Neurophysiology for Computer Scientists

Computational Models of Neural Systems

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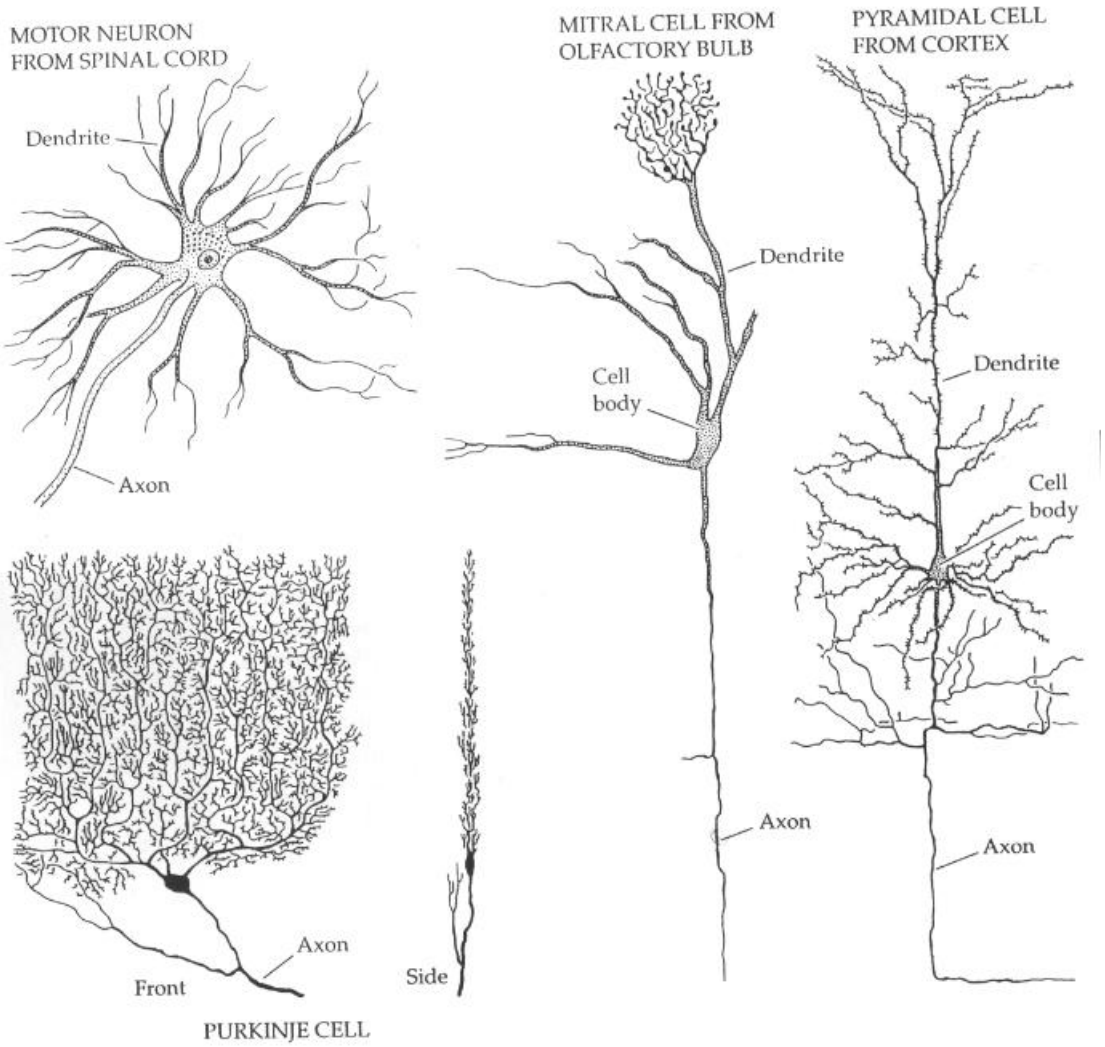
August, 2023

Outline

- Parts of a neuron
- Ionic basis of the resting potential
- Ionic basis of the action potential (spikes)
- Ligand-gated channels
- Synaptic transmission
- Second messengers
- Properties of dendritic trees

Neurons Come in Many Shapes



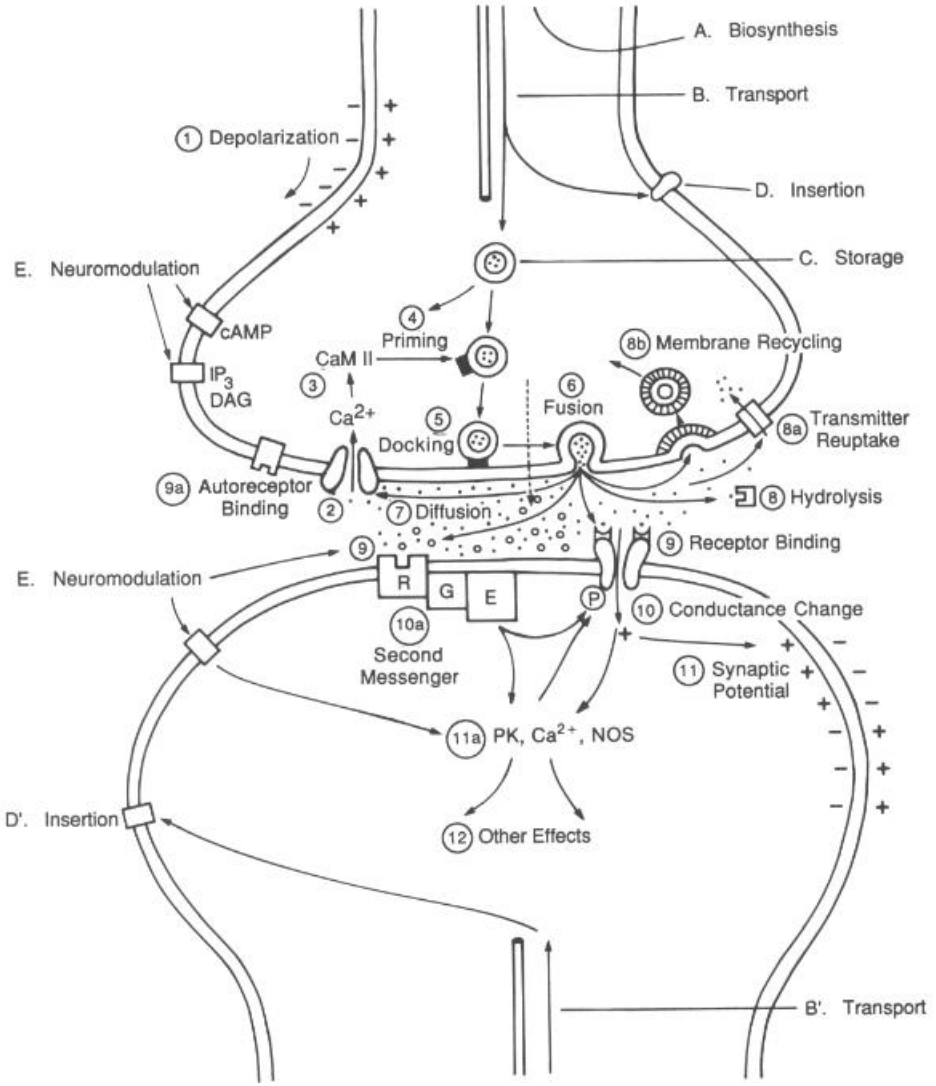
Nichols et al., From Neuron to Brain

Parts of a Neuron

1. Cell body (soma)
2. Dendrites
3. Axon

- Some cells lack dendrites, e.g., dorsal root ganglion cells in the spinal cord.
- Some cells lack axons, e.g., some types of amacrine cells in the retina.
- What is the difference between axon and dendrite?
  - Presence of spikes
  - Distribution of channel types
  - Pre- vs. post-synaptic structures

Strucure of a Synapse

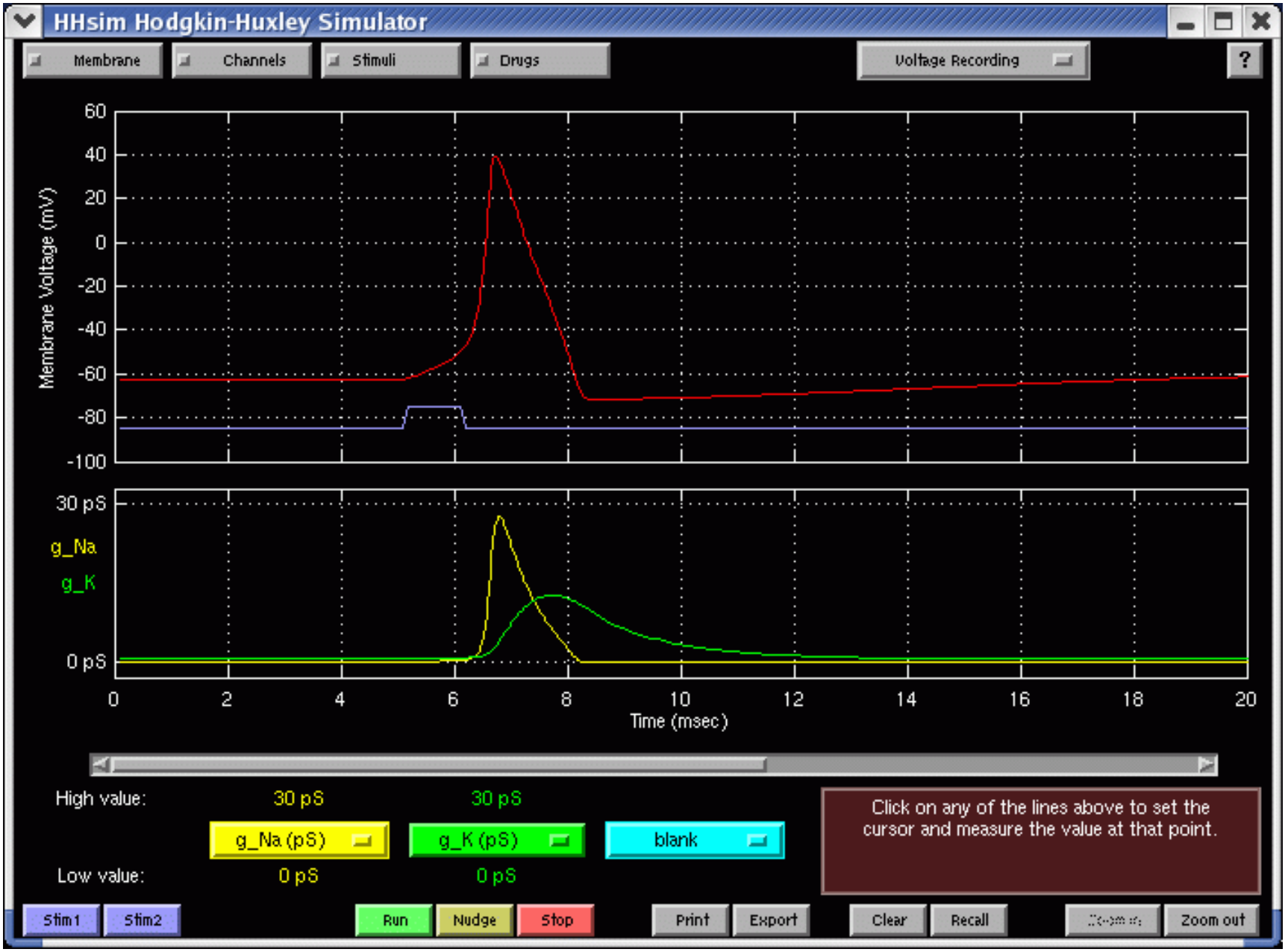


Gordon Shepherd, The Synaptic Organization of the Brain

Properties of Typical Cortical Neurons

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

The Action Potential



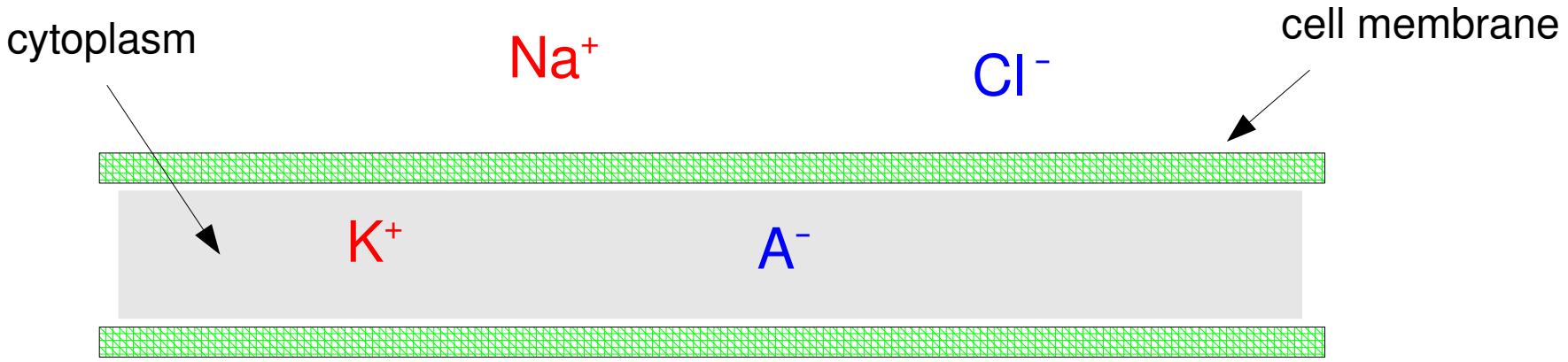
(Intra/Extra)-Cellular Ion Concentrations

Values are in mM, for typical CNS neurons:

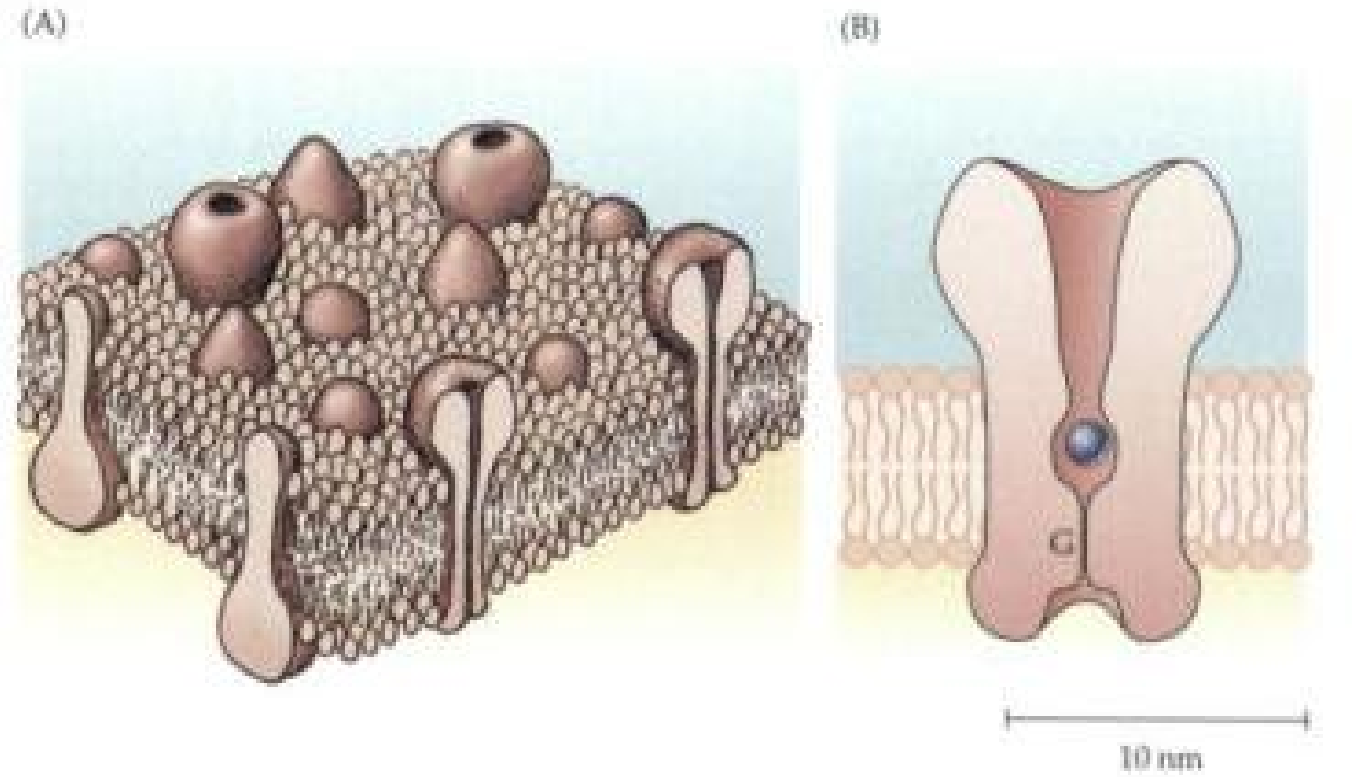
	Extracellular	Intracellular
Na^+	150	30
K^+	3	140
Ca^{2+}	1.2	0.1
Cl^-	130	8
A^-	25	162

Positive and negative charges balance, inside & outside.

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



Passive Ion Channels



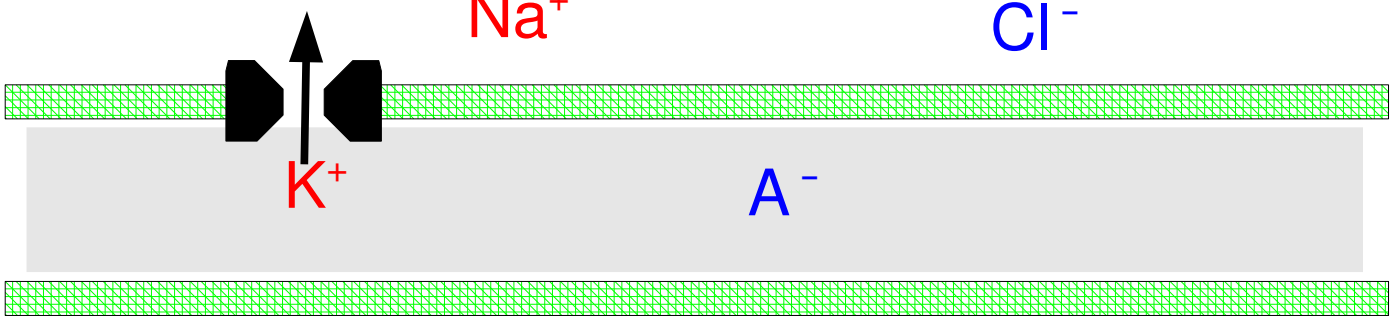
Nichols et al., From Neuron to Brain

Passive Ion Channels

- Membrane contains channels selectively permeable to K^+. Concentration gradient favors K^+ flowing out of cell.

  $[K^+]_i = 140$ mM $[K^+]_o = 3$ mM

- K^+ ions continue to flow out until the cell's membrane potential V_m is -96 mV.
- Now the outward concentration gradient for K^+ is exactly counterbalanced by the inward electrical force.
- The cell's negative internal charge attracts positive ions, but only K^+ can pass through the channel.
- Positive charges cluster along the outer wall of the membrane; negative charges cluster along inner wall.

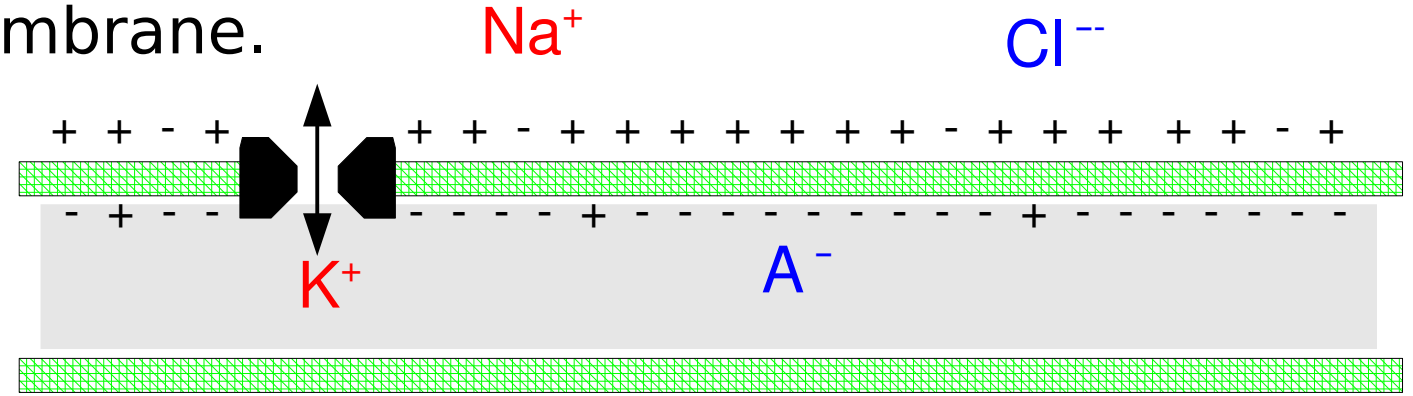


Reversal Potential for K^+

- The Nernst Equation defines the equilibrium potential:

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

- R = thermodynamic gas constant;
  T = temperature in °K;
  z = valence (+1 for K^+); F = Faraday's constant
- k = RT/zF = 25 mV at room temperature; E_K = –96 mV
- The cell membrane is only 50 Angstroms thick, so a -96 mV potential is like 192,000 V across a 1 cm membrane.



Manipulating the Reversal Potential

- By changing the extracellular concentration of K^+, we can change the reversal potential.
- Example: we want E_K to go from -96 mV to -75 mV.
- This is exactly 3 times the RT/zF value of 25 mV.
- Calculate the K_o that will produce this reversal potential.

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

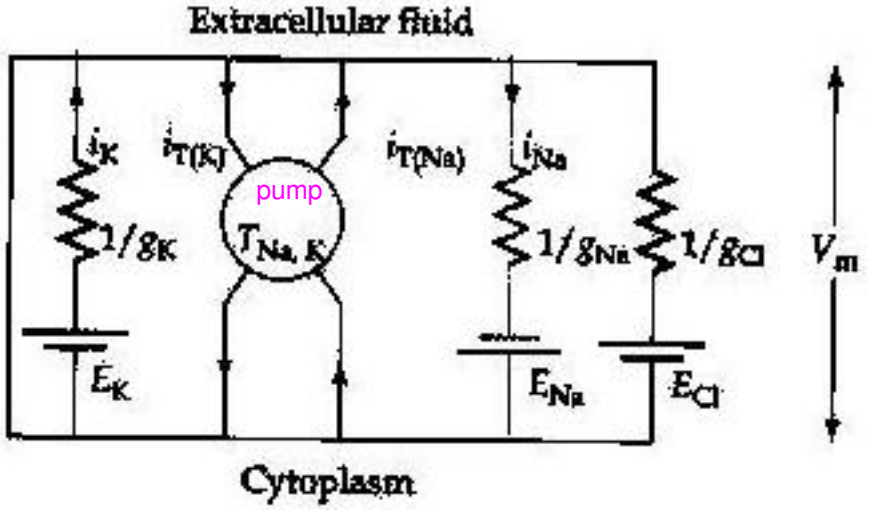
- Solution: increase extracellular K^+ from 3 mM to 7 mM.

Two Other Ionic Currents

- Passive sodium channels allow inward sodium leakage.

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

- Passive chloride channels allow an inward Cl^- leakage. $E_{Cl} = -75$ mV.
- There is a simultaneous flow of K^+, Na^+, and Cl^- ions into and out of the cell.



Nichols et al., From Neuron to Brain

The Resting Potential

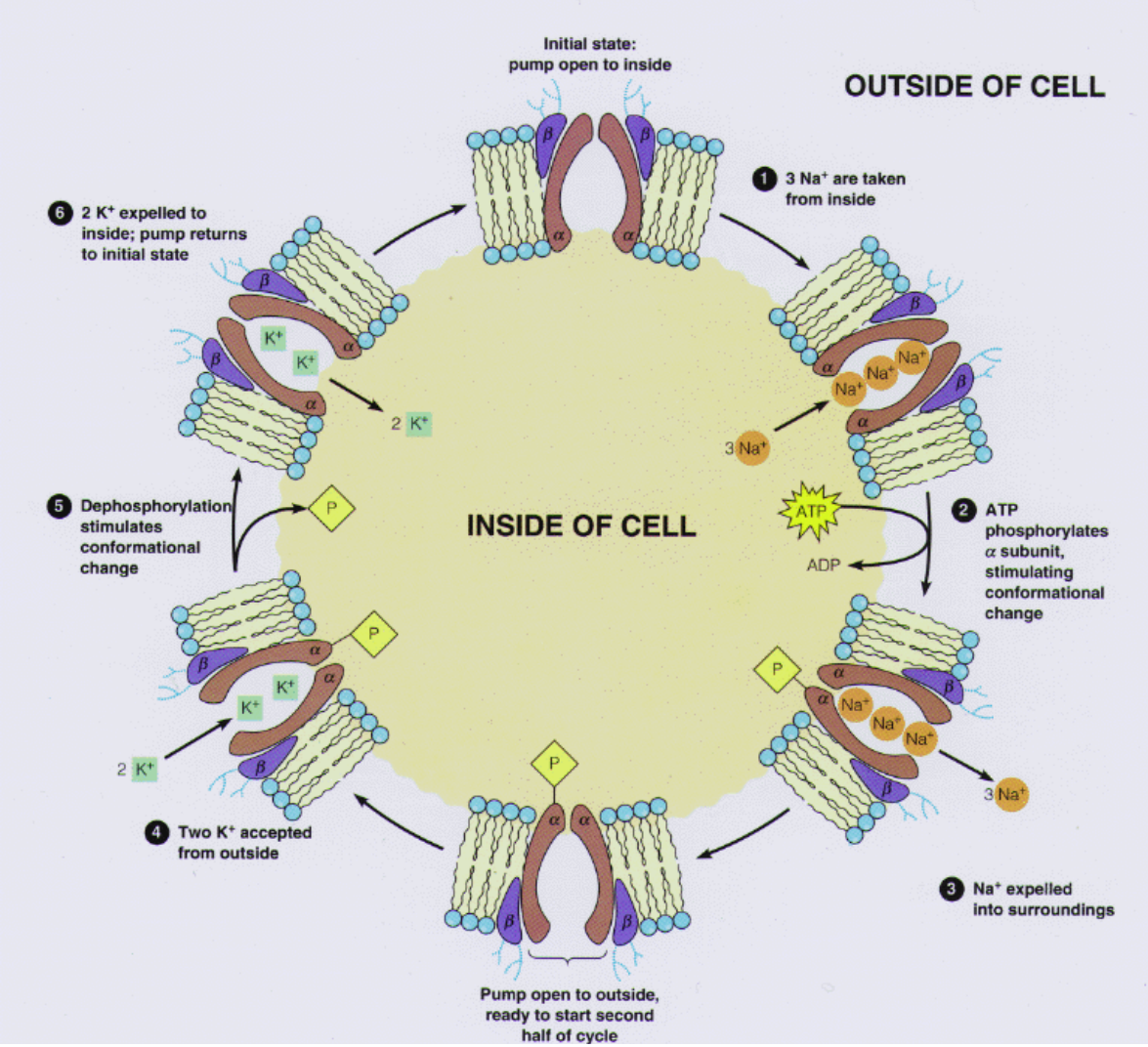
- The cell's membrane potential V_m is a weighted combination of the K^+, Na^+, and Cl^- reversal potentials.
- The different ion channels have different conductances: g_K, g_{Na}, and g_{Cl}.
- The Goldman-Hodgkin-Katz Equation:

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

- For typical cortical neurons the resting potential V_r is in the range of –60 to –75 mV.
- V_r is bounded from below by E_K and from above by E_{Na}.
- How could we increase g_K?
  - Modify the channel structure
  - Add more channels to the membrane

The Sodium Pump

- *Why doesn't the cellular battery run down?*
- Electrogenic pumps maintain the cell's ionic balance.
- The sodium pump takes in 2 K^+ ions and expels 3 Na^+ ions on each cycle.
- The pump is powered by ATP (adenosine triphosphate).

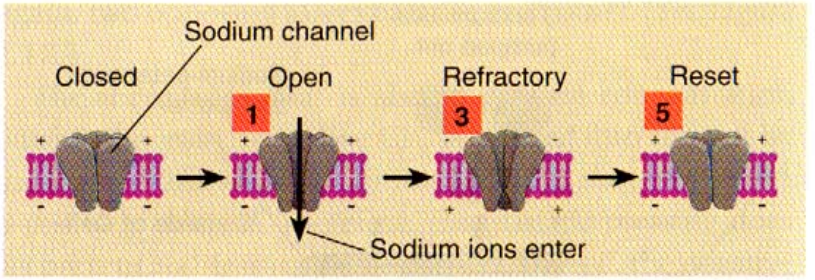


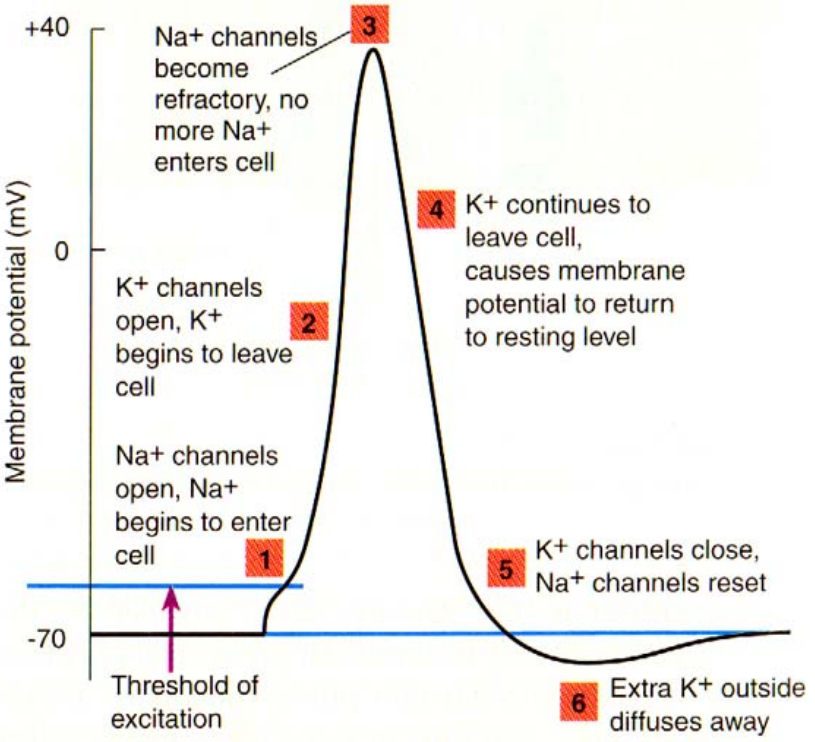
From Mathews and van Holde: *Biochemistry 2/e.* The Benjamin/Cummings Publishing Co., Inc.

The Action Potential

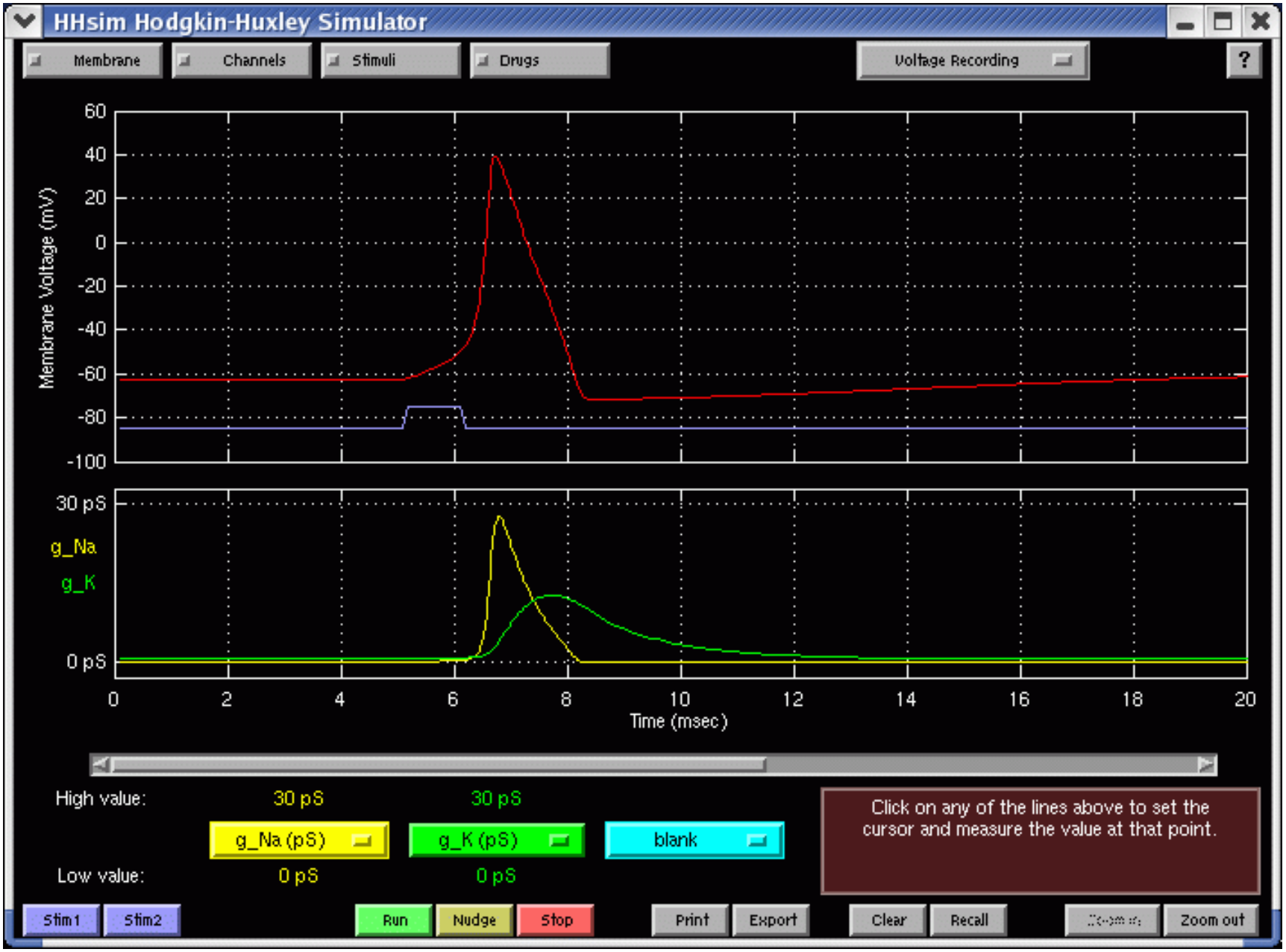
Suppose V_m rises above –55 mV (the spike threshold).

1. Voltage-gated Na^+ channels begin to open.
2. This increases g_{Na}, so more Na^+ ions enter the cell. The membrane beomes further depolarized, causing more channels to open and even more Na^+ ions to enter the cell.
3. Sodium channels become refractory and incoming Na^+ current stops.





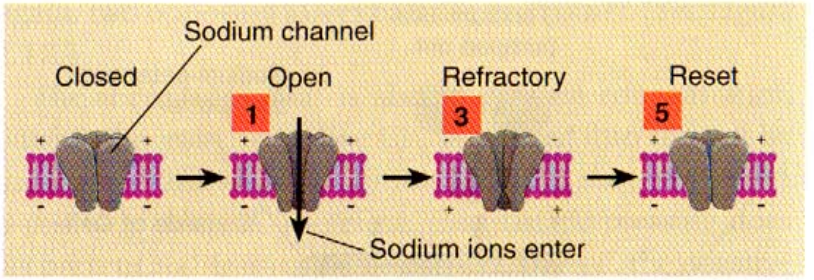
The Action Potential (cont.)

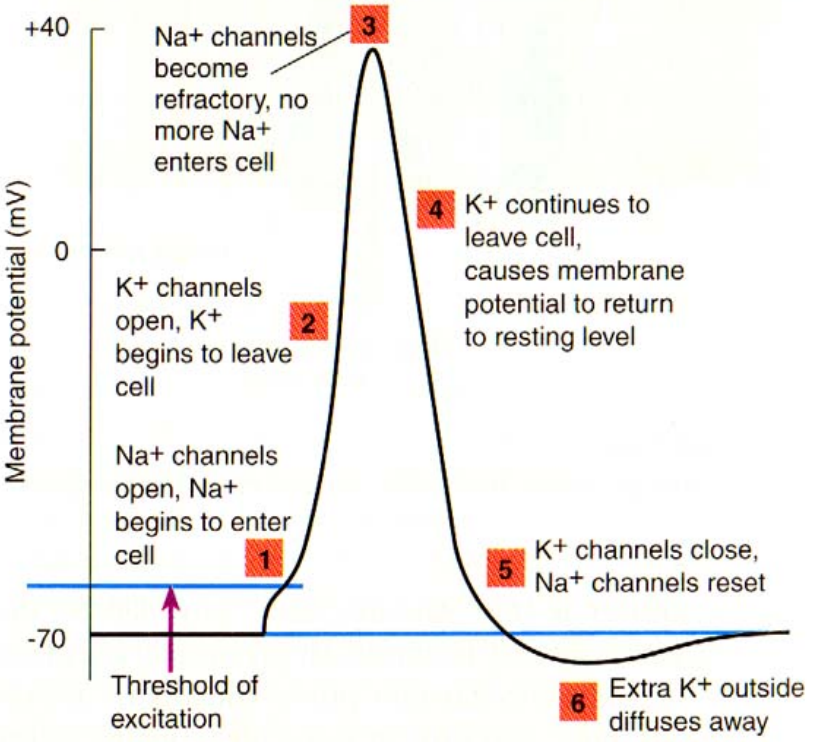


The Action Potential (cont.)

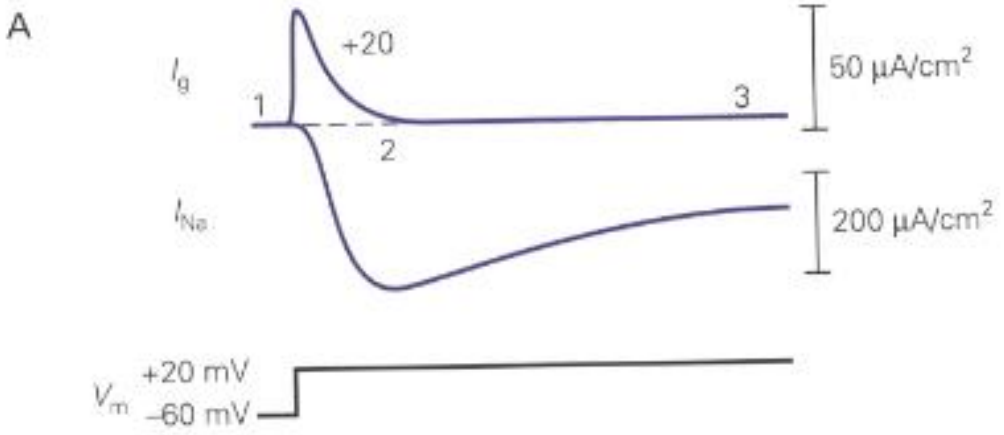
- Why are spikes sharp?
  2. As V_m rises, voltage-gated K^+ channels begin to open.
  3. Rise in gk is slow at first, then speeds up, so K^+ ions leave the cell at a high rate.
  4. The membrane potential drops.
  5. Since g_K is higher than normal, V_m can even temporarily drop to below V_r (but not below E_K).

     (This is the cause of after-hyperpolarization.)
  6. As V_m drops, the voltage-gated K^+ channels gradually close, and the passive current flows bring the cell back to V_r.



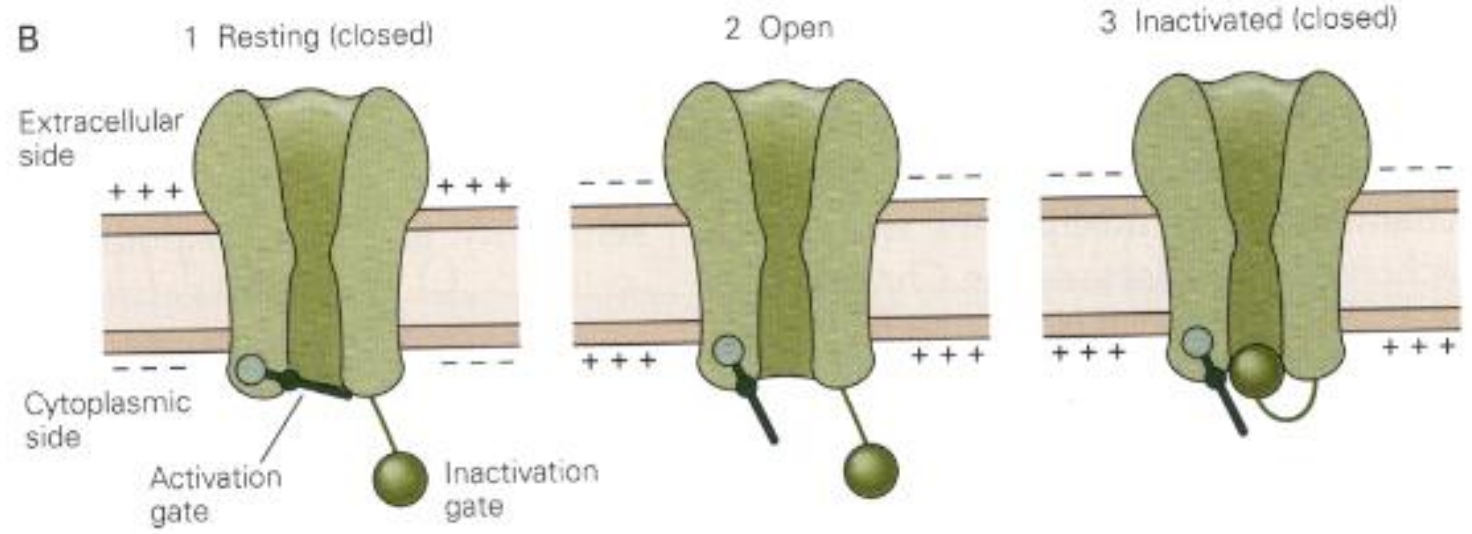


Sodium Channel States



gating current from channel conformation change

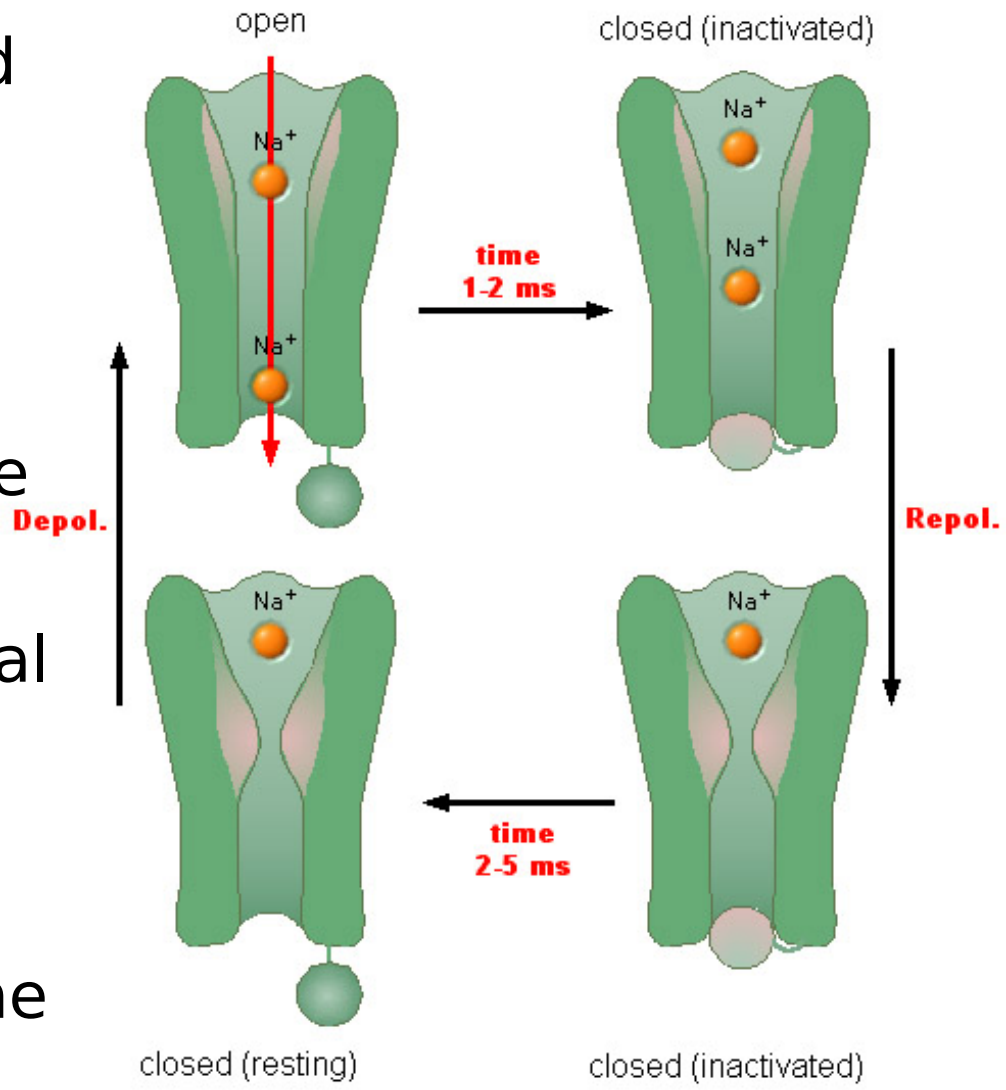
ionic current from flow of Na^+ ions through the channel



Kandel, Schwartz, and Jessel, Princples of Neural Science, 4th ed

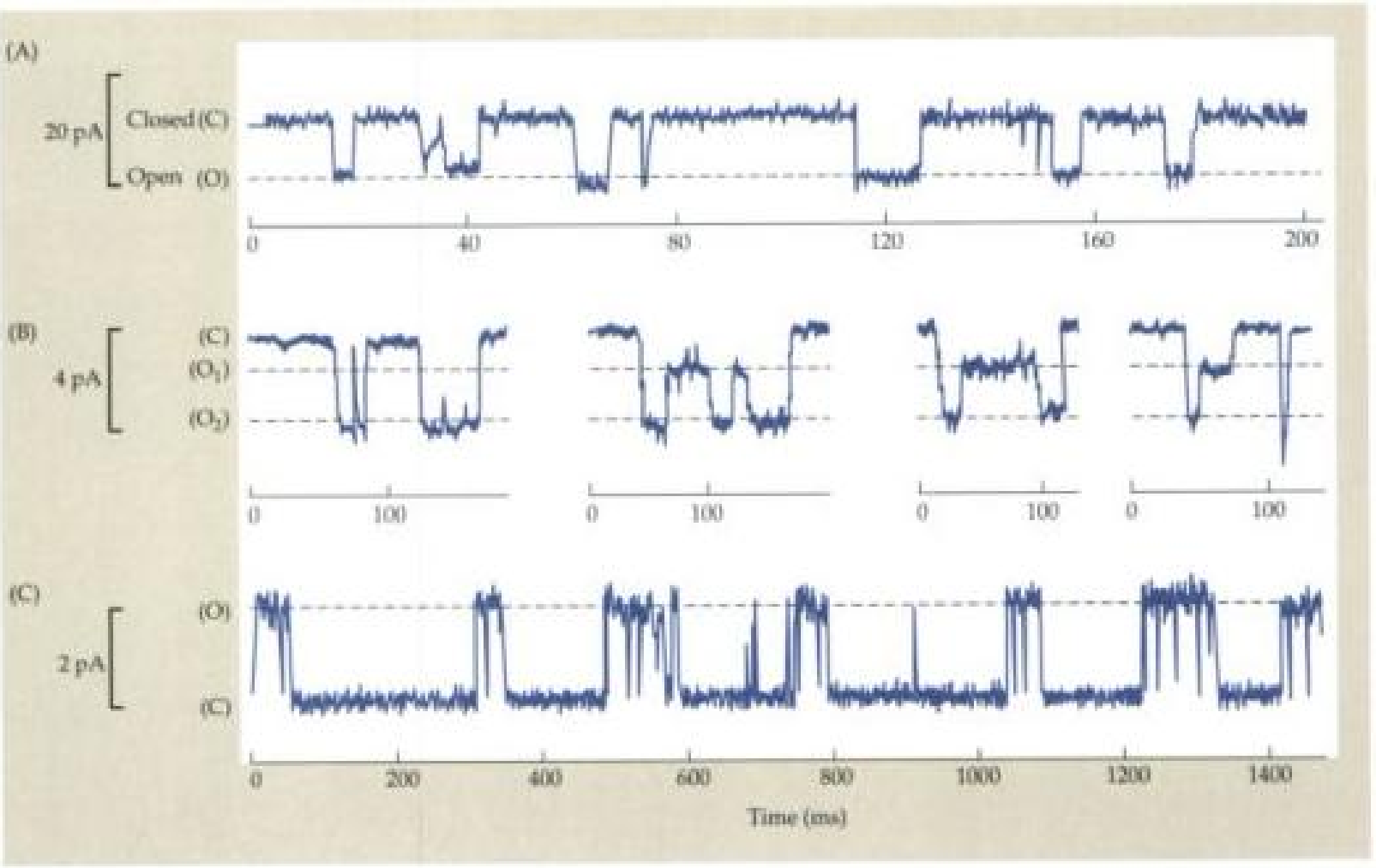
Channel Behavior

- The sodium channel has several states: open, closed (with several substates), and inactive.
- Each state corresponds to a movement of charge within the channel, causing a conformational change in the protein.
- A series of 3-4 conformational changes bring the channel from the closed to the open state.
- Once the channel is open, the inactivation gate can close, blocking ion flow again.



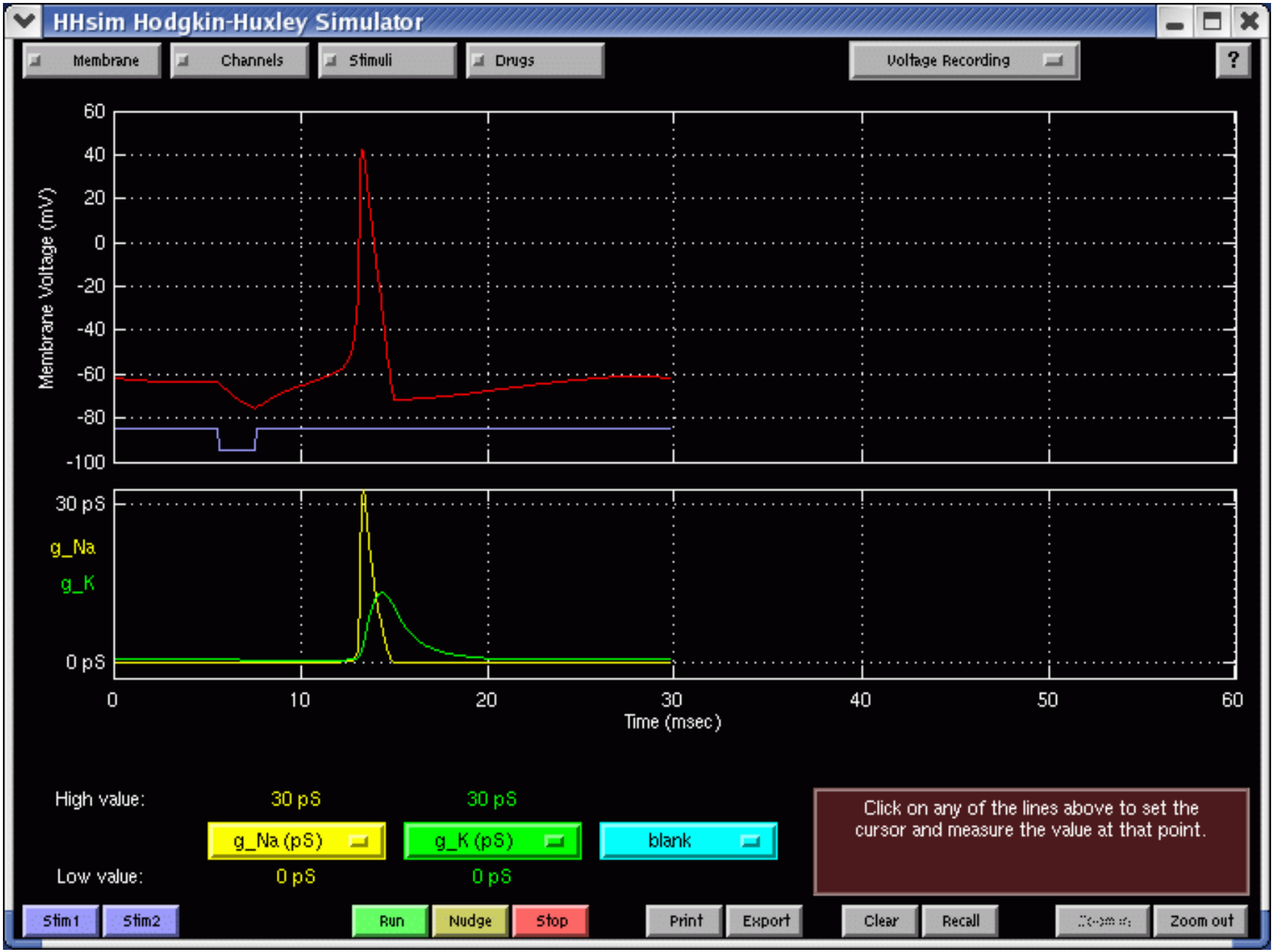
Channel Behavior

- State changes are stochastic, influenced by V_m.



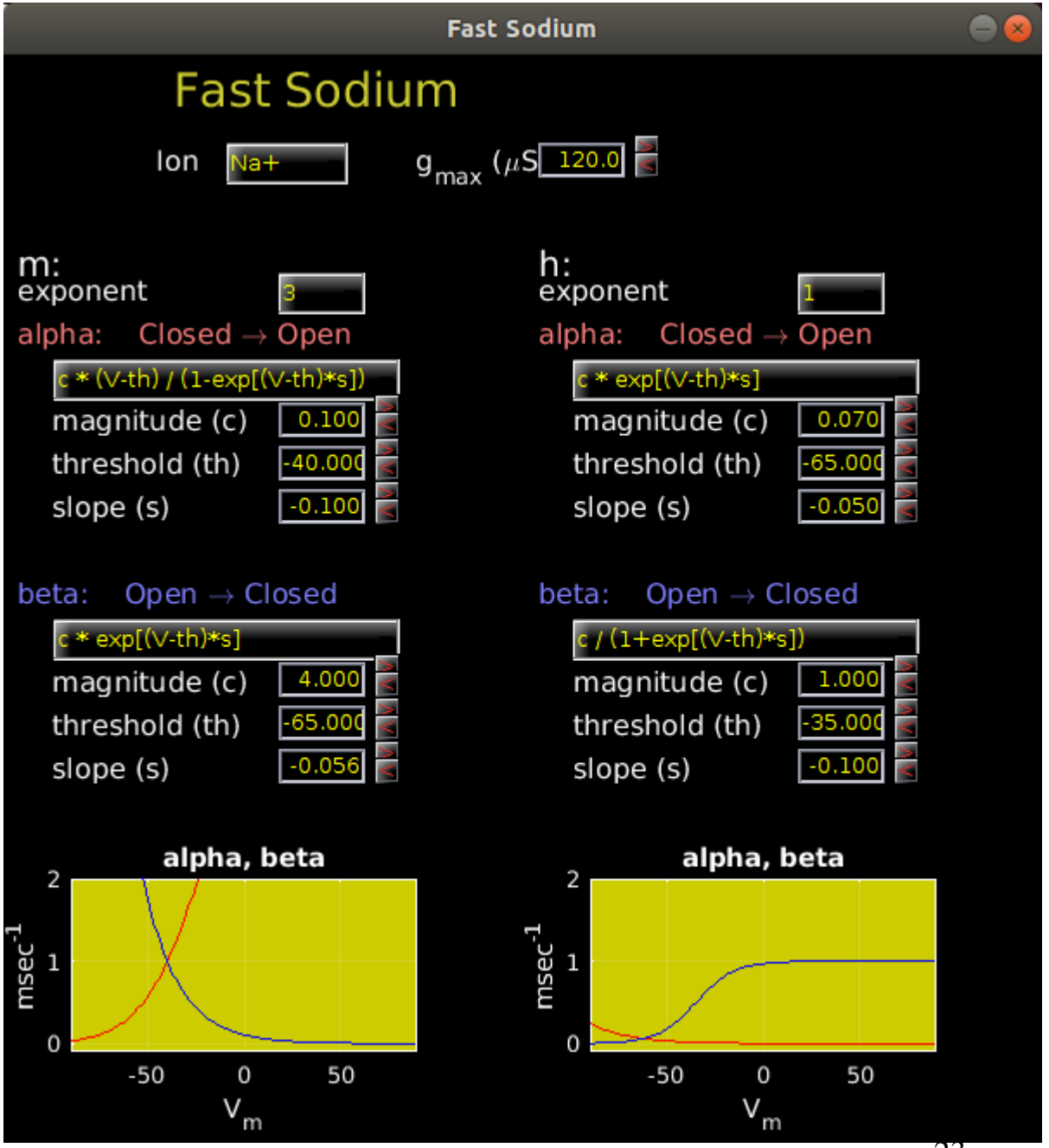
Nichols et al., From Neuron to Brain

Post-Inhibitory Rebound



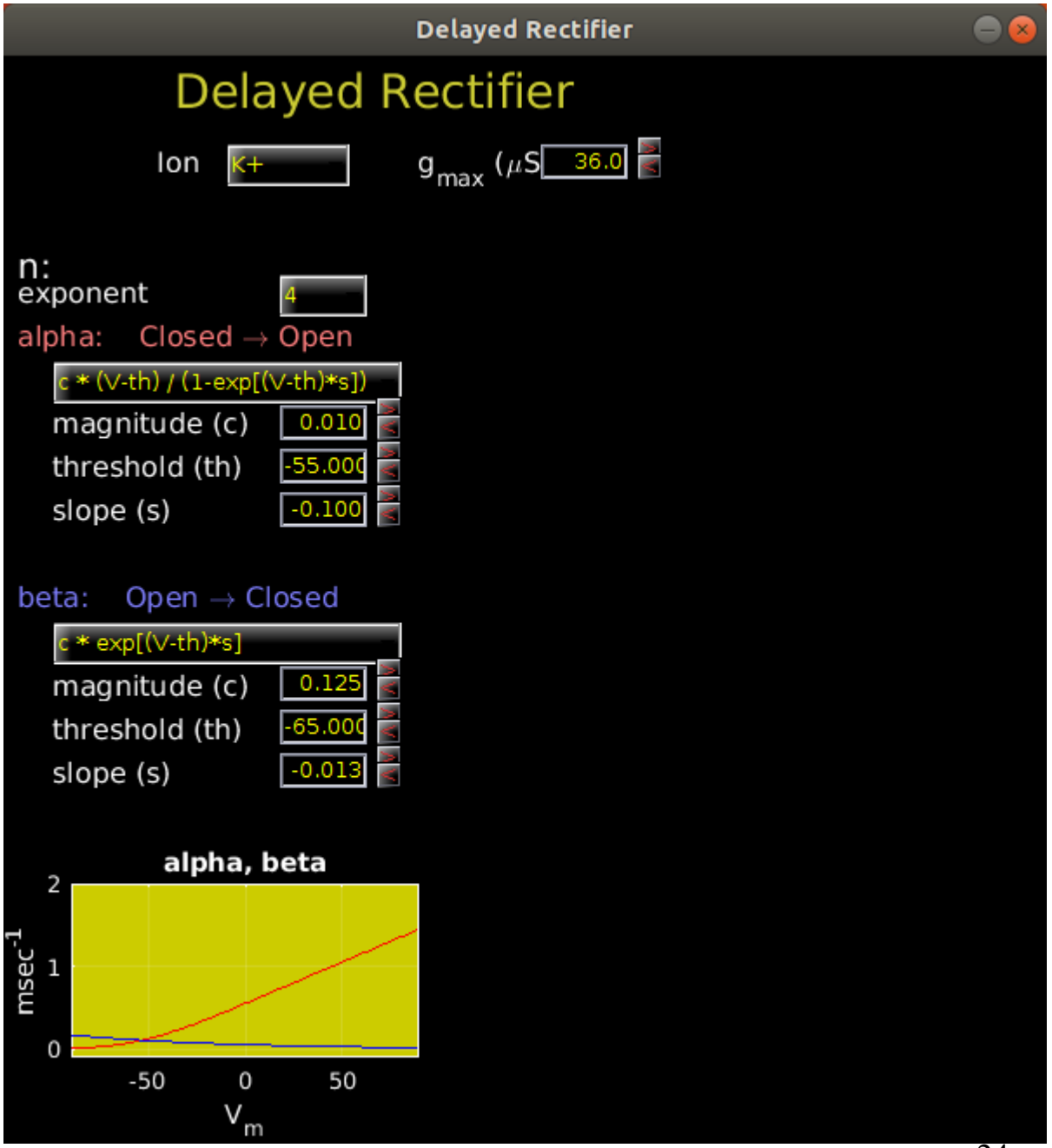
The Hodgkin-Huxley Model

- The voltage-gated sodium channel has 3 activation subunits (m) and one inactivation subunit (h).
- All subunits must be in the “open” state for Na^+ ions to flow.
- Conductance is proportional to m^3h.

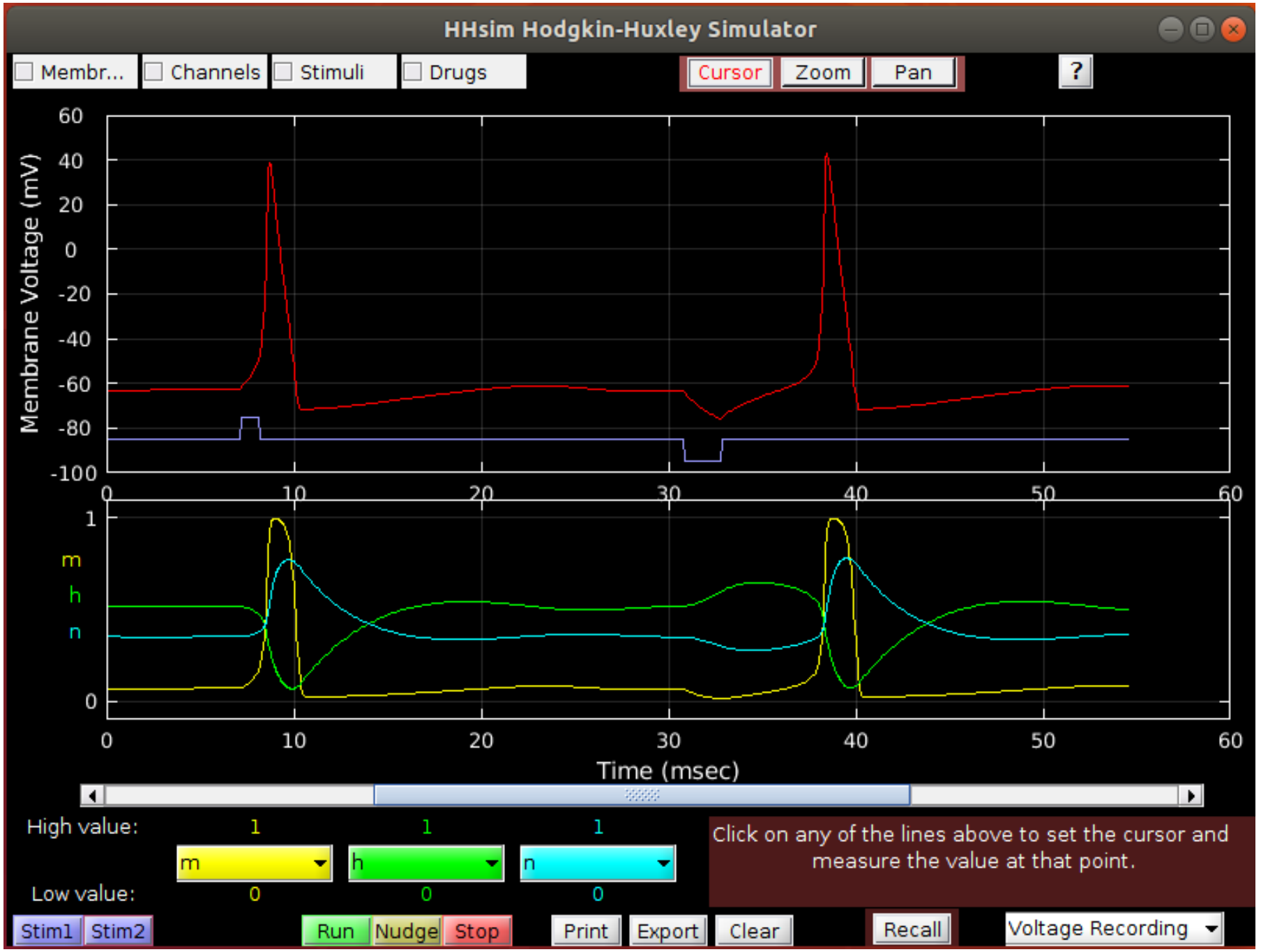


The Hodgkin-Huxley Model

- The voltage-gated potassium channel as 4 activation subunits (n).
- All subunits must be in the “open” state for K^+ ions to flow.
- Conductance is proportional to n^4.



Hodgkin-Huxley Spiking

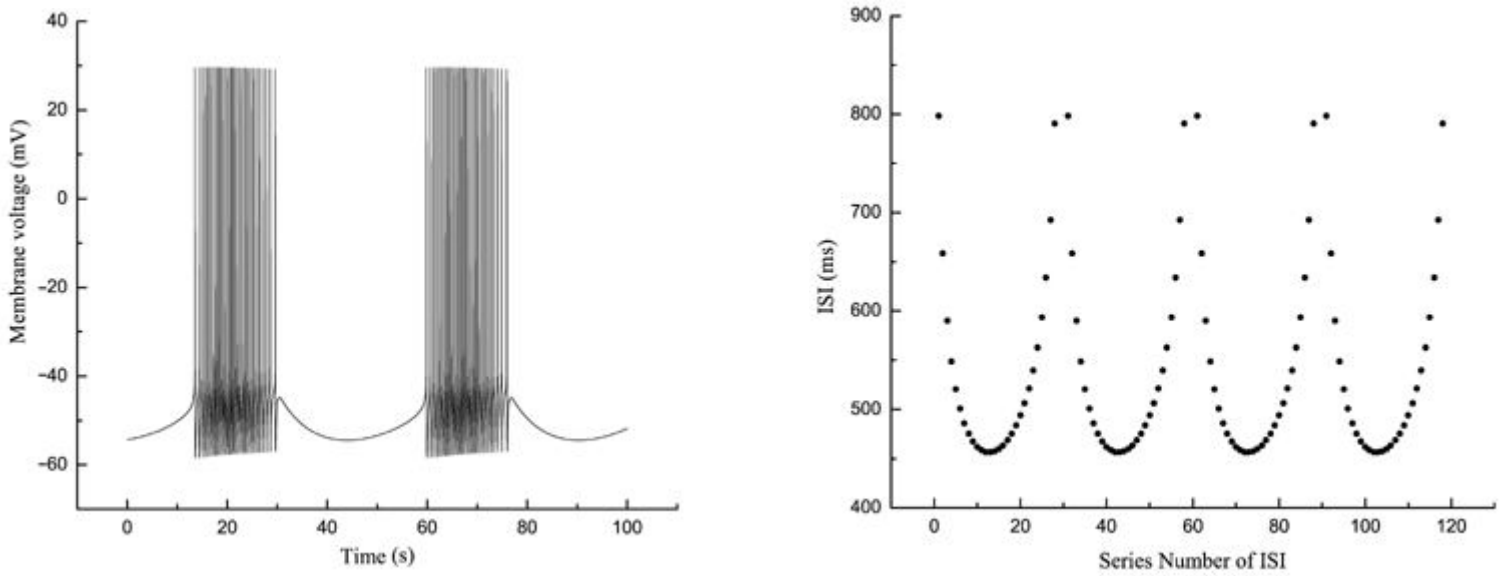


Types of Ionic Currents

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

Parabolic Bursting

- Parabolic bursting in rat sciatic nerve:



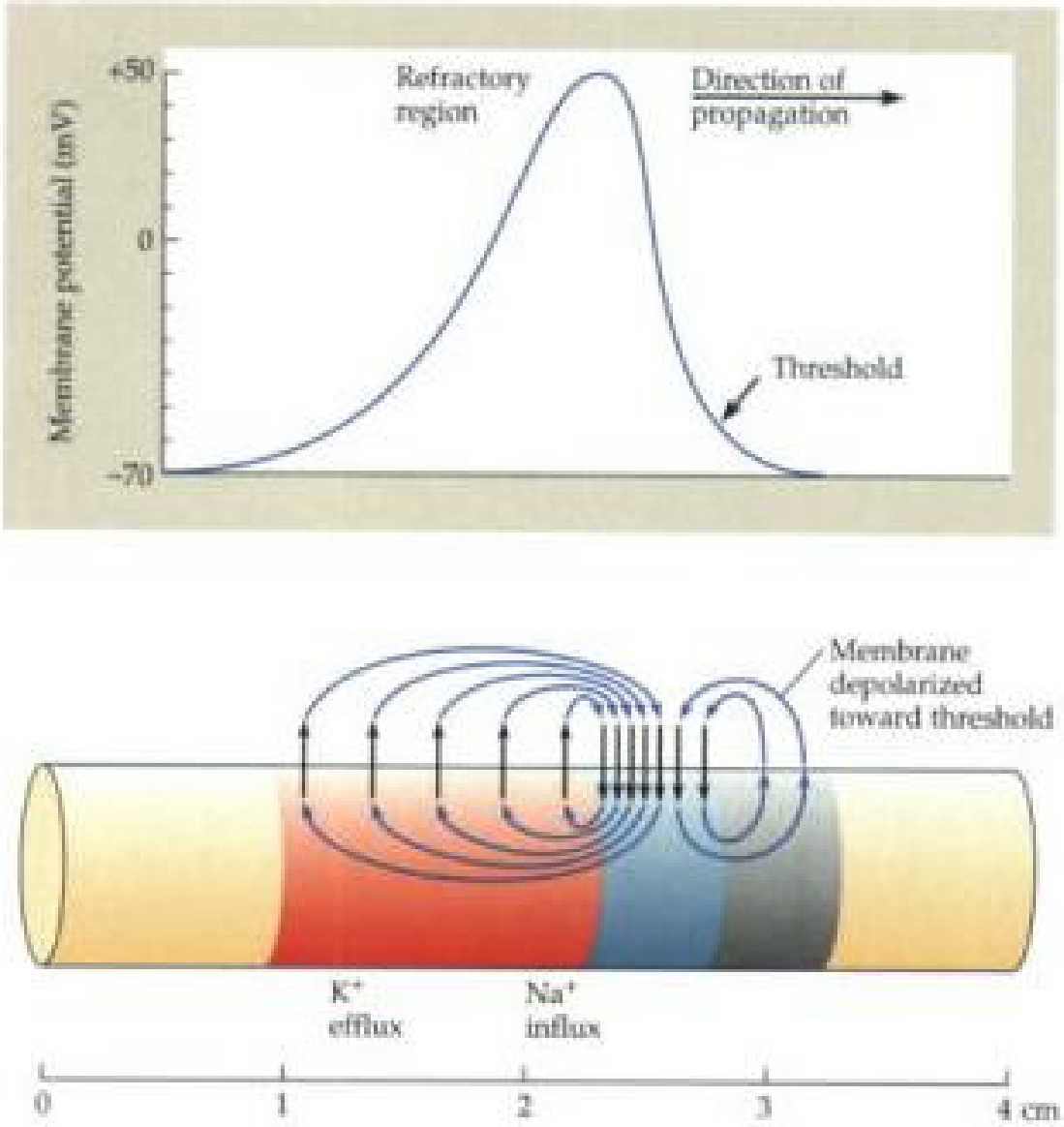
Yong et al. (2003) Parabolic bursting induced by veratridine in rat injured sciatic nerves.

- Aplysia R15 parabolic cell: parabolic bursting involves at least 7 different channel types.

Propagation of the Action Potential

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

Propagation of the Action Potential



Nichols et al., From Neuron to Brain

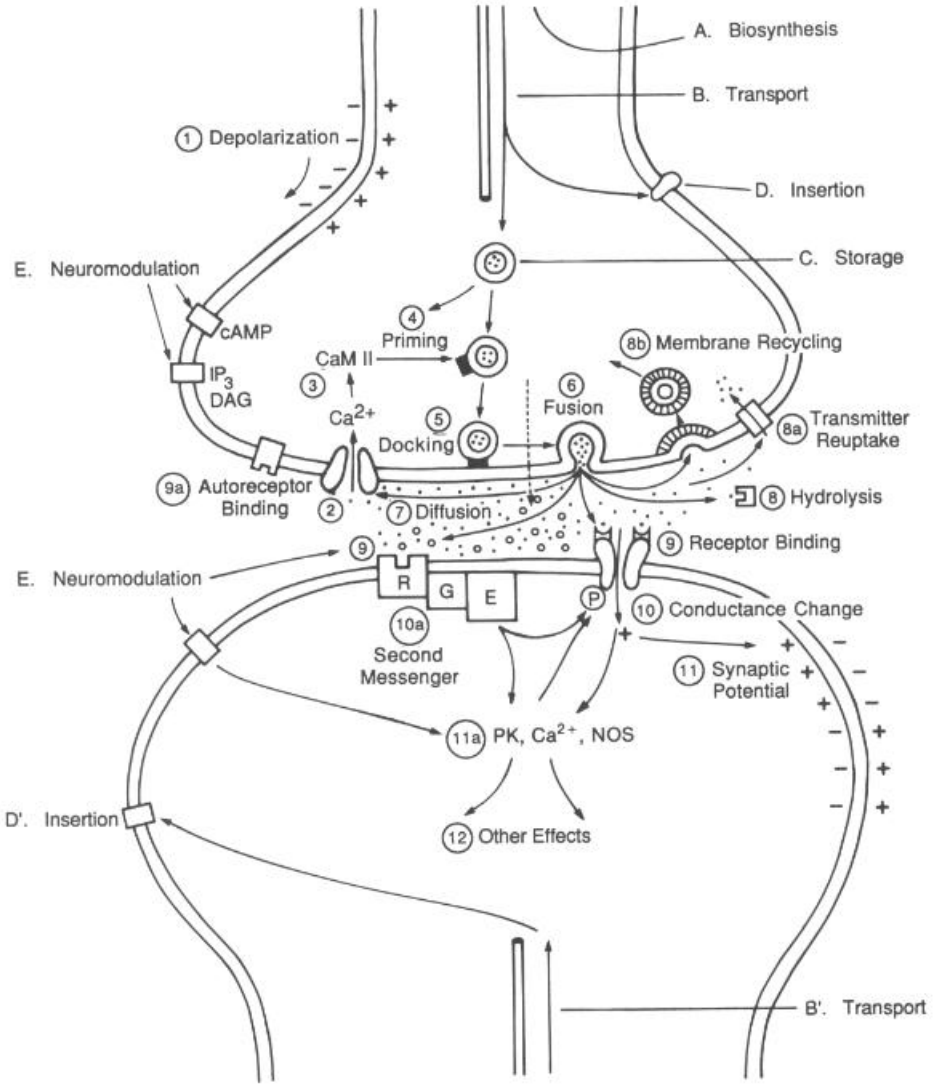
What About Calcium?

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

Transmitter Release

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

Transmitter Release (cont.)



Gordon Shepherd, The Synaptic Organization of the Brain

Neurotransmitters

- A few neurotransmitters you should know about:

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

- Dozens of substances can act as neurotransmitters , including both simple molecules (glutamate, GABA, ACh, dopamine, norepinephrine) and proteins (enkephalin, substance P.)
- Many kinds of channels can be sensitive to the same neurotransmitter.

Neurotransmitters (cont.)

- GABA = gamma aminobutyric acid
- $GABA_A$ receptor: fast shunting inhibition via Cl^- channel.
- $GABA_B$ receptor: slow, long-lasting inhibition via a K^+ current. Not directly coupled to a single ion channel.

- Some receptors are named after substances that enhance or block their response (agonists/antagonists):
  - Muscarinic vs. nicotinic ACh receptors
  - NMDA vs. AMPA glutamate receptors

    NMDA = N-methyl-d-aspartate

    AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

Ligand-Gated Ion Channels

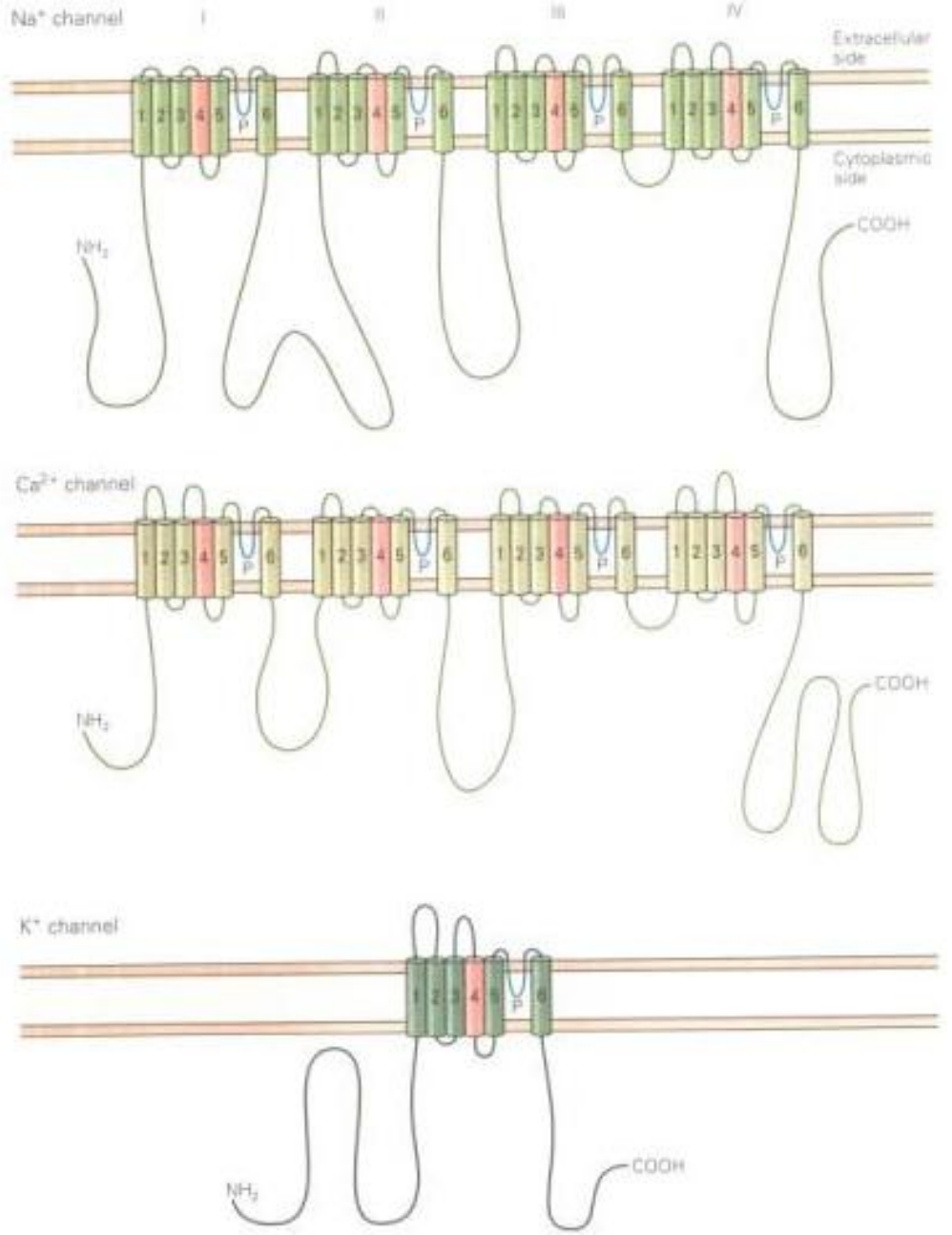
- In the dendrites and soma there are receptors sensitive to particular neurotransmitters.
- In the simplest case, the receptor and ion channel are parts of the same complex. This is a *ligand-gated ion channel.*
- When transmitter binds to the receptor, the channel opens and ions flow.
- Whether a channel is excitatory or inhibitory depends on the kinds of ions it passes.
- For some inhibitory channels, binding of neurotransmitter *prevents* the channel from opening.

Ion Channels Are Proteins

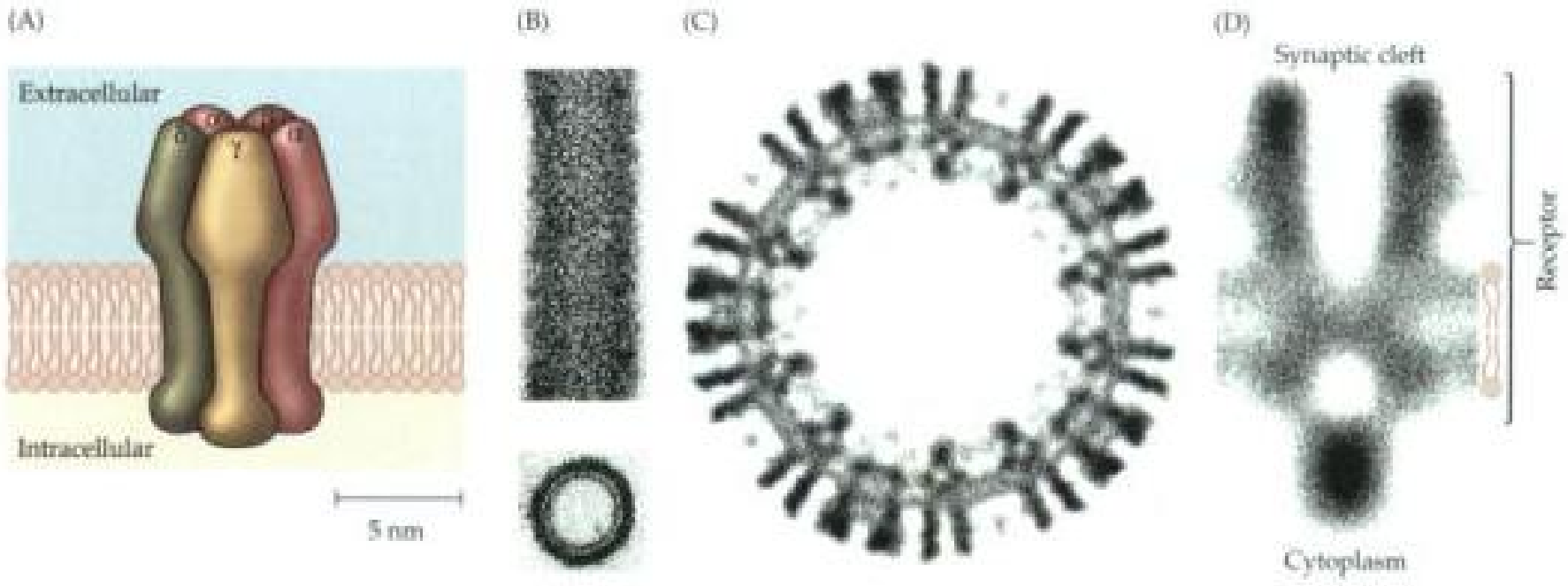
Na^+ channel

Ca^{2+} channel

K^+ channel



ACh Receptor



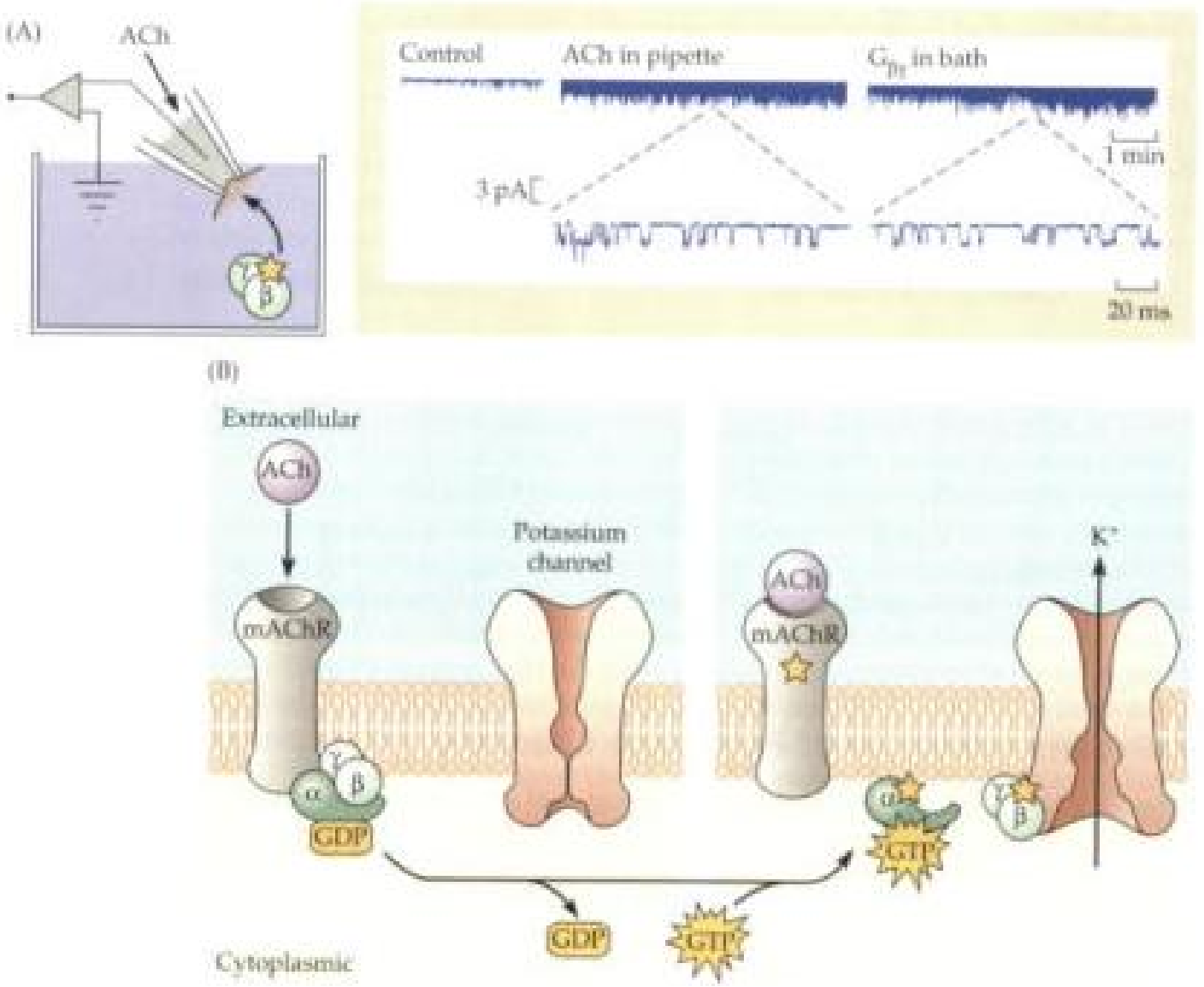
Ion Channels Are Proteins

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

Second Messenger Systems

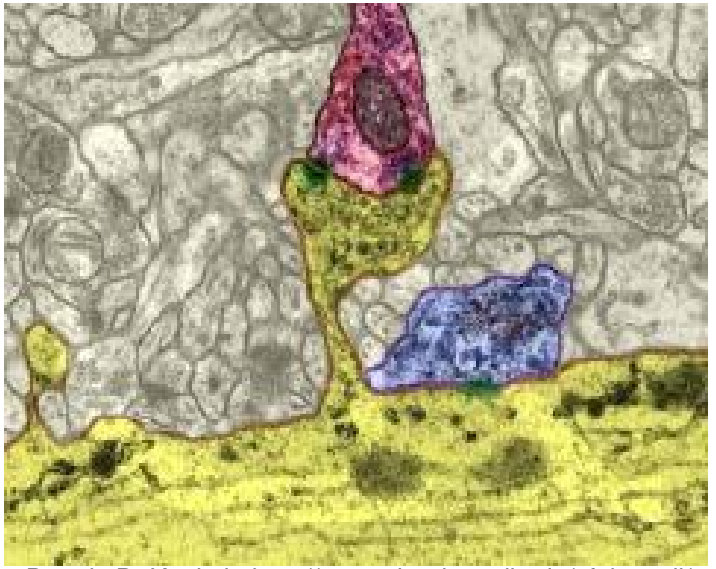
- Instead of being directly coupled to a channel, a receptor can be coupled to a G-protein.
- When transmitter binds to the receptor, this allows GDP (guanosine 5'-diphosphate) bound to the α subunit to be converted to GTP (guanosine 5'-triphosphate).
- The GTP-α subunit complex then detaches from the receptor and can interact with a variety of targets, including ion channels.
- This mechanism allows a single receptor to control several intracellular processes at once.
- The $GABA_B$ receptor is an example of a second messenger system.

Second Messengers



Properties of Dendrites

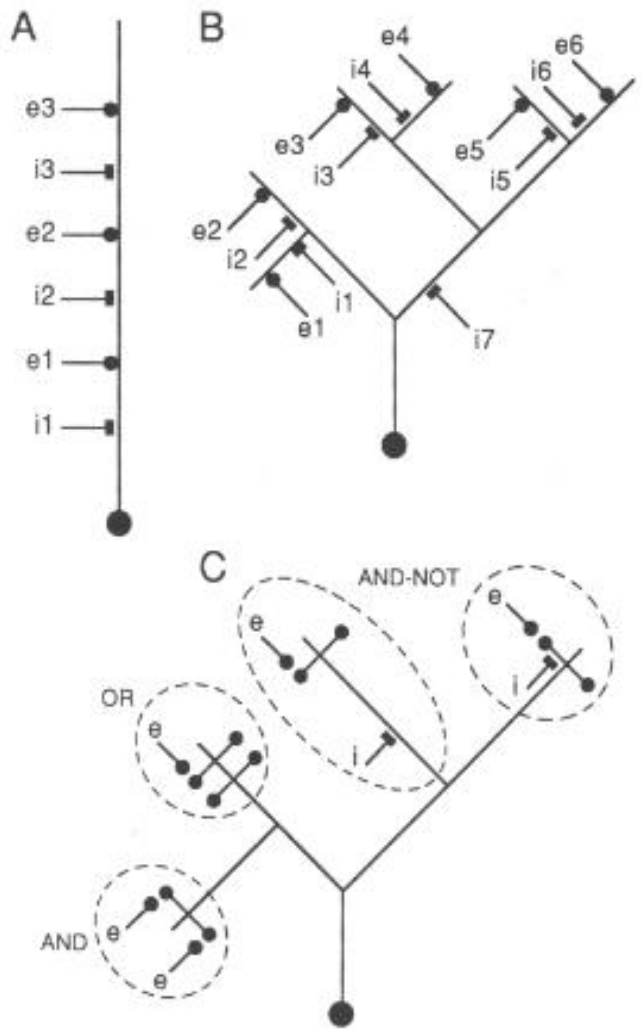
- Passive current flow? Can have Ca^{2+} spikes.
- The *cable equation* defines how current flows in dendritic segments.
  - Must deal with resistance, capacitance, multiple current sources, branched dendritic trees.
- Many synapses in the brain are made onto dendritic spines. Why are there spines?
  - small diameter neck gives high input impedance
  - mini-chemical reactors
- Spines can change shape with experience; another mechanism of learning?



Dennis D. Kunkel; http://www.pbrc.hawaii.edu/sfnhawaii/

Dendritic Information Processing

- Local interactions in the dendritic tree are non-linear.
- Active membrane areas have been found in some dendrites, permitting dendritic spikes to occur.
- “Cold spots” are regions where shunting inhibition suppresses distal epsps, preventing them from traveling further toward the soma.
- AND gates, OR gates, and even AND-NOT gates are possible.
- What do neurons compute? Possibly very complex functions, since there can be 10,000 synapses coming into a pyramidal cell.



Gordon Shepherd, The Synaptic Organization of the Brain

Miscellaneous Items

- Terms to know:

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

- How neuroscientists draw pyramidal cells: