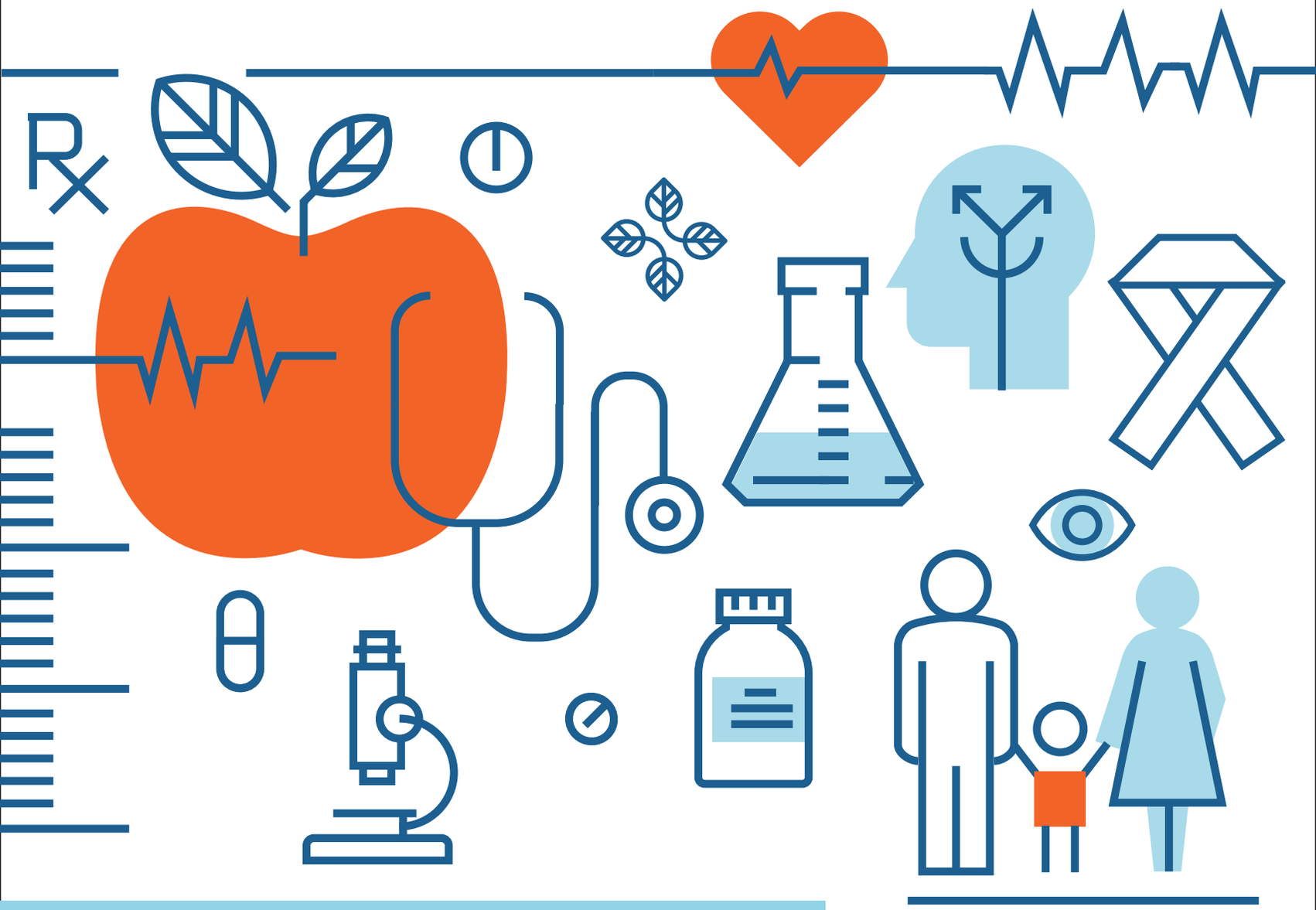


PSL300H:

Fall 2021

Human Physiology I

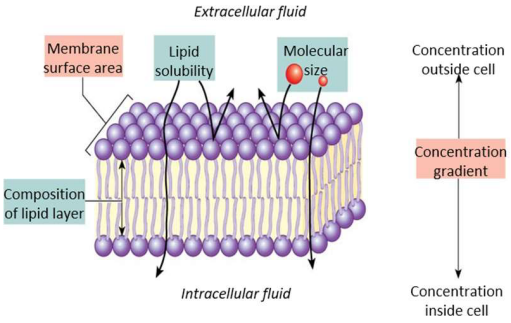
Week 0-1

TABLE OF CONTENTS

FUNDAMENTALS

MEMBRANE

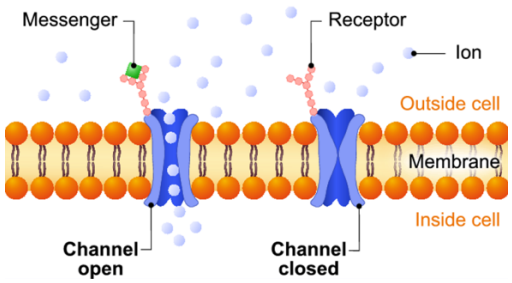
1. Composition of cell membrane
    a. Phospholipid
    b. Protein
2. Permeability
    a. Membrane which will only allow certain molecules or ions to pass through by diffusion.
    b. Determined by molecular size, charge, lipid solubility.



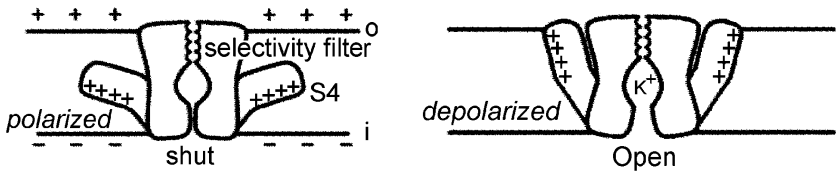
TRANSPORTATION ACROSS MEMBRANE

1. **Passive diffusion (Down electrochemical gradient, Energy from ATP is NOT required)**
    a. Simple diffusion
        i. Small lipid soluble molecules.
        ii. Gases.
    b. Facilitated diffusion.
        i. Require assistance from carrier protein.
        ii. Polar or charged molecules (sugar, amino acid).
2. **Active Transport (Against electrochemical gradient)**
    a. Active transport
        i. Energy from ATP hydrolysis is required.
        ii. Require protein pump.
    b. Secondary active transport
        i. Energy from ATP is NOT required.
        ii. Protein is required.
        iii. Requires other molecules that are moving down the electrochemical gradient.

3. **Channel**
    a. Can be classified as facilitated diffusion.
    b. Do NOT require energy from ATP.
    c. Channel can be OPEN or CLOSED.
    d. Channel can be gated:
        i. Ligand-gated: Open once a chemical ligand is bound.



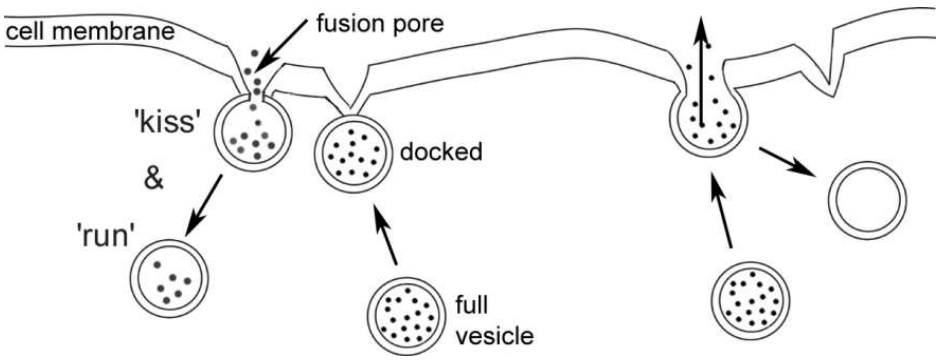
        ii. Voltage-gated: Open once a voltage changed in the membrane potential.



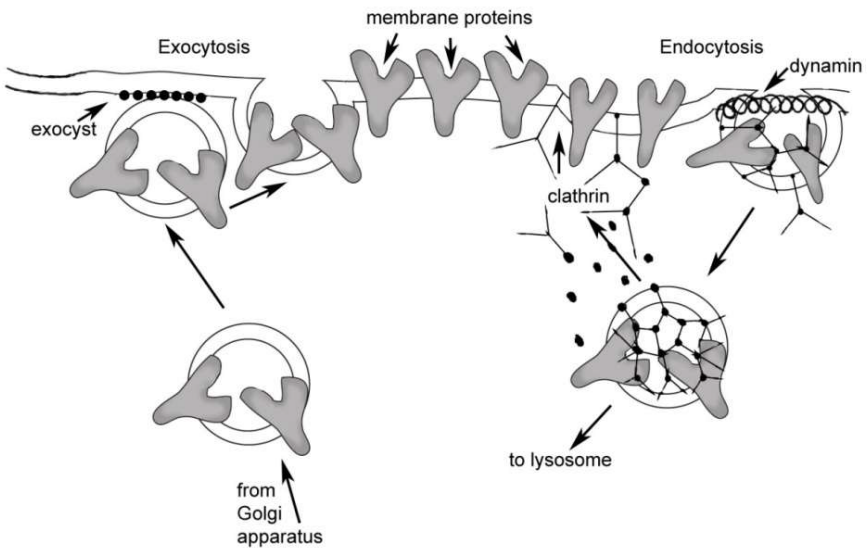
        iii. Mechanically-gated: Open in response to physical deformation.

ENDO/EXOCYTOSIS

1. Endocytosis:
    a. Inward 'pinching' of membrane to create a vesicle.
    b. Capture proteins from outside to inside.
2. Exocytosis:
    a. Partial or complete fusion of vesicles with cell membrane for bulk trans-membrane transport of specific molecules, from inside to outside.
    b. Types of exocytosis:
        i. Kiss and Run



ii. Full exocytosis



MEMBRANE POTENTIAL

RESTING MEMBRANE POTENTIAL

1. Generating membrane potential:
    a. Concentration gradient
    b. Semi-permeable membrane
2. Value of resting membrane potential: **-70 mV**:
    a. Equilibrium potential of K^+: -90 mV:
        i. Membrane is most permeable to K^+.
        ii. K^+ ions are moving out of the cells until reaches the equilibrium potential.
        iii. Due to K^+ leaking out of the cells, inside of membrane will be negative.

    b. Na+/K+ pump
        i. **1 ATP hydrolysis = 3 Na^+ are pumped OUT + 2 K^+ are pumped IN the cells**.
        ii. Due to Na^+/K^+ inequality, the potential difference wil be -10 mV.

3. Calculation of potential
    a. Nernst Equation:

$$V_{\text{Eq.}} = \frac{RT}{zF} \ln\left(\frac{[X]_{\text{out}}}{[X]_{\text{in}}}\right)$$

        i. The equation gives the potential difference across the membrane, inside with respect to outside, at equilibrium.
        ii. The Nernst equation is valid if and only if 1 ion species is diffusing across the membrane.
    b. Goldman Equation

$$E_m = \left(\frac{RT}{F}\right) \ln\left(\frac{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_i}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_o}\right)$$

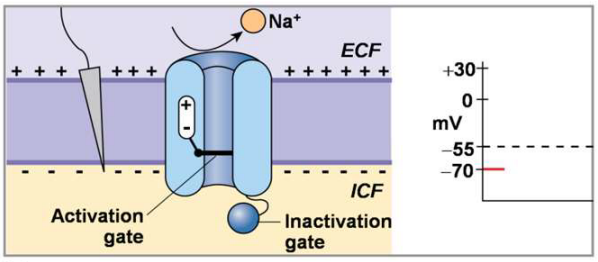
        i. There are several different ions are involved to generate resting membrane potential including K^+, Na^+, and Cl^-.
        ii. Actual membrane potential can be calculated from an expanded equation containing a term for each diffusable ion species.
4. Equilibrium potential for other ions
    a. Na^+ ions
        i. Under certain circumstances (**Opening of Na^+ Channel**), the permeability of Na^+ can be dominant and much more than then K^+ ion and membrane potential can change drastically.
        ii. Membrane potential is positive inside with respect to the outside: E_{Na+} = +60 mV.
        iii. **At equilibrium, there is a net cation accumulation inside the membrane**.
    b. Cl^- ions
        i. Inside the cell, we have large proteins (which are basically trapped, they can only get across to the outside using exocytosis), and since they tend to have "-" charges, the Cl^- ion is pushed out of the cell.
        ii. Therefore, the Cl- ions tend to be more concentrated on the outside in the extracellular space.

ACTION POTENTIAL

SODIUM CHANNEL

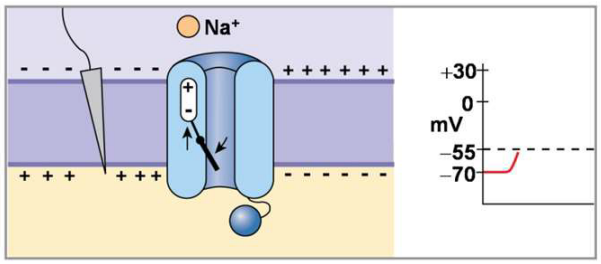
1. Na+ channel is **voltage-gated**.
2. Under normal resting membrane potential, the Na^+ channels are closed.
3. Na+ channels are open in response to **depolarization**.

4. Mechanism of actions
   a. Na^+ channel is normally closed at -70 mV.



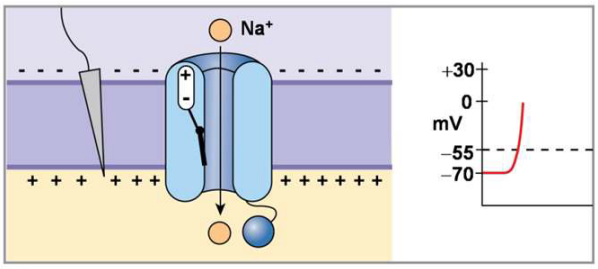
(a) At the resting membrane potential, the activation gate closes the channel.

   b. Na^+ channel is only opened by depolarizing the membrane to a threshold potential of about -55 mV.

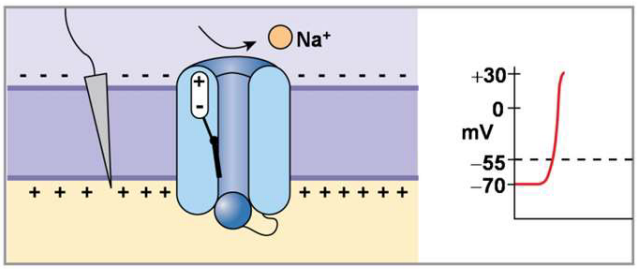


(b) Depolarizing stimulus arrives at the channel. Activation gate opens.

   c. Na^+ channel inactivation then takes place.

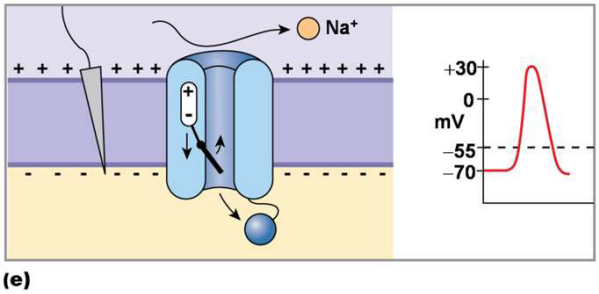


(c) With activation gate open, Na^+ enters the cell.



(d) Inactivation gate closes and Na^+ entry stops.

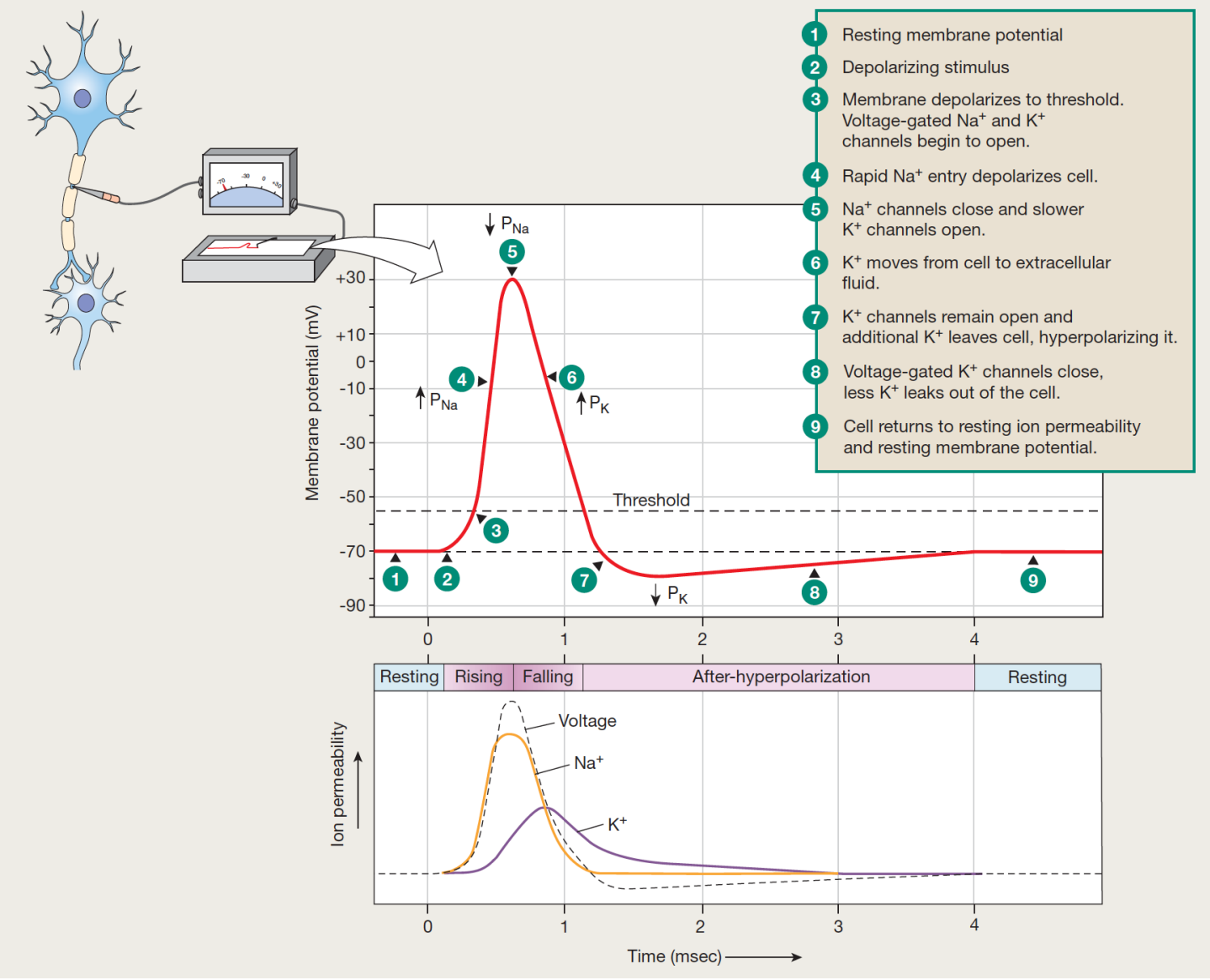
   d. To remove inactivation, the membrane potential needs to fall below threshold again.



(e)

ACTION POTENTIAL

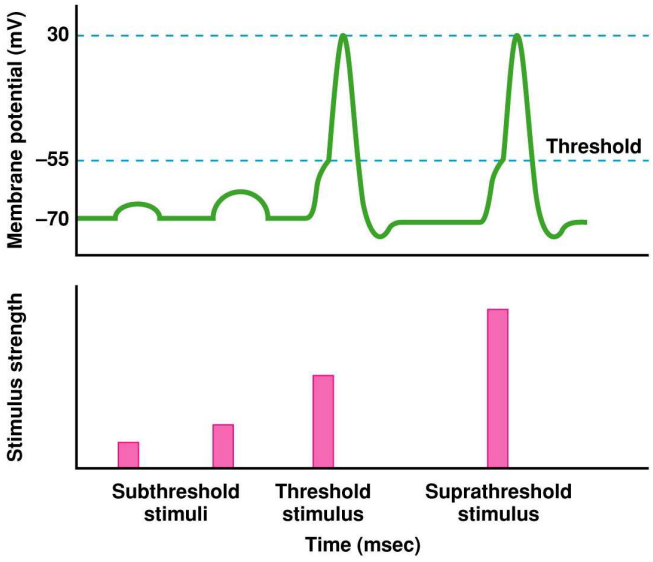
TYPICAL ACTION POTENTIAL



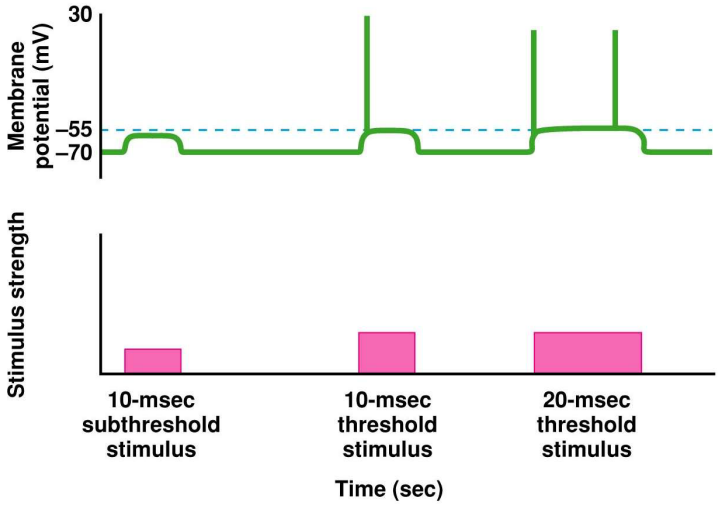
FEATURE OF ACTION POTENTIAL

1. Threshold
    a. Minimum depolarization (-55mV) is required to induce an action potential (opening of Na^+ channel).
        i. Sub-threshold stimulus
        ii. Threshold stimulus
        iii. Supra-threshold stimulus

2. All or None Principle
    a. Action potential from threshold and supra-threshold stimulus have the same magnitude.

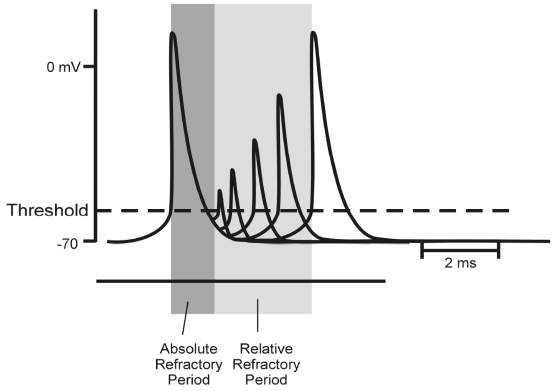


3. Frequency Coding
    a. Information pertaining to stimulus intensity is coded by the changes in the frequency of the Action Potential



4. Refractory Period
    a. After we generate an AP and inactivate the Na^+ channels, we have a period in which all or some Na+ channels are inactivated.
    b. Na+ channels remain inactivated until membrane potential drops below 'threshold', then channels reconfigure to their original state and membrane becomes excitable again.
    c. Types of refractory period:
        i. Absolute: None of channels are reconfigured.

ii. Relative: Some but not all of channels are reconfigured.

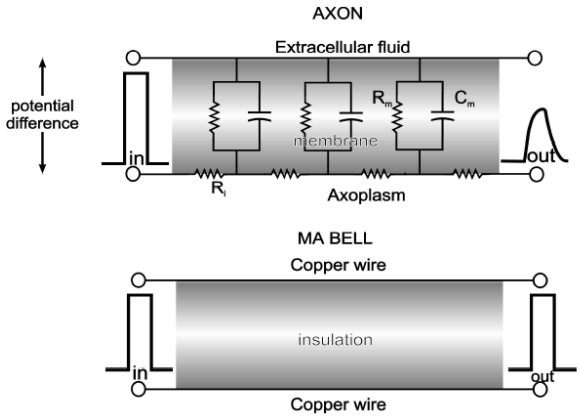


5. Depolarization Block (To prevent the membrane from producing an action potential)
    a. Keep the membrane depolarized
    b. Depolarization will keep the Na^+ channels permanently inactivated → No action potential can be generated.
    c. Achieved by disruption of K^+ gradient (Inject high concentration of K^+).
6. After-hyperpolarization
    a. K+ channel will repolarize membrane potential to -90mV.
    b. This phase brings membrane back to -70mV.
    c. Potassium leaking channel and Na^+/K^+ ATPase together contribute to this phase.

IMPULSE CONDUCTION

EXCITABLE CELLS

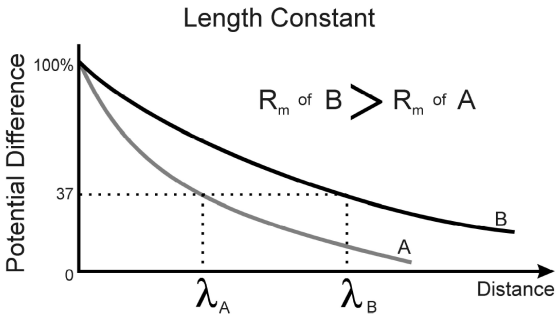
1. Most cells do not generate AP (lack of Na^+ channels), but conduct passive currents.
2. Most cells only propagate current to adjacent cells only (lack of axons).
3. Only cells with long axons and muscle cells generate propagating action potential.
4. Signal conduction in biological tissue:



1. Membrane properties shape the form of the signal.
2. Signal is losing as the current travel along the membrane

CABLE PROPERTIES

1. Length constant: **λ**
   a. Defined as the distance you can travel, to the point where the voltage drops to about 37% of its original value)



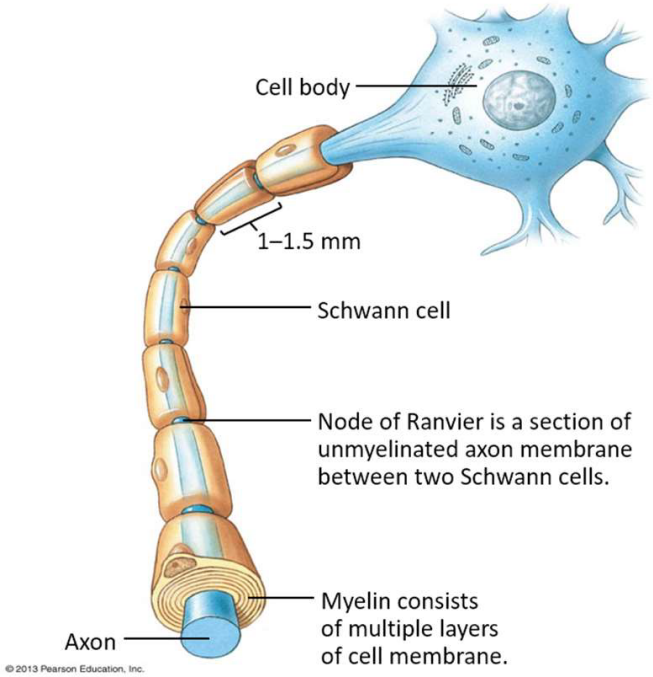
We wish to increase λ as much as possible to make the current travel a great distance.

   b. Equation:

$$\lambda = \sqrt{\frac{R_m}{R_o + R_i}}, \because R_i \gg R_o, \lambda \approx \sqrt{\frac{R_m}{R_i}}$$

      i. λ is increased by increasing diameter.
      ii. λ is increased by increasing membrane resistance.

   c. Increase membrane resistance by Myelination
      i. PNS → Schwann cells (Schwann cell wraps around a single portion of the one axon).
      ii. CNS → Oligodendrocytes (Oligodendrocytes can wrap a whole bunch of axons).

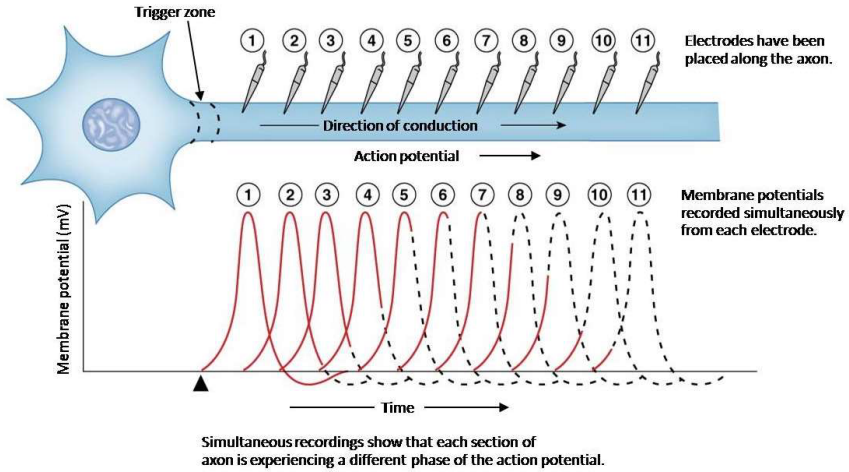


1. Myelinated axons have fast conduction velocity.
2. Unmyelinated axons have slow conduction velocity.
   a. Na^+ and K^+ voltage-gated channels are intermixed.
   b. Majority of axons are unmyelinated.

Multiple Sclerosis (MS) is a demyelinating disease.

SALTATORY CONDUCTION

1. In myelinated axons, only the membrane exposed at the nodes is excitable.
2. Action potential will 'jump' from one place to the next.
3. Action potential will only travel in a single direction due to refractory period.

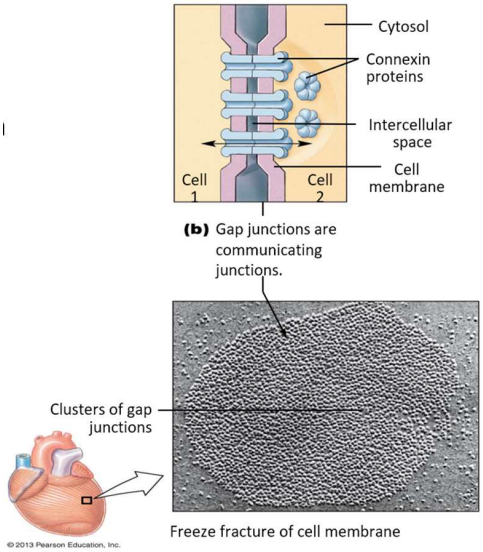


4. Poisoning some of the nodes and the depolarizing current will just skip past that and move on to the next healthy patch of membrane.

SYNAPSE

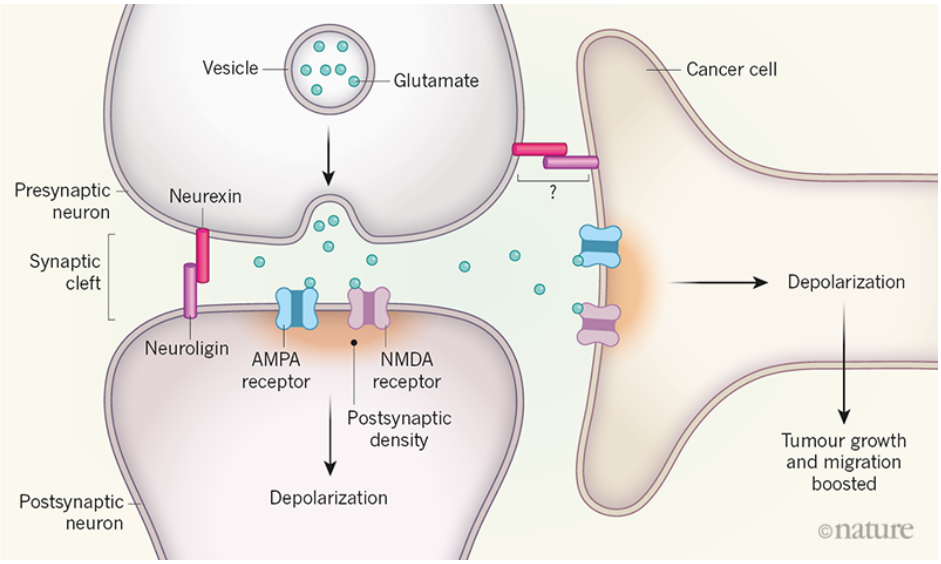
ELECTRICAL SYNAPSE

1. Gap junction between cells.
2. Gap junction bridged by connexins which allow small ions (and depolarization) to cross.



CHEMICAL SYNAPSE

1. The transmitter is released into the extracellular space which exists between adjacent cells.



2. Structure of a synapse:
    a. Pre-synaptic membrane
    b. Synaptic cleft (200Å)
    c. Post-synpatic membrane
3. Release of neurotransmitter-containing vesicles
    a. Trigger by increased level of Ca^{2+} ions.
    b. Ca2+ ions move into the cell by voltage-gated Ca^{2+} channels.
    c. Fusion of vesicles requires SNARE proteins.
    d. Vesicle release is probabilistic (1 Action potential has an 10-90% of chance of releasing 1 vesicle.)

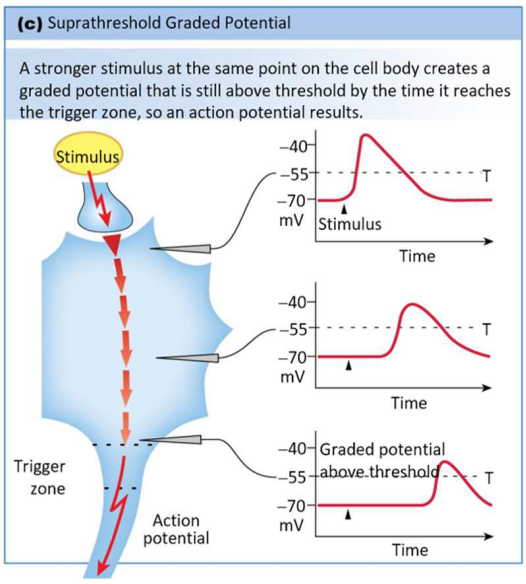
POST-SYNAPTIC RECEPTORS

IONOTROPIC RECEPTORS

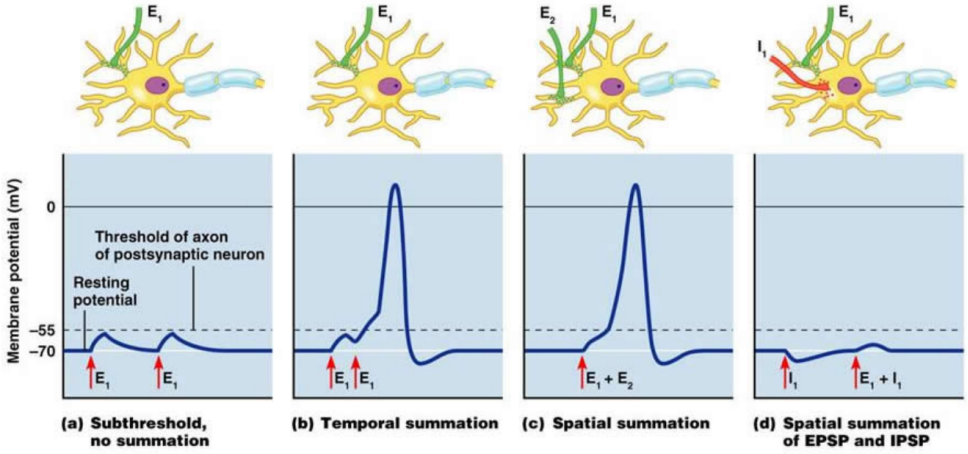
Directly opens ion channels.

1. Common ionotropic receptor ligands
    a. Acetylcholine
    b. Glutamate
    c. GABA
    d. Glycine

2. Spread of post-synaptic potentials (PSPs)



3. Type of PSPs
    a. EPSP – Excitatory PSP
    b. IPSP – Inhibitory PSP (Usually involves opening of Cl^- channels → Hyperpolarize the cells)
4. Summation of PSPs



    a. Spatial summation
    b. Temporal summation
5. Spike Train (Continuous stream of action potentials)
    a. Generated by a very powerful synaptic input to the postsynaptic neuron persisting in time lasting very long time.
    b. After each 'spike', the membrane 'hyperpolarized' to restore the Na^+ channels to re-open them for the next one.
    c. Hyperpolarization is required to generate another action potential.

d. Voltage-gated K^+ channels at trigger zone cause afterhyperpolarizations.

METABOTROPIC RECEPTORS

Initiates a metabolistic cascade to activate enzymes)

1. Usually G-protein coupled receptors
2. Common second messengers:
    a. cAMP, cGMP, InP3
3. Common ligands for metabotropic receptors:
    a. Acetylcholine
    b. Peptides: substance P, β-endorphin, ADH
    c. Catecholamines: noradrenaline, dopamine
    d. Serotonin
    e. Purines: adenosine, ATP
    f. Gases: NO, CO