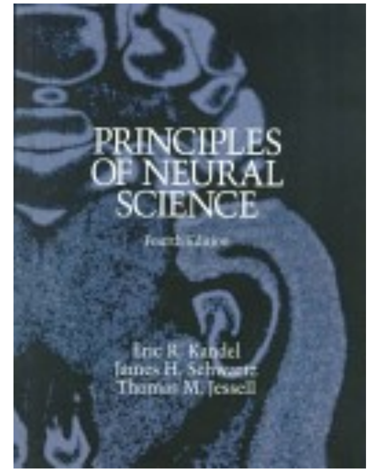
PNS Chapter 7

Membrane Potential

Plan of Action

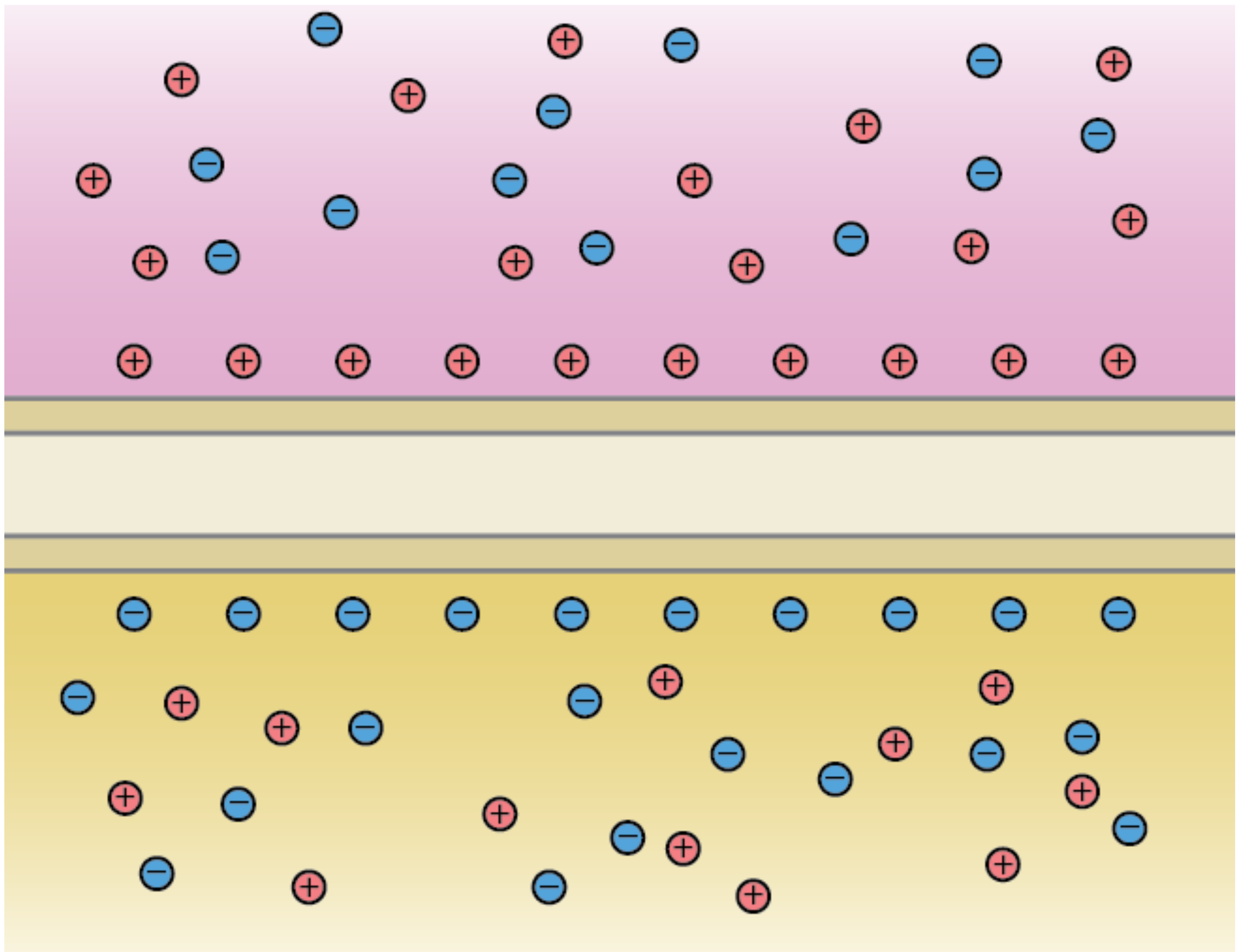


- Introduction to neuroscience
  - Chapter 1 – *The brain and behavior*
  - Chapter 2 – *Nerve cells and behavior*
- How are neural signals generated?
  - Chapter 7 – *Membrane potential*
  - Chapter 9 – *Propagated signaling: the action potential*
- How do neurons communicate with each other?
  - Chapter 10 – *Overview of synaptic transmission*
  - Chapter 12 – *Synaptic integration*

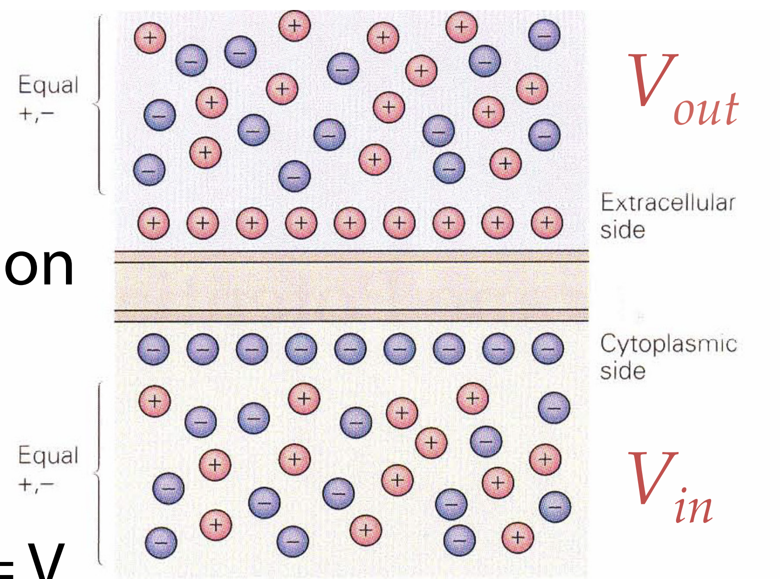
Membrane Potential

- Reading assignment from *Principles of Neural Science*:
  - Chapter 7 – Membrane Potential
  - Chapter 9 – Propagated Signaling: The Action Potential
- Information carried within & between neurons w/ electrical & chemical signals.
- Transient electrical signals (action potentials) critical for transmitting time-sensitive data rapidly and over long distances.
- Action potentials produced by temporary changes in current flow in/out of cell.
- This is turn changes the electrical potential across the cell membrane – the membrane potential.
- Current flow controlled by ion channels in membrane.

Membrane Potential



Charge Separation Across Membrane



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

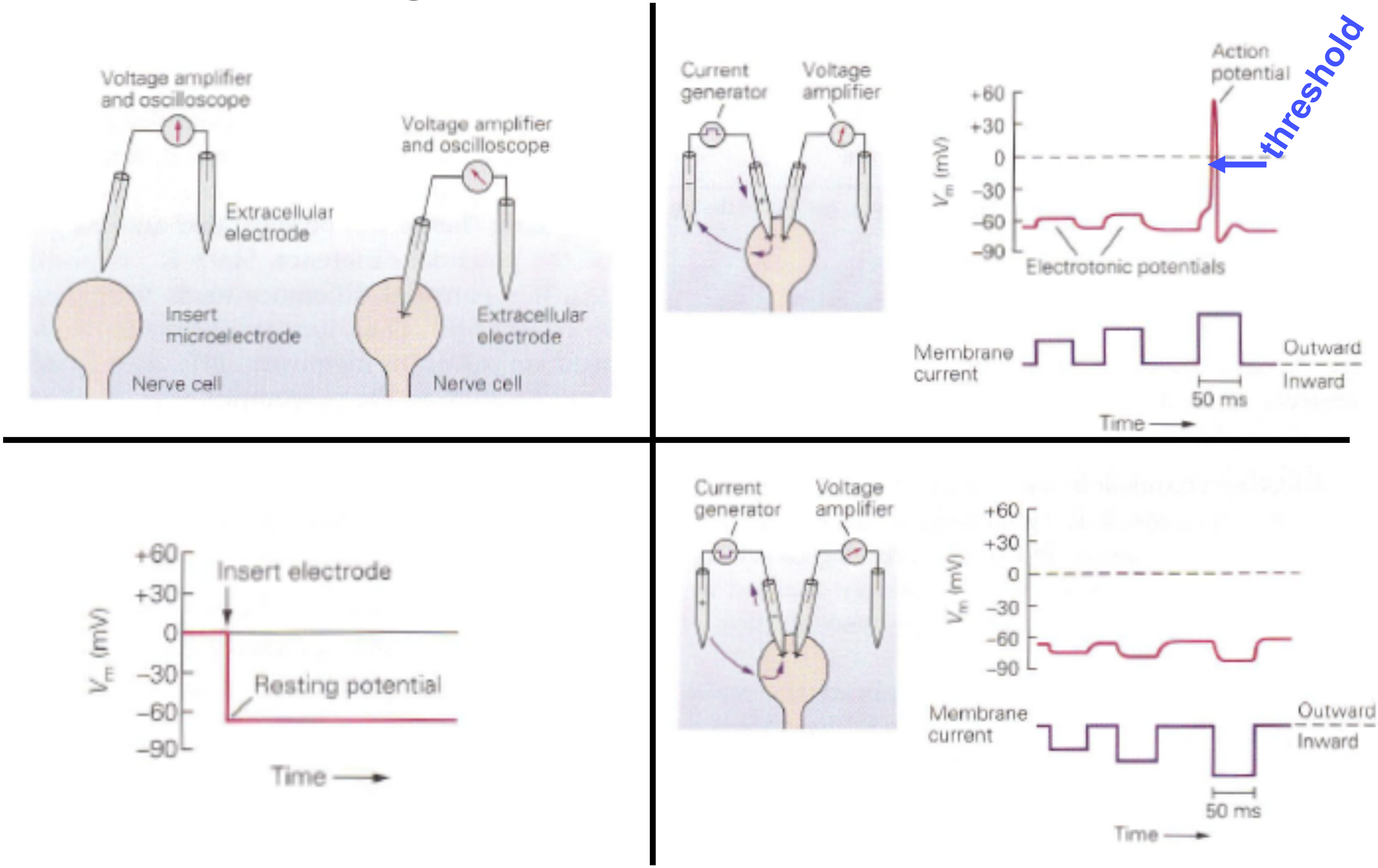
$$V_m = V_{in} - V_{out}$$

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

Resting and Gated Ion Channels

- Resting channels
  - Normally open.
  - Not influenced by membrane potential.
  - Important for maintaining resting membrane potential.
- Gated channels
  - Normally closed.
  - Probability of opening is a function of external factors.
  - External factors: mechanical (pressure or strech) forces, changes in membrane potential, or ligand (chemical transmitter) binding

Recording the Membrane Potential



Resting Potential Determined by Resting Ion Channels

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

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

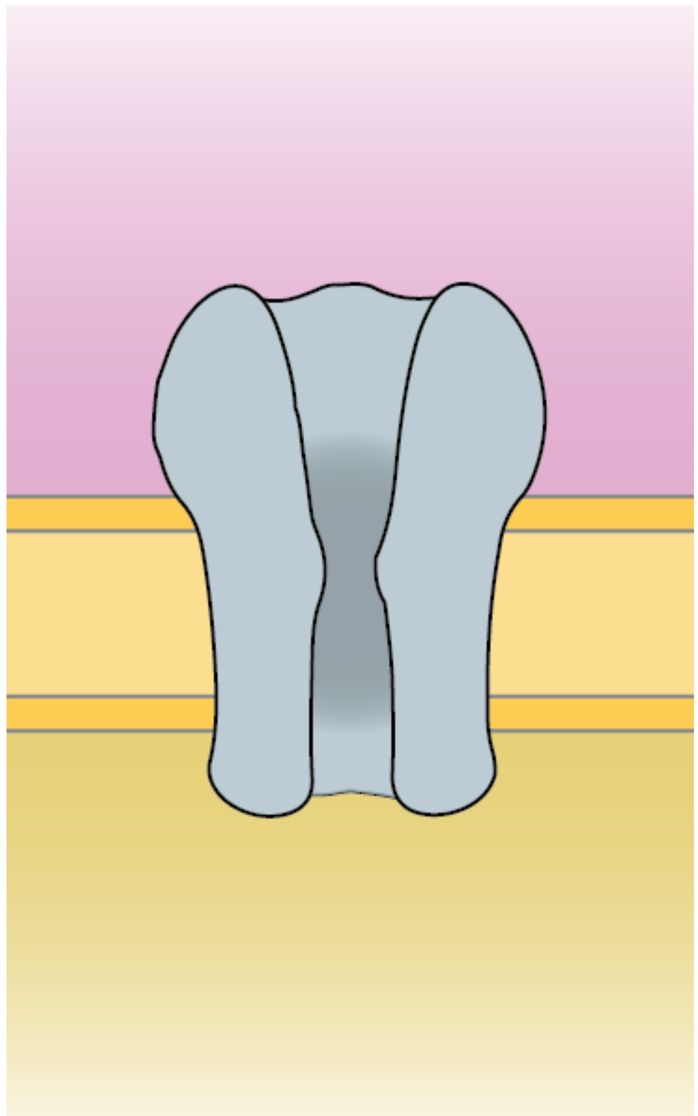
Species of ion	Concentration in cytoplasm (mM)	Concentration in extracellular fluid (mM)	Equilibrium potential[1] (mV)
K^+	400	20	−75
Na^+	50	440	+55
Cl^-	52	560	−60
A^- (organic anions)	385	—	—

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

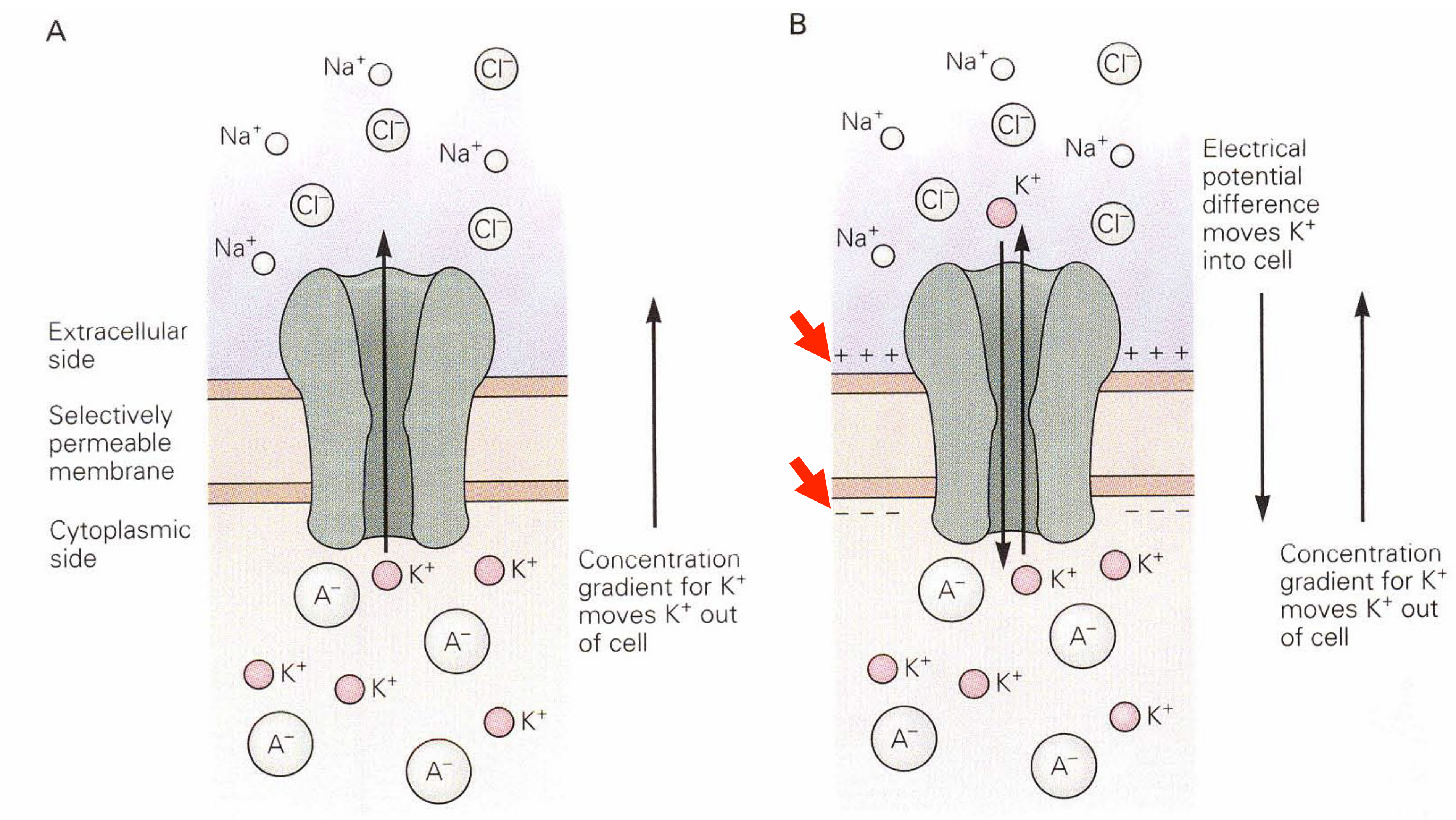
Concentration Gradients & Resting Potential

- Start with glia (membranes permeable to only K^+)
- A high concentration of K^+ and A^- exists inside the cell.
- A high concentration of Na^+ and Cl^- exists outside the cell.
- Intuition:
  - species that *can't* transport through ion channels must stay put (inside or outside of cell)
  - species (i.e., K^+) that *can* transport through ion channels can potentially do so – but there must be a driving force.

Equilibrium Potential



Sketch of Drift and Diffusion Currents



Concentration Gradients & Resting Potential

1. K^+ ions diffuse from inside to outside of cell (down concentration gradient) creating *diffusion current*.
2. Thus, outside accumulates a slight excess of + charge (K^+) and inside accumulates a slight excess of – charge (lack of K^+).
3. Excess charges attract, forming sheet charges along membrane.
4. Sheet charges create electric (E) field, pointing from outside to inside (+ to –).
5. E-field applies force (drift) on K^+ ions in direction of E-field (outside to in). This creates *drift current*.
6. At equilibrium (no net current flow), a specific E-field exists such that drift current is equal and opposite diffusion current.

Deriving the Nernst Equation

Concentration Gradients & Resting Potential

- The potential difference across the membrane associated with this specific E-field is termed the equilibrium potential (E_K).
- As per previous table, $E_K = -75$ mV.
  Note: don't be confused, here E is a voltage not an electric field.
- Equilibrium potential for arbitrary ion X given by Nernst equation:

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

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

Calculating Resting Potential

Calculating Resting Potential

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

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

- Or, including a factor of 2.3 to convert ln to $\log_{10}$:

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

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

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

Calculating Resting Potential

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

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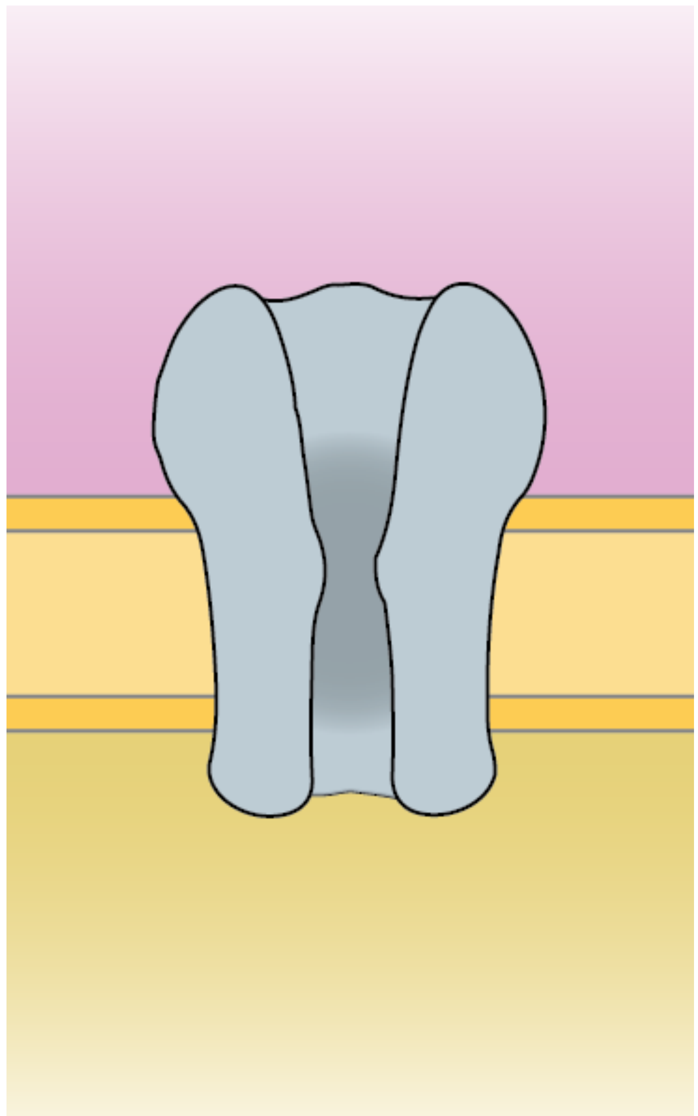
[1]The membrane potential at which there is no net flux of the ion species across the cell membrane.

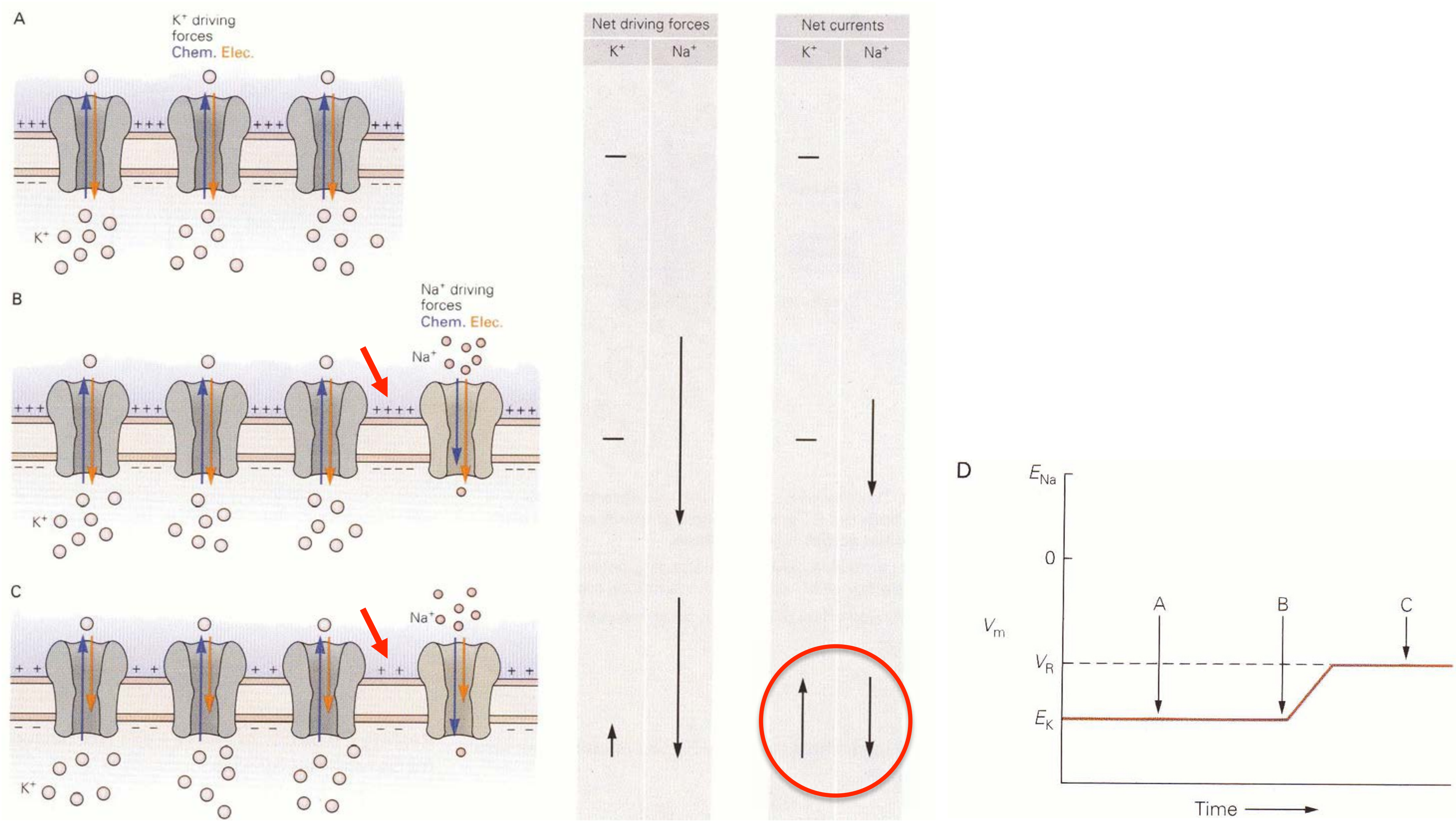
Concentration Gradients & Resting Potential

- What about neurons (instead of glia)?
  - Neurons at rest are permeable to Na+ and Cl- ions, in addition to K+ ions.
  - A- ions unable to permeate; thus set aside.
  - When multiple ion species can permeate membrane, a new resting potential is established such that net current flow is zero (steady state).

Equilibrium Potential with 2 Ions

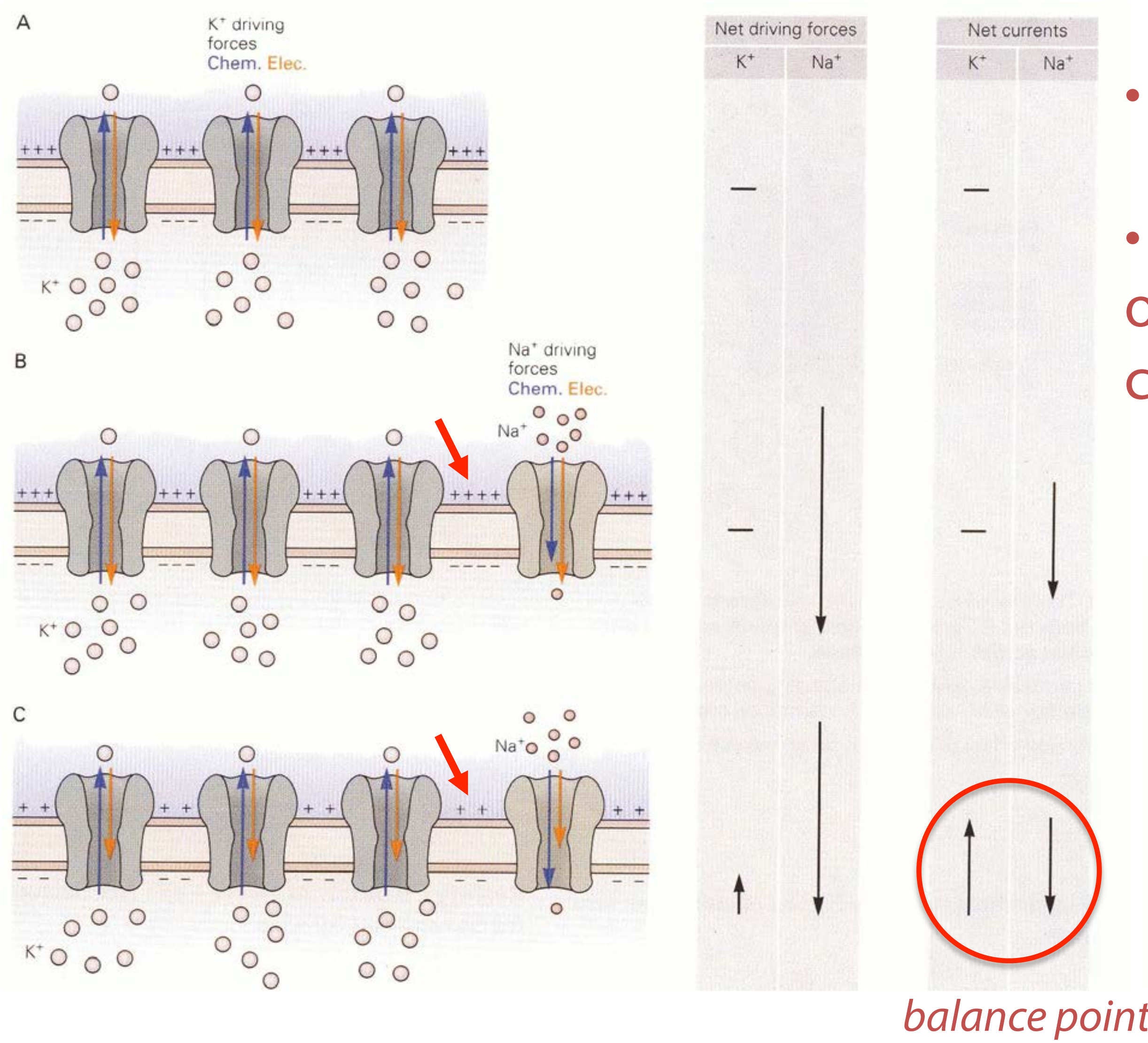


Understanding Resting Potential w/ 2 Species

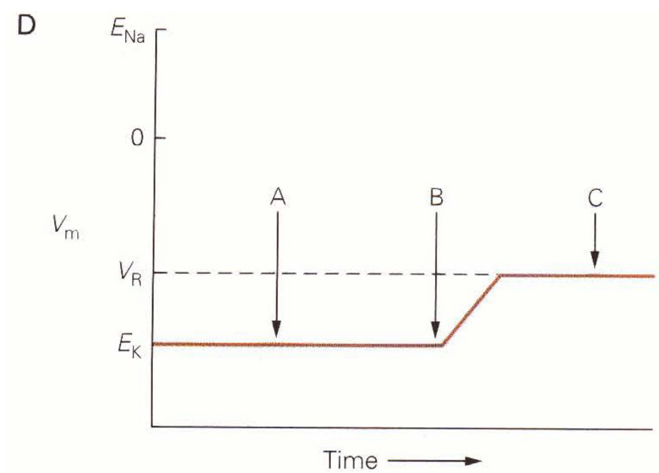


balance point

Understanding Resting Potential w/ 2 Species



- Why isn't Na^+ flux huge?
- Can these equal and opposite K^+ and Na^+ continue indefinitely?



Why isn't Na^+ influx huge?

- Ion flux is the product of electrochemical driving force and membrane conductance to that ion:

  ion flux = (electrical driving force + chemical driving force) × membrane conductance

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

Na+ - K+ Pump

- Now assume that the resting potential has been achieved.
- Passive movement of K^+ out of cell = passive movement of Na^+ into cell.
- But these concentrations gradients will eventually run down, thereby reducing the resting membrane potential!
- Need Na^+ - K^+ pump.
- Moves Na^+ and K^+ against their net electrochemical gradients.
- Moves Na^+ out of cell; moves K^+ into cell.
- Pump requires energy (ATP hydrolysis).
- Continuous passive influx of Na^+ and efflux of K^+ through resting channels is counterbalanced by Na^+ - K^+ pump.
- Pump: membrane-spanning protein; 3 Na^+ ions out for every 2 K^+ ions in.

Quick Peek at Action Potentials

- If the membrane is depolarized past the "threshold voltage" then voltage-gated Na^+ channels open rapidly.
- Thus Na^+ influx exceeds K^+ efflux → further depolarization → even more voltage-gated Na^+ channels open → …   (positive feedback system)
- Takes V_R very close to $E_{Na} = +55$ mV because permeability to Na^+ is predominant.
- Why does membrane ever repolarize, to end action potential?
  - Voltage-gated Na^+ channels gradually inactivate.
  - Voltage-gated K^+ channels are slow, but eventually open.

Multiple Ions: Goldman Equation

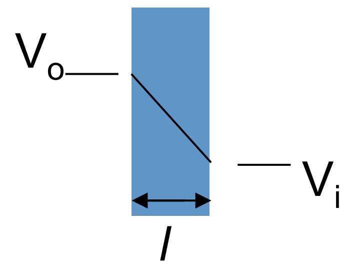
Goldman-Hodgkin-Katz or Constant Field Model

Nernst Planck Equation:

$$I_j = -z_j F D_j \left(\frac{d\left[C_j\right]}{dx} + \frac{F z_j \left[C_j\right]}{RT} \frac{dV}{dx} \right)$$

Assumptions:

- Ions move independently through the membrane
- Variation in the electric field across membrane is constant



$$\frac{dV}{dx} = \text{constant} = \frac{V_m}{l}$$

Solution:

$$I_j = -z_j^2 P_j \frac{F^2 V_m}{RT} \left(\frac{\left[C_j\right]_i - \left[C_j\right]_o e^{-\frac{z_j F V_m}{RT}}}{1 - e^{-\frac{z_j F V_m}{RT}}} \right)$$

Where:

$$P_j = permeability = \frac{D_j}{l}$$

This is the GHK Current Equation

Deriving the GHK Voltage Equation

- For multiple ion species, at equilibrium, the net current flux is zero. So, starting with:

$$\sum_j I_j = \sum_j -z_j^2 P_j \frac{F^2 V_m}{RT}\left(\frac{\left[C_j\right]_i - \left[C_j\right]_o e^{-\frac{z_j F V_m}{RT}}}{1 - e^{-\frac{z_j F V_m}{RT}}}\right) = 0$$

- If only monovalent ions are present, then:

$$V_m = \frac{RT}{F}\ln\left(\frac{\sum\limits_{\text{positive ions}} P_X\left[X\right]_{outer} + \sum\limits_{\text{negative ions}} P_Y\left[Y\right]_{inner}}{\sum\limits_{\text{positive ions}} P_X\left[X\right]_{inner} + \sum\limits_{\text{negative ions}} P_Y\left[Y\right]_{outer}}\right)$$

Goldman Equation: V_R w/ Multiple Species

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

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

- Species with highest concentration and permeability dominates. Consider limit cases:
  - At rest, permeability of K^+ dominates.
  - At peak of action potential, permeability of Na^+ dominates.

Dynamic range of action potential waveform

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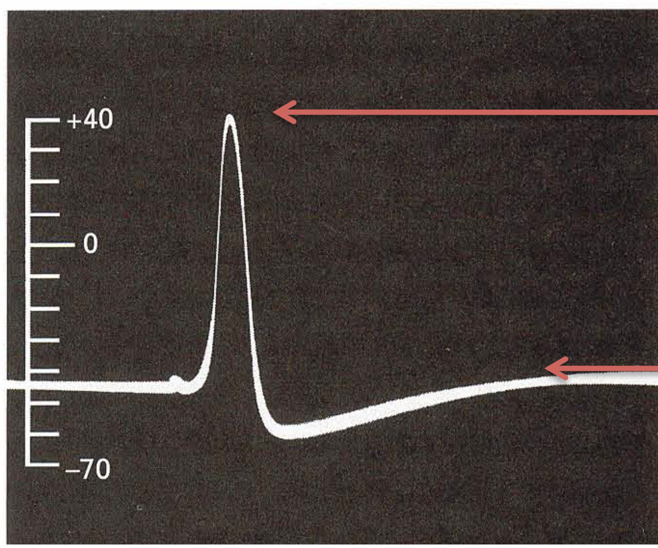
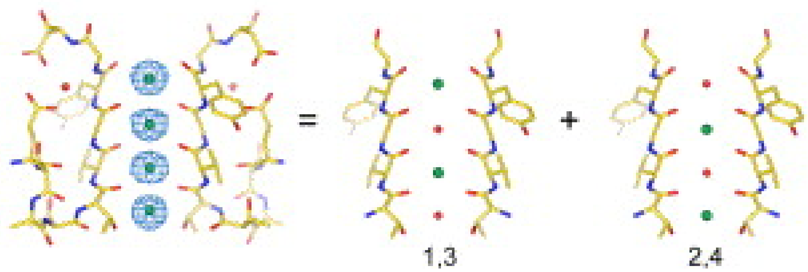
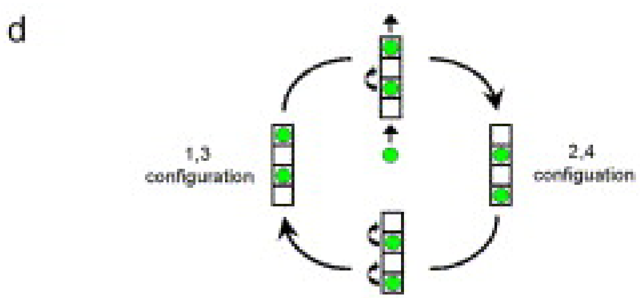


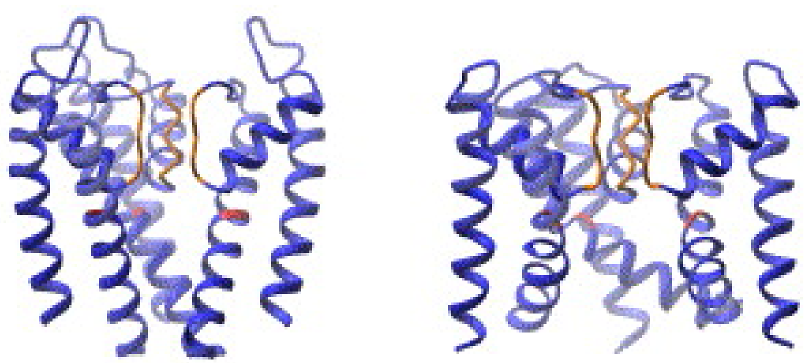
Near E_{Na}

Near E_K

K^+ Channel

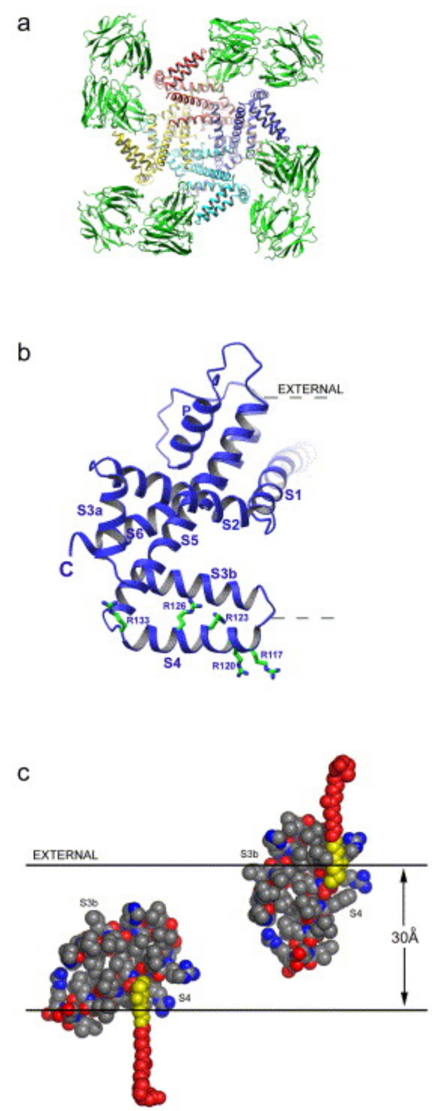






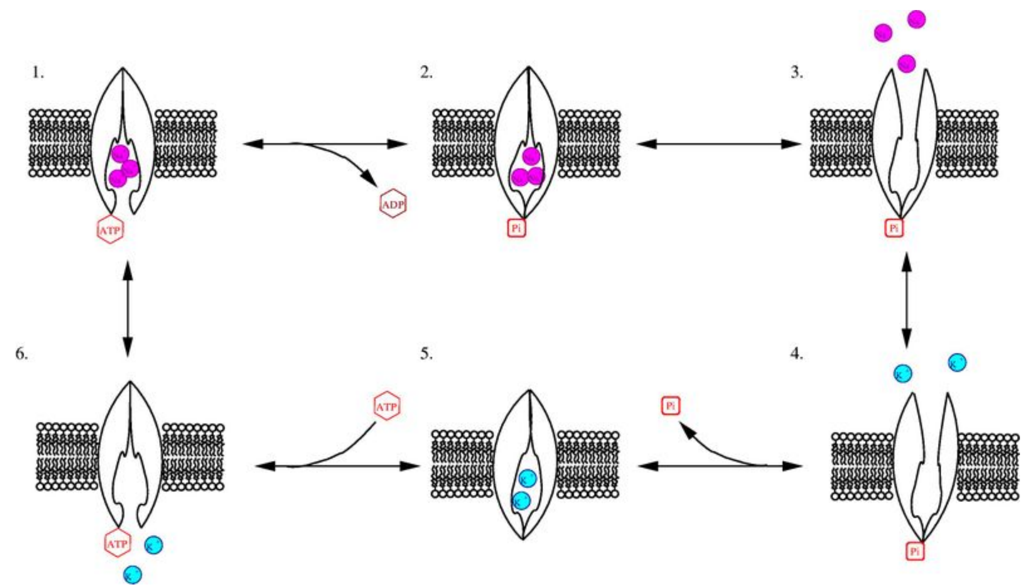
Closed

Opened



Mechanism of Na^+/K^+ ATP-ase

1. Pump bound with ATP binds 3 intracellular Na+ ions
2. ATP hydrolized
3. Pump undergoes conformation change, Na+ ions released outside
4. Pump binds 2 extracellular K+ ions
5. Pump reverts conformational state
6. K+ ions released inside



http://en.wikipedia.org/wiki/Sodium_potassium_ATPase

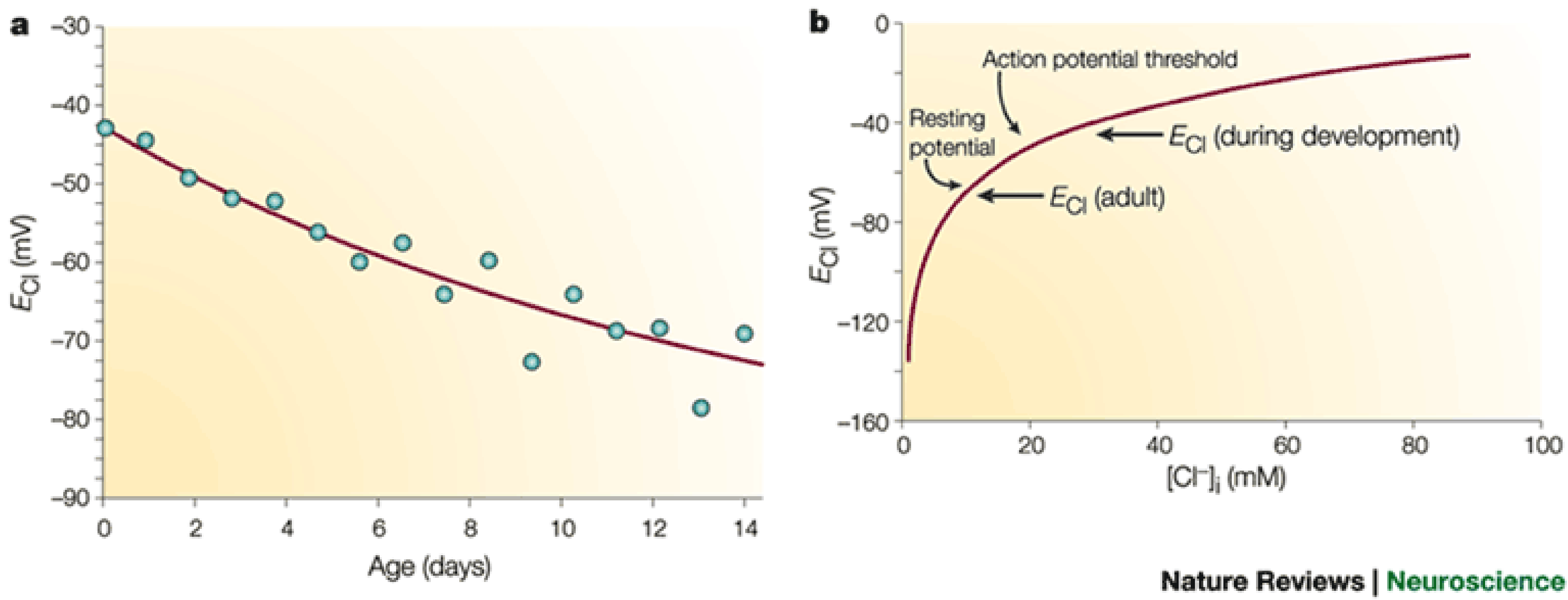
GABA during development

- γ-aminobutyric acid is a "neurotransmitter" that is usually inhibitory
- $GABA_A$ receptor is a "ligand-gated" ion channel
- Potassium-chloride transporters normally maintain
- In adult neurons, $[Cl^-]$ is 140 mM outside and 7 mM inside.
- In baby neurons, $[Cl^-]$ inside is closer to 40 mM
- What are the different resting membrane potentials?

Chloride Resting Potentials

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

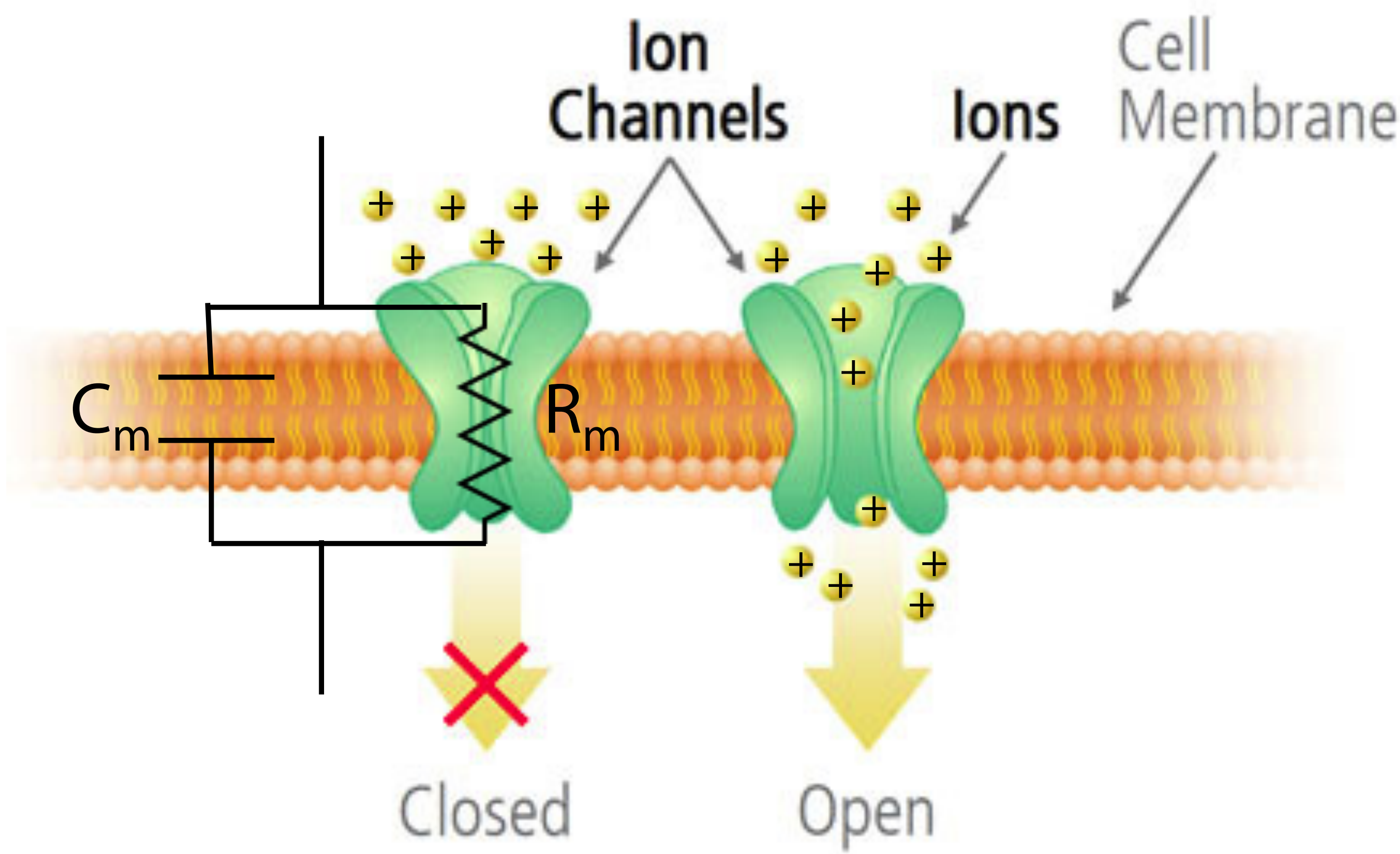
GABA during development



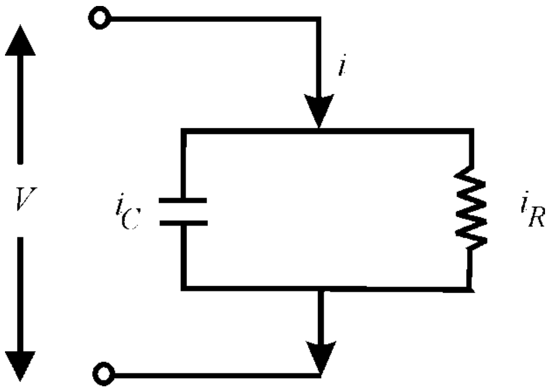
- GABA excitatory during development, inhibitory in adulthood!

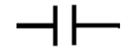
[Ben-Ari, Y., *NRN* 2002]

The cellular membrane as an equivalent circuit



Passive Membrane Properties

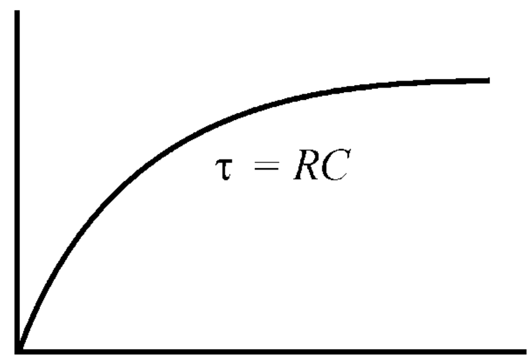


- R is the resistance of the membrane 
- C is the capacitance. 
- V is the voltage across the membrane.
- i_C and i_R are currents through the capacitor and resistor.

$$i = i_c + i_R \quad \Rightarrow \quad i = C\frac{dV}{dt} + \frac{V}{R}$$

$$\frac{i}{C} = \frac{d(V)}{d(t)} + \frac{1}{RC}V$$

$$V = iR(1 - e^{-\frac{t}{RC}})$$



<u>Typical values for resistance and capacitance</u>

Specific resistance = 10^4-10^5 Ω cm^2

Total resistance = 1-10 GΩ

Specific capacitance = 1 μF cm^{-2}

Total capacitance = 10 pF

The RC time constant is typically 1-10 ms.

Passive Membrane Properties

- What is the relative capacitance of a big neuron vs a small neuron?
- Which will be able to depolarize faster?

Equivalent Circuit w/Ion Channels

Equivalent Circuit w/Ion Channels