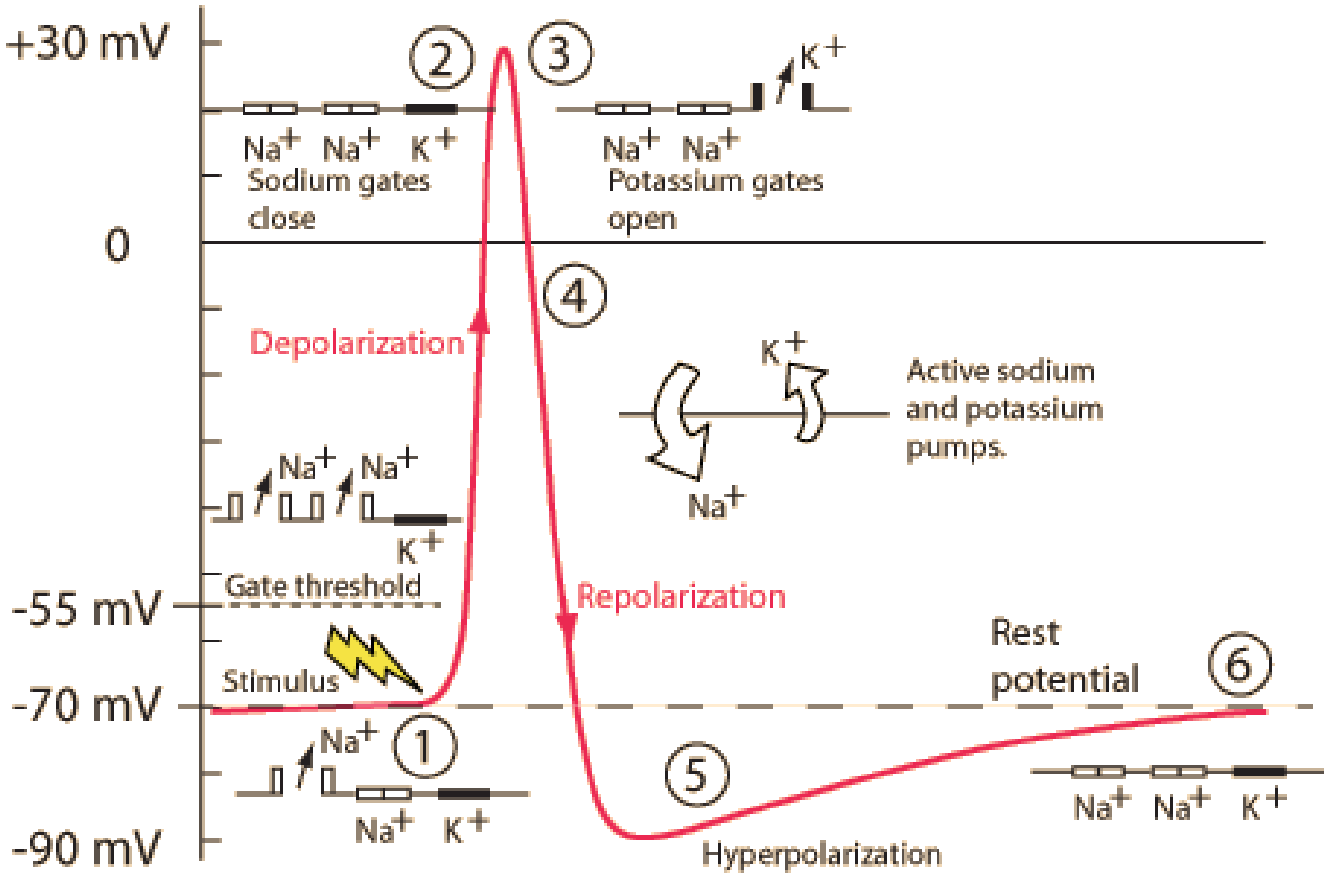
Absolute refractory phase

- Cannot generate action potential (AP) no matter the size of the stimulus
- Membrane potential more negative (-90 mV) than at rest (-70 mV)
- Voltage-gated Na^+ channels still inactivated
    - Driving force on Na^+ high (-90 mv - 55 mV = -145 mV), but too bad

Absolute refractory phase

- Voltage-gated K^+ channels closing
  - Driving force on K^+ tiny or absent
- Na^+/K^+ pump restoring concentration balance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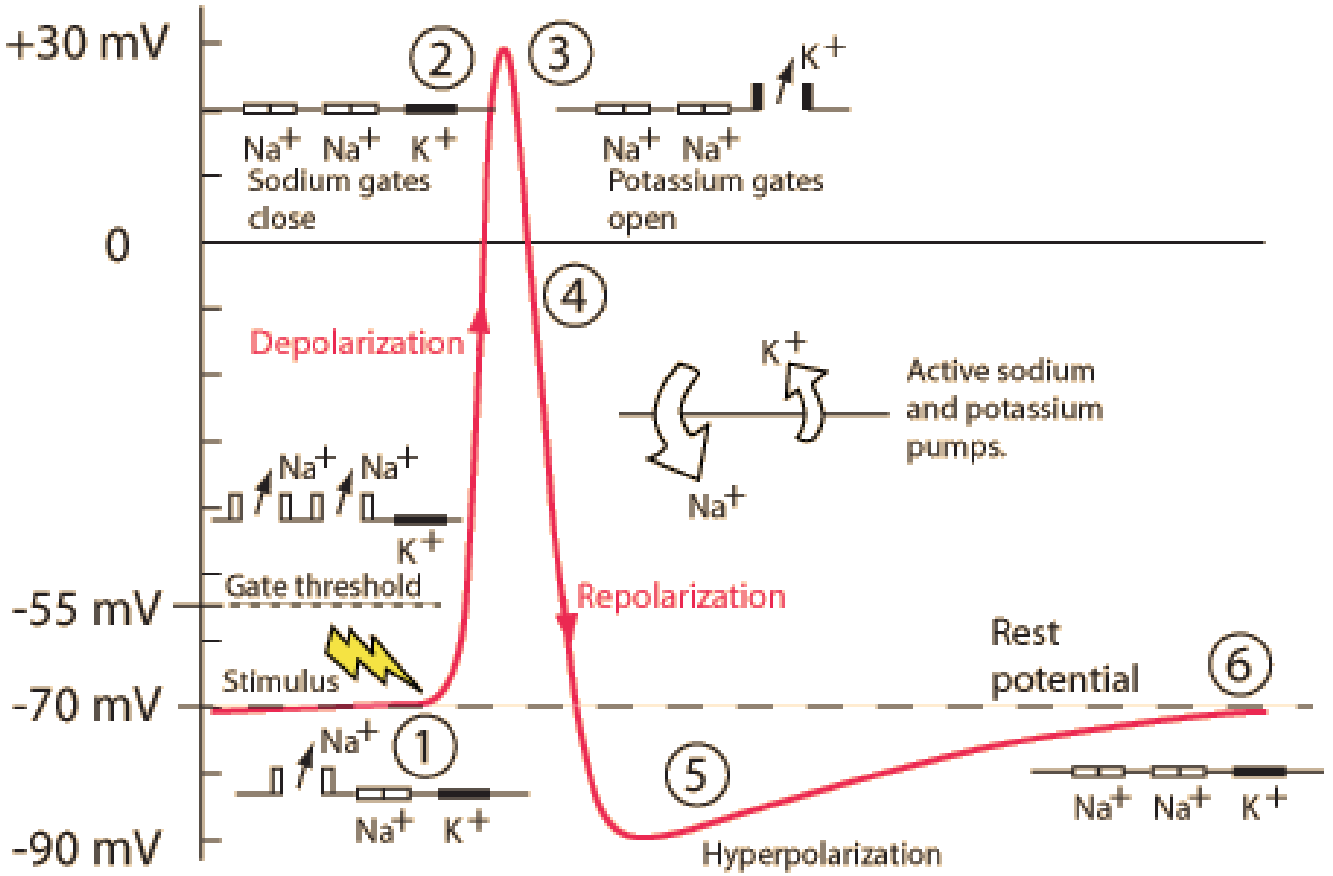
Relative refractory period

- Can generate AP with larg(er) stimulus
- Some voltage-gated Na^+ 'de-inactivate', can open if
  - Larger input
  - Membrane potential is more negative than resting potential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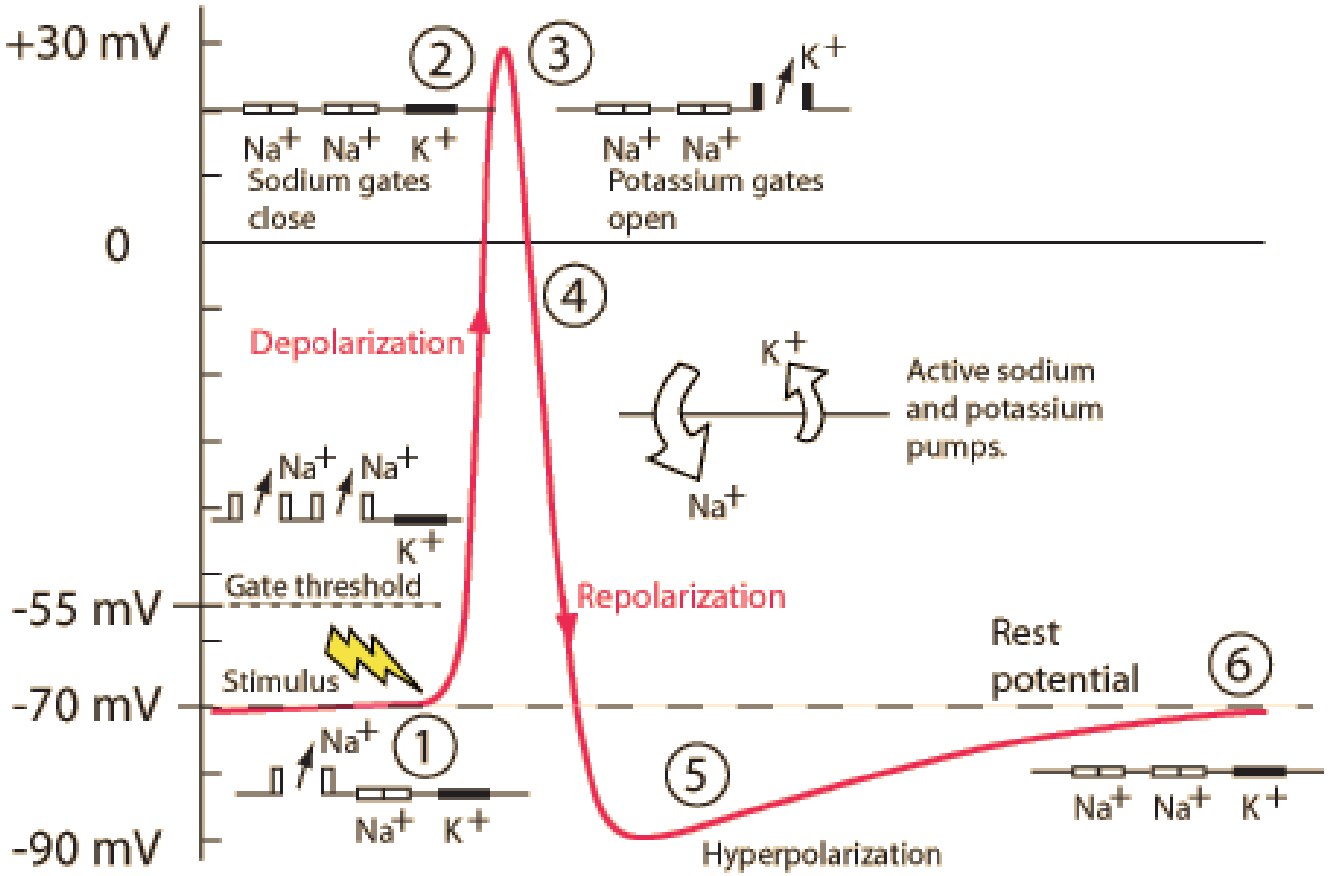
Review AP phases and driving forces

Neuron at rest

- Voltage-gated Na^+ closed, but ready to open
- Voltage-gated K^+ channels closed, but ready to open
- Membrane potential at rest
- Na^+/K^+ pump still working…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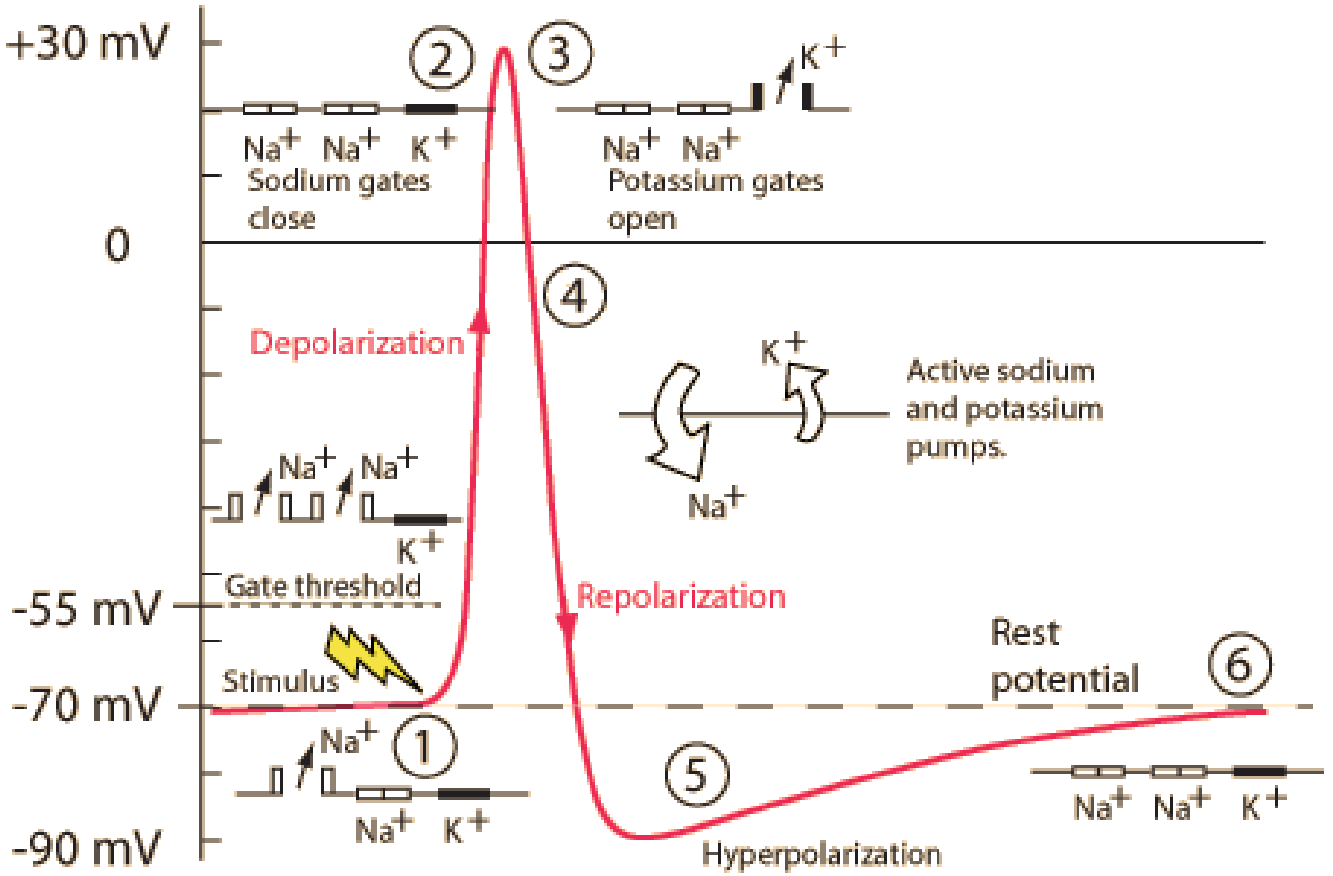
Phase	Ion	Driving force	Flow direction	Flow magnitude
Rest	K^+	20 mV	out	small
	Na^+	125 mV	in	small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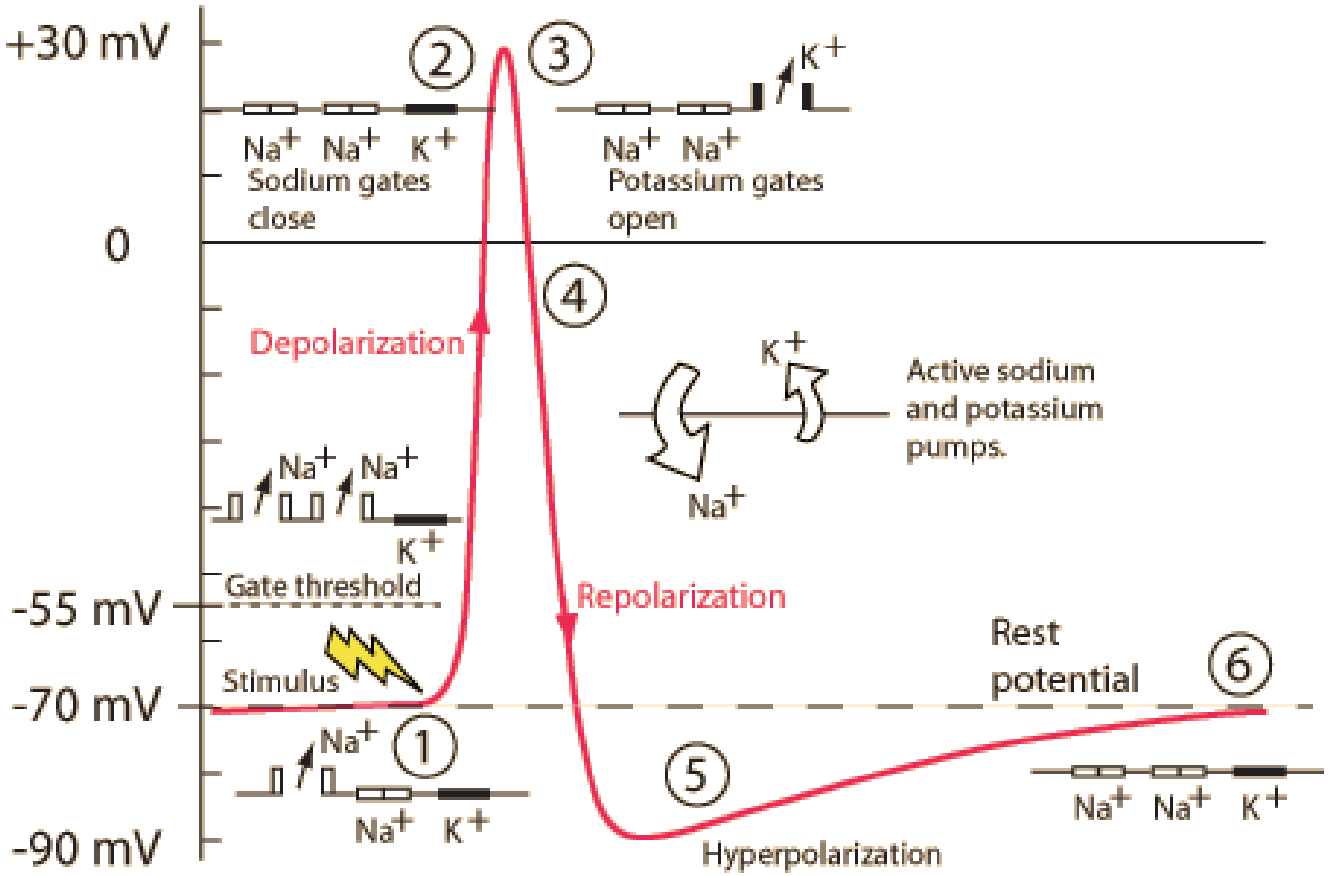
Phase	Ion	Driving force	Flow direction	Flow magnitude
Rising	K^+	growing	out	growing
	Na^+	shrinking	in	high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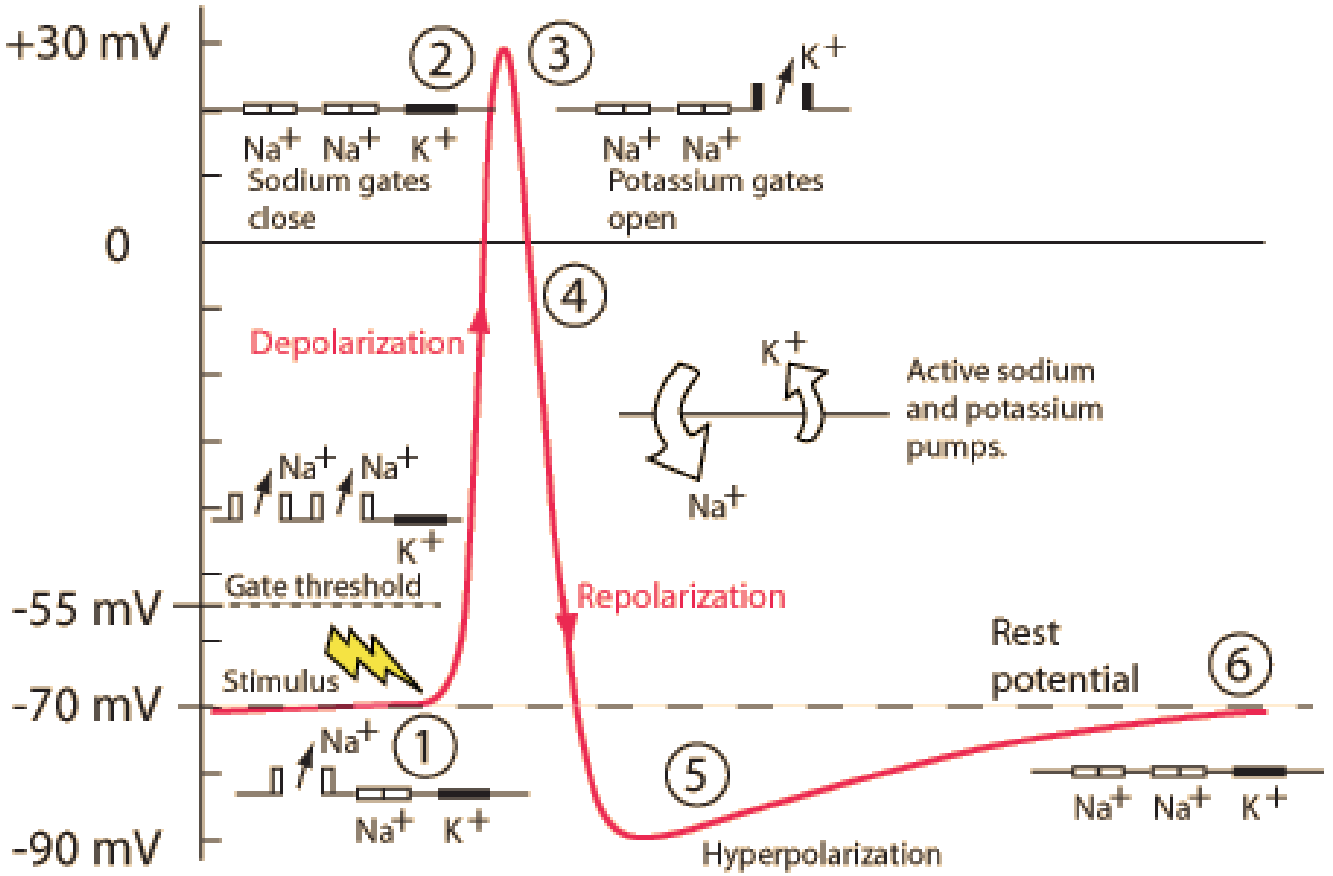
Phase	Ion	Driving force	Flow direction	Flow magnitude
Peak	K^+	120 mV	out	high
	Na^+	20 mV	in	small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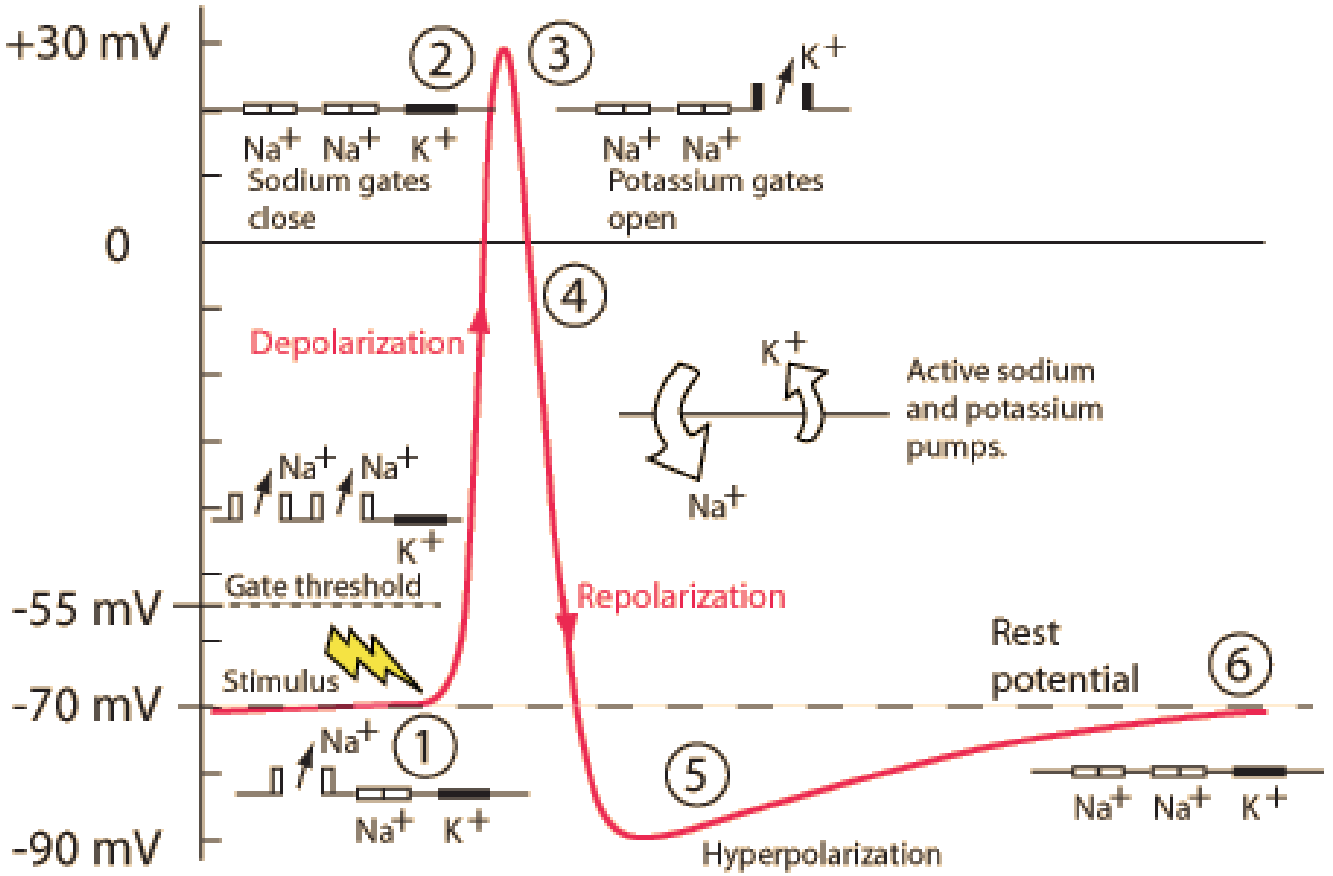
Phase	Ion	Driving force	Flow direction	Flow magnitude
Falling	K	shrinking	out	high
	Na^+	growing	in	small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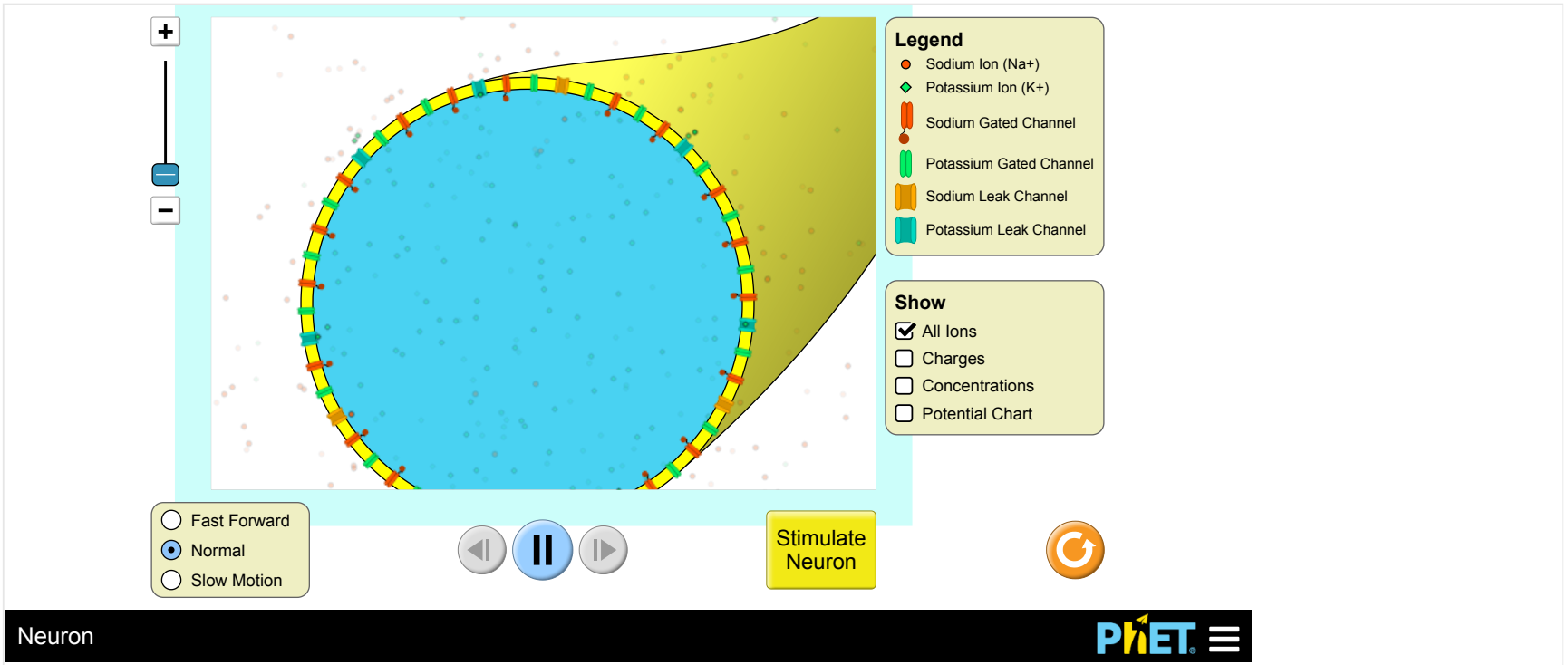
Phase	Ion	Driving force	Flow direction	Flow magnitude
Refractory	K	~0 mV	out	small
	Na^+	145 mV	in	small

Animation

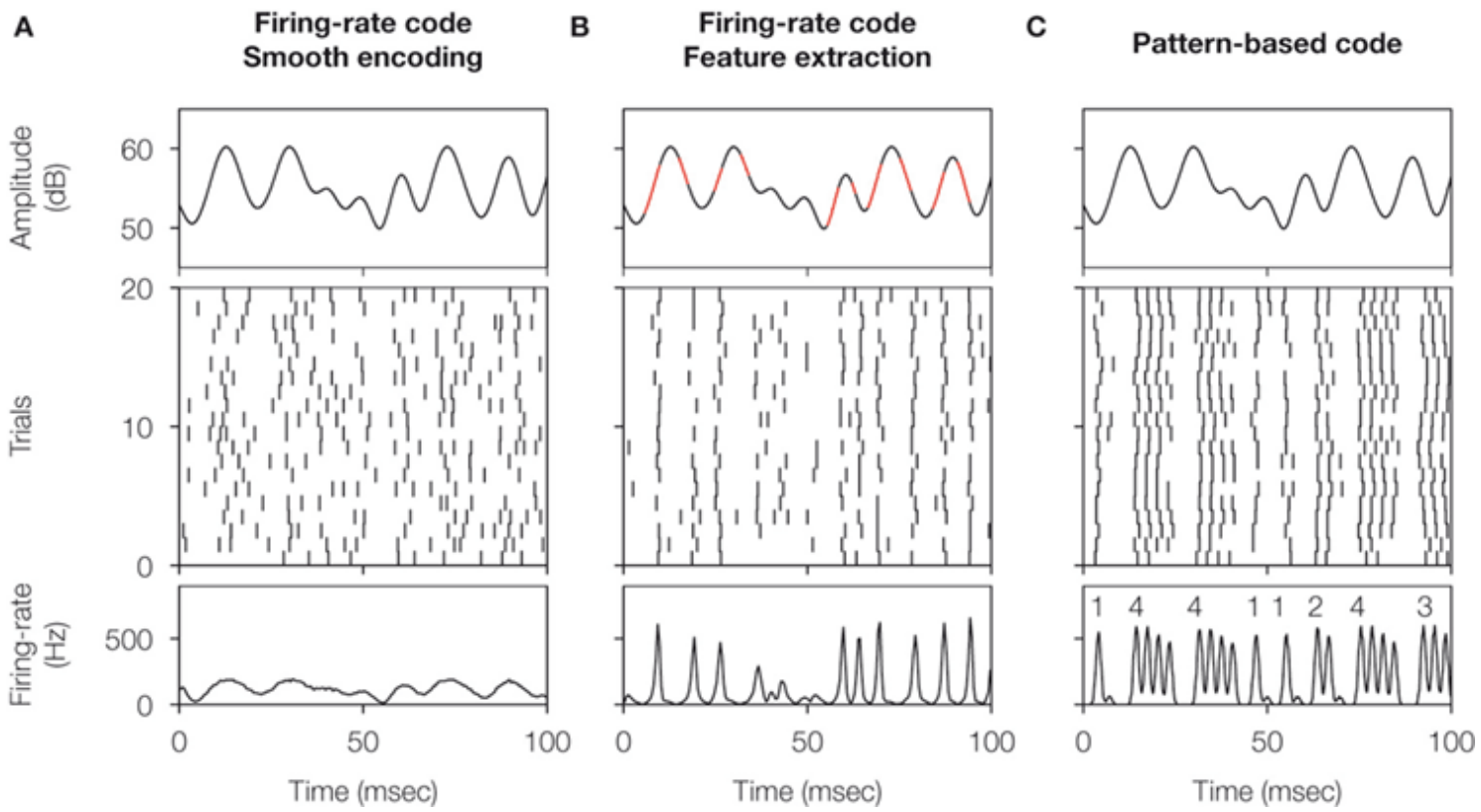

Legend
Sodium Ion (Na+)
Potassium Ion (K+)
Sodium Gated Channel
Potassium Gated Channel
Sodium Leak Channel
Potassium Leak Channel
Show
All Ions
Charges
Concentrations
Potential Chart
Fast Forward
Normal
Slow Motion
Stimulate Neuron
Neuron
PhET

APs and Information Processing

Information processing

- AP amplitudes don't vary (much)
  - All or none
  - And V_K V_{Na} don't vary much b/c Na^+/K^+ pump always working
- AP frequency and timing vary
  - Rate vs. timing codes
  - Same rates, but different timing
  - "Grandmother" cells and single spikes

Information processing



(Eyherabide et al., 2009)

Generating APs

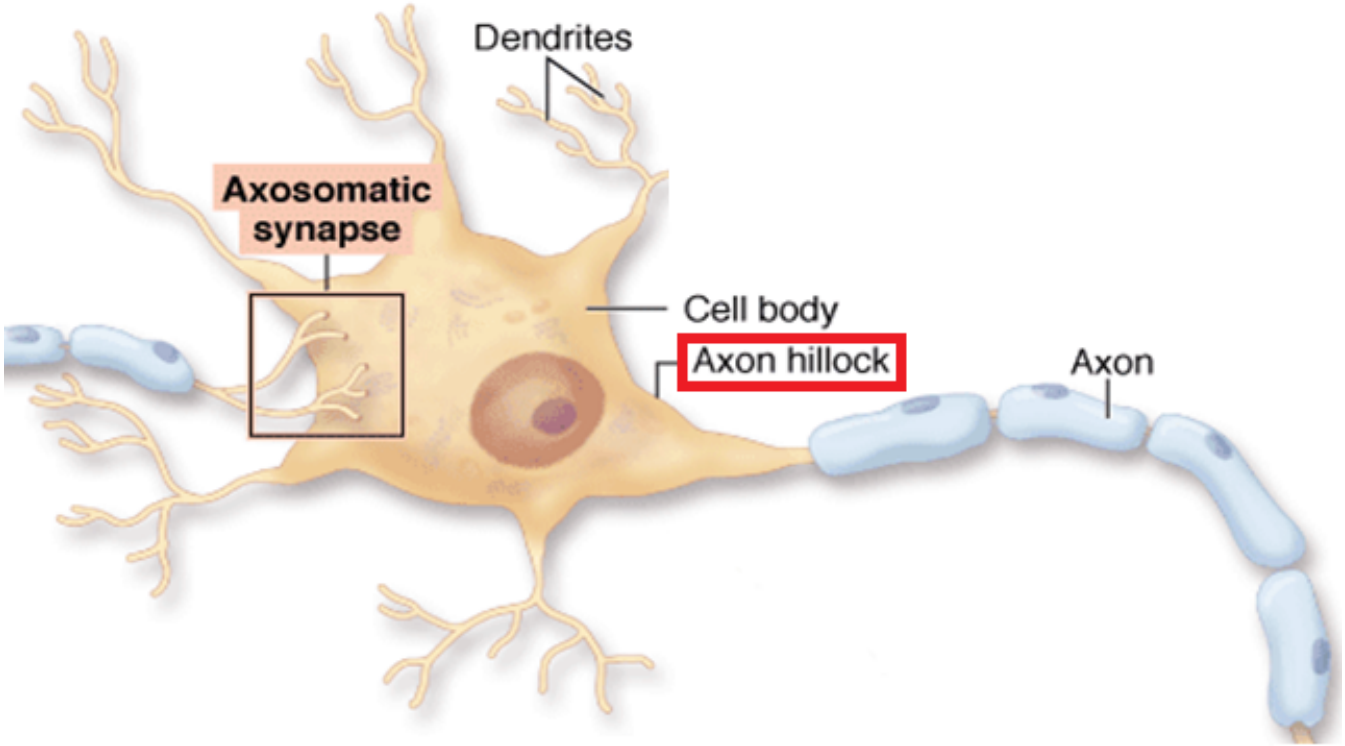
.

- Portion of soma adjacent to axon
- Integrates/sums input to soma

.

- Umyelinated portion of axon adjacent to soma
- Voltage-gated Na^+ and K^+ channels exposed
- If sum of input to soma > threshold, voltage-gated Na^+ channels open

Axon hillock, axon initial segment



AP propagation

- Propagation
  - move down axon, away from soma, toward axon terminals.
- Unmyelinated axon
  - Each segment "excites" the next

AP propagation is like

AP propagation

- Myelinated axon
  - AP "jumps" between –>
  - Nodes of Ranvier == unmyelinated sections of axon
  - voltage-gated Na^+, K^+ channels exposed
  - Current flows through myelinated segments

Question

- Why does AP flow in one direction, away from soma?
  - Soma does not have (many) voltage-gated Na^+ channels.
  - Soma is not myelinated.
  - Refractory periods mean polarization only in one direction.

Question

- Why does AP flow in one direction, away from soma?
  - **Soma does not have (many) voltage-gated Na^+ channels.**
  - Soma is not myelinated.
  - **Refractory periods mean polarization only in one direction.**

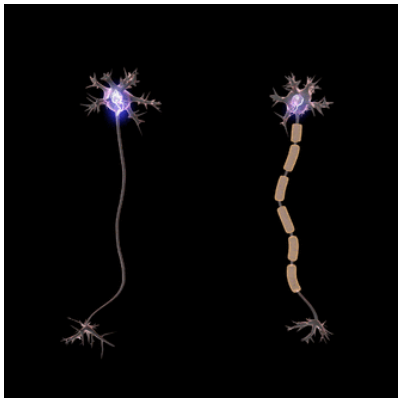
Conduction velocities

WIKIPEDIA

Nerve conduction velocity

Nerve conduction velocity is an important aspect of nerve conduction studies. It is the speed at which an electrochemical impulse propagates down a neural pathway. Conduction velocities are affected by a wide array of factors, including age, sex, and various medical conditions. Studies allow for better diagnoses of various neuropathies, especially demyelinating conditions as these conditions result in reduced or non-existent conduction velocities.

Contents



Saltatory Conduction

Hodgkin-Huxley Equations

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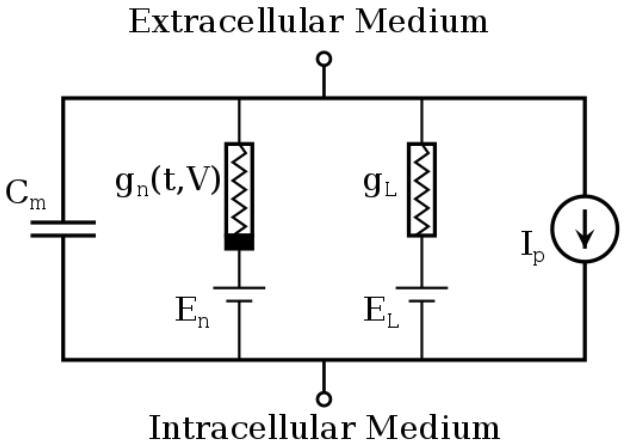
Hodgkin–Huxley model

The **Hodgkin–Huxley model**, or **conductance-based model**, is a mathematical model that describes how action potentials in neurons are initiated and propagated. It is a set of nonlinear differential equations that approximates the electrical characteristics of excitable cells such as neurons and cardiac myocytes. It is a continuous time model, unlike, for example, the Rulkov map.

Alan Lloyd Hodgkin and Andrew Fielding Huxley described the model in 1952 to explain the ionic mechanisms underlying the initiation and propagation of action potentials in the squid giant axon.[1] They received the 1963 Nobel Prize in Physiology or Medicine for this work.



Basic components of Hodgkin–Huxley-type models. Hodgkin–Huxley type models represent the biophysical characteristic of cell membranes. The lipid bilayer is represented as a capacitance (C_m). Voltage-gated and leak ion channels are represented by nonlinear (g_n) and linear (g_L) conductances, respectively. The electrochemical gradients driving the flow of ions are represented by batteries (E), and ion pumps and

Contents

More on HH

- Measuring APs in actual neurons.
  https://www.youtube.com/embed/k48jXzFGMc8
- Interview with Sir Alan Hodgkin,
  https://www.youtube.com/embed/vSIXbfunHYg
- Simulations
  - http://alexhwilliams.info/code/pyneuron_morph.html
  - http://briansimulator.org/demo/
  - http://www.gribblelab.org/compneuro/3_Modelling_Action_Potenti

Synaptic transmission

What happens when AP runs out of axon?

- Rapid change in voltage triggers neurotransmitter (NT) release
- Voltage-gated calcium Ca++ channels open
- Ca++ causes to bind with presynaptic membrane, merge
- NTs diffuse across
- NTs bind with on
- NTs unbind, are inactivated

Receptor/channel types

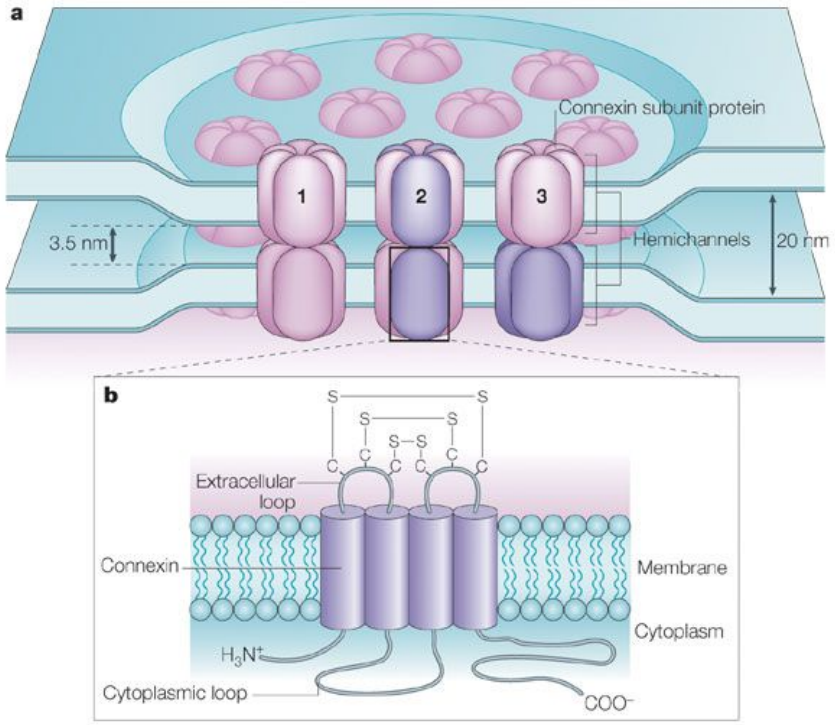
- Leak/passive
  - Vary in selectivity, permeability
- Transporters/exchangers
  - Ionic
    - Na^+/K^+
  - Chemical
    - e.g., Dopamine transporter (DAT)

Receptor/channel types

- Ionotropic receptors (receptor + ion channel)
  - Ligand-gated
  - Open/close channel
- Metabotropic receptors (receptor only)
  - Triggers 2nd messengers
  - G-proteins
  - Open/close adjacent channels, change metabolism

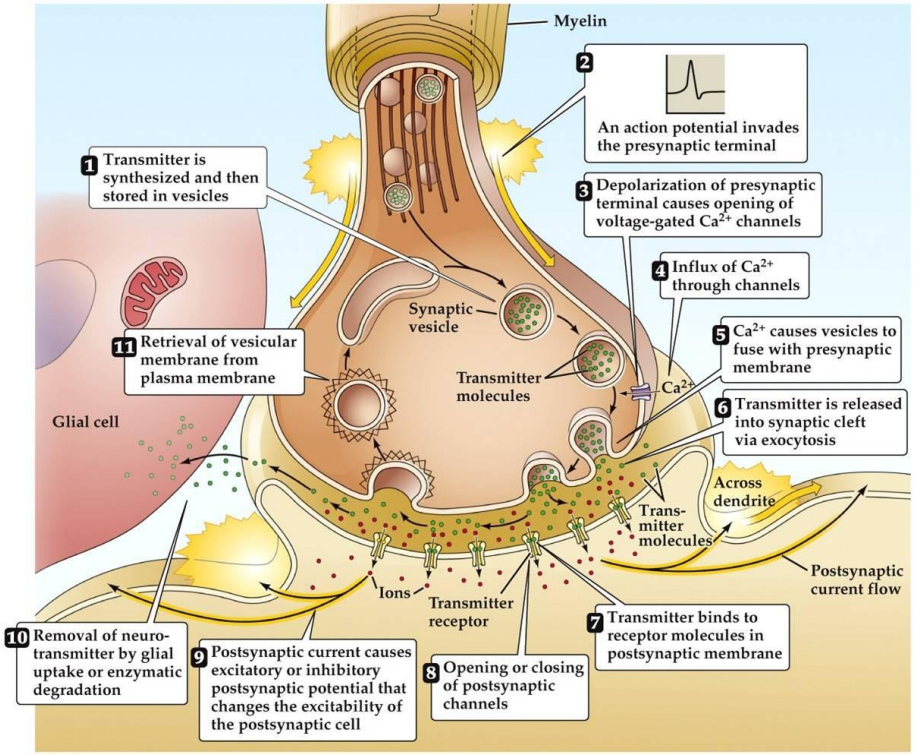
Gap junctions

- flows through adjacent neurons



Nature Reviews | Neuroscience

Chemical synapse



***NEUROSCIENCE 5e*, Figure 5.3**

Receptor types

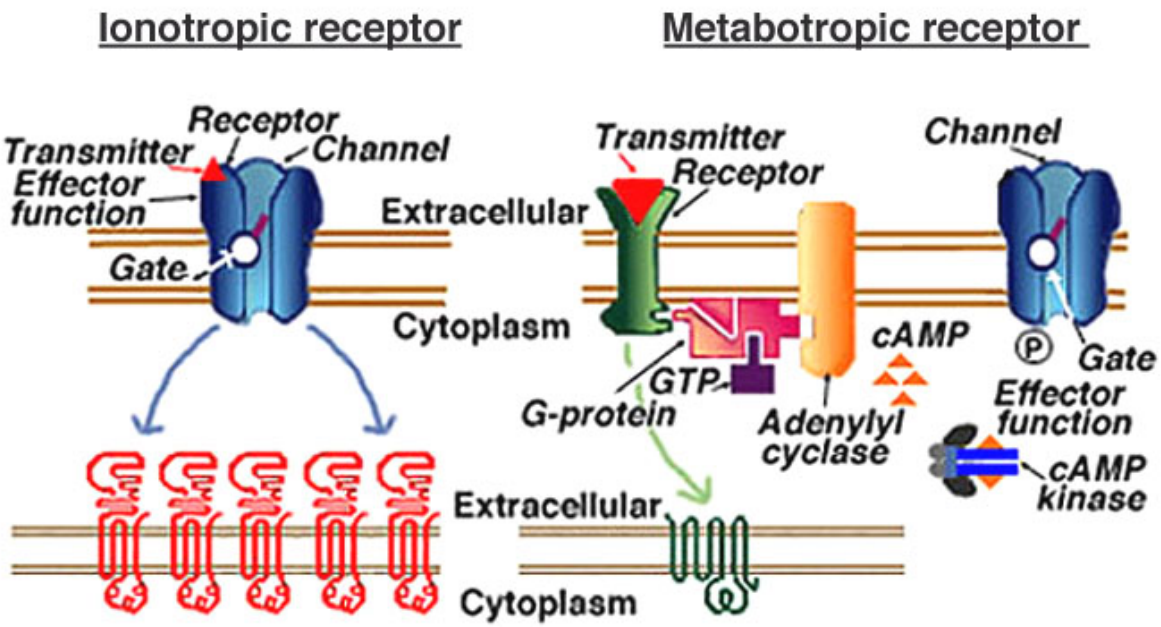


Fig. 5a. Ionotropic receptors and their associated ion channels form one complex (top). Each iGluR is formed from the co-assembly of multiple (4-5) subunits (From Kandel et al., 1991).

Fig. 5b. Metabotropic receptors are coupled to their associated ion channels by a second messenger cascade (top). Each mGluR is composed of one polypeptide, which is coupled to a G-protein (from Kandel et al., 1991).

Receptors generate

- Small voltage changes
- Amplitude scales with # of receptors activated
-
    - Depolarize neuron (make more +)
-
    - Hyperpolarize neuron (make more -)

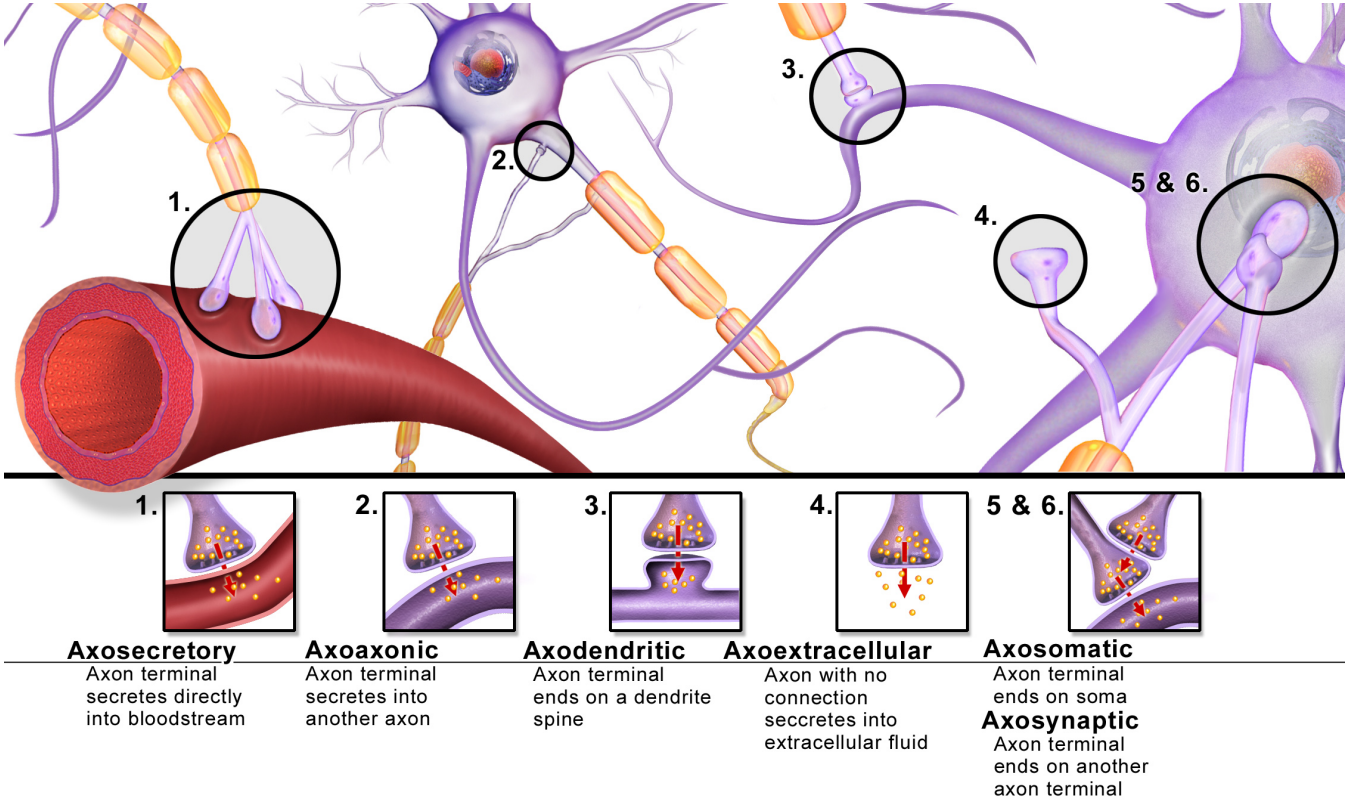
NTs inactivated

- Buffering
  - e.g., glutamate into astrocytes
- Reuptake via transporters
  - e.g., serotonin via serotonin transporter (SERT)
- Enzymatic degradation
  - e.g., AChE degrades ACh

Questions to ponder

- Why must NTs be inactivated?
- What sort of PSP would the following induce:
  - Open Na^+ channel
  - Open K^+ channel
  - Open Cl- channel, $[Cl^-]_{out}$>>$[Cl^-]_{in}$

Types of synapses



References

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