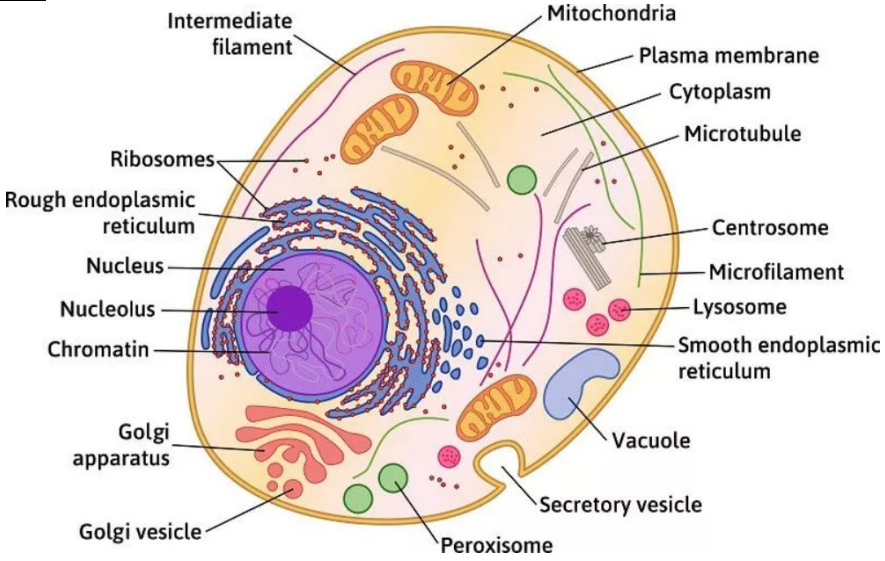
1.2 Levels of Organization

1. **Molecular/chemical**: a molecule a cell
2. **Cellular**: a cell, cells are specialized
3. **Tissue**: group of same specialized cells
    1. **Epithelial**: cells specialized in exchange of materials, 2 types
        1. Epithelial sheets: skin, stomach linings…, serve as boundaries
        2. Secretary glands: endocrine vs exocrine
    2. **Muscle**: cells specialized for contracting; skeletal, cardiac, smooth
    3. **Nervous**: cells specialized for initiating and transmitting electrical impulses
    4. **Connective**: few cells dispersed in lots of extracellular material
4. **Organ**: 2 or more types of tissues together
5. **System**: groups of organs, 11 systems - circulatory, digestive, respiratory, urinary, skeletal, muscular, integumentary, immune, nervous, endocrine, and reproductive
6. Organism

1.3-1.4 **Homeostasis**

- Tendency towards a state of equilibrium, prevent extremes
    - Often controlled by different but interdependent organs
    - Temperature, pH, oxygen and CO2 concentration, water concentration, etc.
- **Intrinsic** (local to organ) vs **extrinsic** (whole body, involves other organs)
- **Feedback** vs **feedforward** (act on predicted future variables)
- **Negative feedback loop** (act in opposite direction, ex: oxygen, water, pH control) vs **Positive feedback loop** (act in same direction, rare, ex: action potential, clotting)
    - **Controlled variable**: something to regulate
    - **Sensor/receptor**: detect change in the variable from its set point
        - Stimulus: movement of the system away from its set point
    - **Control center**: figure out what to do when the stimulus is detected
    - **Effector**: move variable back to normal
- Positive feedback loop must terminate with some distinct event
- Positive feedback can go out of control and result in pathology/pathophysiology

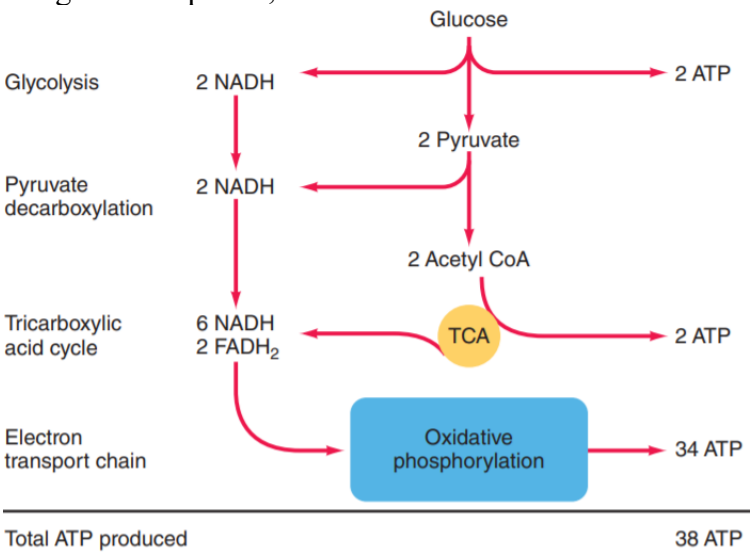
2.2 Cell Structure



Cell Part	Structure	Function
Plasma membrane	Lipid bilayer studded with proteins and small amounts of carbohydrate	Acts as selective barrier between cellular contents and extracellular fluid; controls traffic in and out of the cell
Nucleus	DNA and specialized proteins enclosed by a double-layered membrane	Acts as control centre of the cell, providing storage of genetic information; nuclear DNA provides codes for the synthesis of structural and enzymatic proteins and serves as blueprint for cell replication
Cytoplasm		
Organelles		
Endoplasmic reticulum	Extensive, continuous membranous network of fluid-filled tubules and flattened sacs, partially studded with ribosomes	Forms new cell membrane and other cell components and manufactures products for secretion
Golgi complex	Sets of stacked, flattened membranous sacs	Modifies, packages, and distributes newly synthesized proteins
Lysosomes	Membranous sacs containing hydrolytic enzymes	Serve as digestive system of the cell, destroying foreign substances and cellular debris
Centriole	Usually paired, small barrel-shaped organelles that consist of nine short triplet microtubules	Site of growth of new microtubules: both cytoplasmic transport microtubules and the microtubules that form the mitotic spindle
Peroxisomes	Membranous sacs containing oxidative enzymes	Perform detoxification activities
Mitochondria	Rod- or oval-shaped bodies enclosed by two membranes, with the inner membrane folded into cristae that project into an interior matrix	Act as energy-producing organelles; major sites of ATP production; contain enzymes for citric acid cycle and electron transport chain
Vaults	Shaped like hollow octagonal barrels	Serve as cellular trucks for transport from nucleus to cytoplasm
Cytosol: gel-like portion		
Intermediary metabolism enzymes	Dispersed within the cytosol	Facilitate intracellular reactions involving the degradation, synthesis, and transformation of small organic molecules
Ribosomes	Granules of RNA and proteins—some attached to rough endoplasmic reticulum, some free in the cytoplasm	Serve as workbenches for protein synthesis
Transport, secretory, and endocytotic vesicles	Transiently formed, membrane-enclosed products synthesized within or engulfed by the cell	Transport and/or store products being moved within, out of, or into the cell, respectively
Inclusions	Glycogen granules, fat droplets	Store excess nutrients
Cytosol: cytoskeleton portion		As an integrated whole, serves as the cell's "bone and muscle"
Microtubules	Long, slender, hollow tubes composed of secretory vesicles	Maintain asymmetric cell shapes and tubulin molecules; coordinate complex cell movements, specifically facilitating transport of secretory vesicles within cells, serving as main structural and functional component of cilia and flagella, and forming mitotic spindle during cell division
Microfilaments	Intertwined helical chains of actin molecules; microfilaments composed of myosin molecules also present in muscle cells	Play a vital role in various cellular contractile systems, including muscle contraction and amoeboid movement; serve as a mechanical stiffener for microvilli
Intermediate filaments	Irregular, threadlike proteins	Help resist mechanical stress

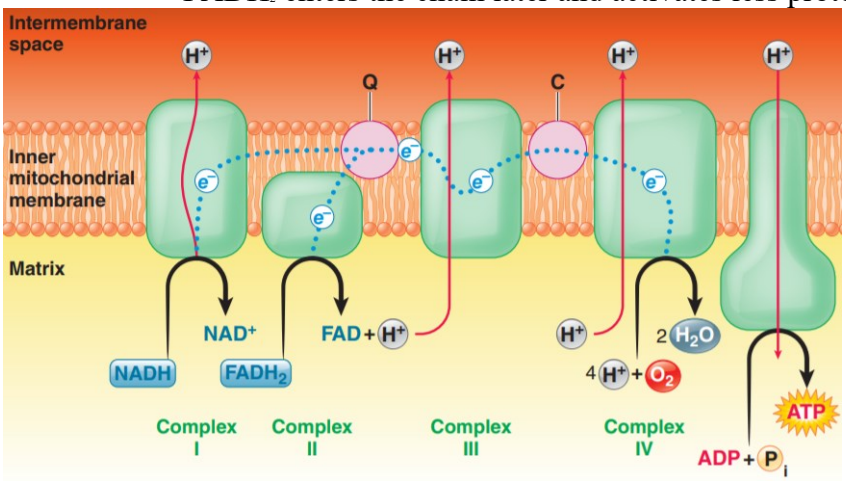
2.3 Cell metabolism (Introduction to the mitochondria and cellular structure)

- **Metabolism** (all energy related reactions in a cell) vs **catabolism** (releases energy by breaking molecules) vs **anabolism** (store energy by forming large molecules)
- **ATP**: adenosine triphosphate, the energy molecule for cells, releases lots of energy when the last phosphate group breaks off; Used for:
  - Synthesis of new chemical compounds, mostly protein
  - Membrane transport / selective transport
  - Mechanical work: contraction of muscle cells
- **Mitochondria**: where ATP is produced
  - Matrix: cavity, where pyruvate oxidation and Krebs cycle happen
  - Cristae: folds of the inner membrane, where electron transport chain happens
  - Intermembrane space: between inner and outer mitochondrial membrane, where the proton gradient builds up (mitochondria has double membrane like nucleus)
- **Electron carriers**: FADH2 (provides electrons for making 2 ATP) vs NADH (provides electrons for making 3 ATP)
- **Phosphorylation**: combine phosphate to an organic compound, ex: formation of ATP from ADP
  - **Substrate-level** phosphorylation (glycolysis, Krebs cycle, creatine phosphate in muscles) vs **oxidative** phosphorylation (ETC in mitochondria)
- **Fermentation**: produce ATP only via glycolysis, doesn't require oxygen (anaerobic)
  - temporary (need oxygen to re-oxidize NADH back to NAD^-), produce lactic acid (human) or ethanol (yeast/bacteria)



- **Cellular Respiration**: the ATP production process, 4 steps
  - **Glycolysis** (step 1): break down of glucose into 2 pyruvate / pyruvic acid
    - Occurs in the cytoplasm of cells
    - Produces 2 NADH and 2 ATP per glucose
  - **Pyruvate oxidation** (step 2): converts pyruvate molecules into acetyl-coA
    - occurs in the mitochondrial matrix
    - release 1 CO_2 and produces 1 NADH per pyruvate (2 per glucose)
  - **Krebs / tricarboxylic acid / citric acid cycle** (step 3): breaks down acetyl-coA
    - Occurs in the matrix
    - Oxaloacetate is an intermediate molecule cycled (not consumed)
    - Releases 2 CO_2 and produces 1 ATP, 3 NADH, 1 $FADH_2$ per acetyl-coA
  - **Electron transport chain** (step 4): produces ATP via oxidative phosphorylation
    - Occurs in the inner mitochondrial membrane
    - Electrons from the carriers are passed on the protein complexes that uses this energy to pump protons into the intermembrane space

- The proton gradient forces protons to go through ATP synthase, which uses this energy to produce ATP
  - 1 NADH produces 3 ATP while 1 $FADH_2$ only produces 2 ATP as $FADH_2$ enters the chain later and activates less protons pumps



  - Total yield of ATP: theoretically 36-38, but actual numbers are around 30-32, ATPs are lost during the transport of electron carriers

2.4 – 2.5 Cellular membrane structure and adhesion

- **Fluid mosaic model**: model of the cell membrane with a phospholipid bilayer with proteins embedded and carbohydrates attached
- **Phospholipid bilayer**: two phospholipids tail to tail
  - **Phospholipid**: like triglyceride; phosphate head (**hydrophilic**) + 2 fatty acid chains with one of them bent (one or more double bonds, **hydrophobic**)
  - **Fluidity** of this layer decides how many molecules can diffuse in/out
    - The bent leg in phospholipid makes it less tight/more fluid
    - Increase in length of the fatty acid chains decreases fluidity
    - Increase in temperature increase the fluidity
    - **Cholesterol:** gets between phospholipids, prevents stacking thus increases fluidity; balances fluidity changes from temperature
  - **Semi-permeable:** Only allows small, uncharged, nonpolar molecules (generally hydrophobic molecules) to pass through freely with the exception of water
- **Proteins**:
  - Integral (embedded) vs peripheral (floats on the surface)
  - **Transport** substance through the phospholipid bilayer, **catalyze** reactions, **bind to signal molecules** like hormones, aid **cell adhesion**
- **Carbohydrates:** attached to the proteins / lipids to form glycoproteins / glycolipids, can be used for cells to **recognize** each other
- Adhesion techniques:
  - Biological glue (extracellular matrix (ECM)
  - Desmosomes (adhering junctions, involves adhesion molecules cell membranes)
  - Tight junctions (impermeable junctions)
  - **Gap junctions** (communicating junctions): gap between cells connected by connexons (six protein subunits arranged in a tube); allows small, water-soluble particles (ions) to be exchanged freely; ex: synchronous muscle contraction

2.6 – 2.8 Transport mechanisms

Methods of Transport	Substances Involved	Energy Requirements and Force-Producing Movement	Limit to Transport
Diffusion			
Through lipid bilayer	Nonpolar molecules of any size (e.g., O_2, CO_2, and fatty acids)	Passive; molecules move down concentration gradient (from high to low concentration)	Continues until the gradient is abolished (steady state with no net diffusion)
Through protein channel	Specific, small ions (e.g., Na^+, K^+, Ca^{2+}, and Cl^-)	Passive; ions move down electrochemical gradient through open channels (from high to low concentration and by attraction of ion to area of opposite charge)	Continues until there is no net movement and a steady state is established
Special case of osmosis	Water only	Passive; water moves down its own concentration gradient (water moves to area of lower water concentration, i.e., higher solute concentration)	Continues until concentration difference is abolished or until stopped by an opposing hydrostatic pressure or until cell is destroyed
Carrier-Mediated Transport			
Facilitated diffusion	Specific polar molecules for which a carrier is available (e.g., glucose)	Passive; molecules move down concentration gradient (from high to low concentration)	Displays a transport maximum (T_m); carrier can become saturated
Primary active transport	Specific ions or polar molecules for which carriers are available (e.g., Na^+, K^+, and amino acids)	Active; ions move against concentration gradient (from low to high concentration); requires ATP	Displays a transport maximum; carrier can become saturated
Secondary active transport	Specific polar molecules and ions for which cotransport carriers are available (e.g., glucose, amino acids, and some ions)	Active; molecules move against concentration gradient (from low to high concentration); driven directly by ion gradient (usually Na^+) established by ATP-requiring primary pump	Displays a transport maximum; cotransport carrier can become saturated
Vesicular Transport			
Endocytosis			
Pinocytosis	Small volume of ECF fluid; also important in membrane recycling	Active; plasma membrane dips inward and pinches off at surface, forming an internalized vesicle	Control poorly understood
Receptor-mediated endocytosis	Specific, large polar molecule (e.g., protein)	Active; plasma membrane dips inward and pinches off at surface, forming an internalized vesicle	Necessitates binding to specific receptor site on membrane surface
Phagocytosis	Multimolecular particles (e.g., bacteria and cellular debris)	Active; cell extends pseudopods that surround particle, forming an internalized vesicle	Necessitates binding to specific receptor site on membrane surface
Exocytosis	Secretory products (e.g., hormones and enzymes) as well as large molecules passing through cell intact; also important in membrane recycling	Active; increase in cytosolic Ca^{2+} induces fusion of secretory vesicle with plasma membrane; vesicle opens up and releases contents to outside	Secretion triggered by specific neural or hormonal stimuli; other controls involved in transcellular traffic and membrane recycling not known

2.9 Intercellular communication & signal transduction

- Direct exchange of molecules through gap junctions
- Interactions provoked by surface identification markers (WBC)
- Specifically released extracellular chemical messengers bind with target cell receptors
    - **Paracrine**: distribute through diffusion, local / short distance, doesn't enter blood stream, ex: histamine dilates blood vessels
    - **Neurotransmitters**: paracrine released by neurons (response to action potentials), also diffusion & local
    - **Hormones**: secreted into the blood by endocrine glands, long-range, only target cells of a particular hormone have receptors for it
    - **Neurohormones**: hormones released by neurosecretory neurons
- Ways of signal transduction
    - Lipid-soluble: diffuse in
    - Water-soluble: bind to receptors
    - Control membrane channels (open/close)
    - Signals second messenger inside cell
        - Fast synapse (alters channels directly) vs slow synapse (triggers second messengers, ex: serotonin)

2.10 Resting membrane potential

- **Membrane potential**: Electrical gradient inside vs outside across cell membrane, measured in millivolt (mV), negative potential means interior is more negative
    - Change in membrane potential requires the movement of ions across membrane, which generates an electrical current and vis versa, follows $V = IR$
- **Resting membrane potential**: constant membrane potential when the cells are not producing electrical signals
    - Primarily responsible ions: Na^+, K^+, anions (A^-; large, negatively charged intercellular proteins)
    - Other important ions: Cl^-, Ca^{2+}
    - Na^+, Cl^-, Ca^{2+} in greater concentration out, K^+ greater in, A^- only in (impermeable)
        - **Sodium potassium pump**: 3 Na^+ out, 2 K^+ in, requires ATP
        - A^- produced and stay inside
        - Membrane much more permeable to K^+ than others

Resting Nerve Cell CONCENTRATION (millimoles/litre)

Ion	Extracellular	Intracellular	Relative Permeability
Na^+	150	15	1
K^+	5	150	50–75
A^-	0	65	0

- **Equilibrium potential**: the membrane potential for a specific ion concentration such that the chemical and concentration gradient for that ion balances out (no net movement)
    - −90 mV for K^+, +60 mV for Na^+, −70 mV for Cl^-, +120 mV for Ca^{2+}

The equilibrium potential for a given ion of differing concentrations across a membrane can be calculated by means of the **Nernst equation**, as follows:

$$E = 61 \log \frac{C_o}{C_i}$$

where

E = equilibrium potential for ion in mV

61 = RT / zF. For any ion with a valence other than 1+, 61 must be divided by z to calculate a Nernst potential.

C_o = concentration of the ion outside the cell in millimoles/litre (millimolars; mM)

C_i = concentration of the ion inside the cell in mM

- Resting membrane potential is **−70 mV** controlled by percentage permeability of K^+ & Na^+, tend more towards K^+'s equilibrium since it is more permeable
  - Not all ions matter! Only permeability of ions with set concentrations (controlled by the pumps) matter, other ions alter concentrations instead
  - Ex: most cells don't active transport Cl^- but is highly permeable, the membrane potential determines its concentration / distribution, which is why it also has −70 mV equilibrium

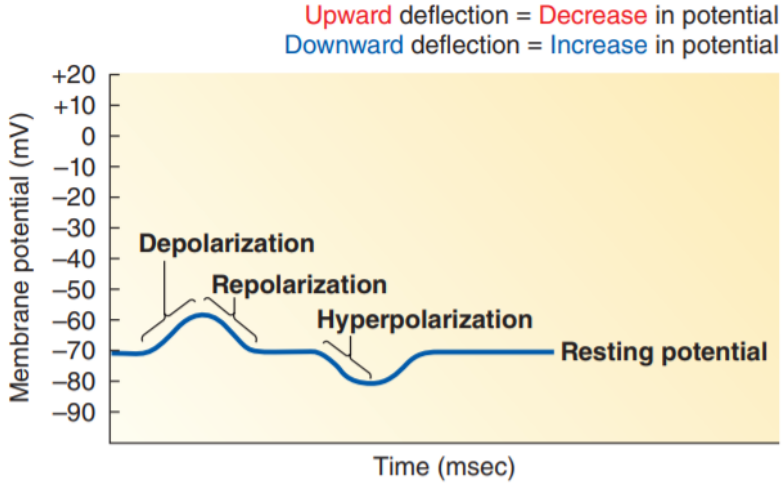
Goldman-Hodgkin-Katz Equation

$$V_m = \frac{RT}{zF} ln\left(\frac{P_{NA}[Na^+]out + P_K[K^+]out + P_{Cl}[Cl^-]in}{P_{NA}[Na^+]in + P_K[K^+]in + P_{Cl}[Cl^-]out}\right)$$

Where:

- Vm = membrane potential
- P_{ion} = the selectivity for that ion, typically given as a ratio with respect to Potassium

- **Excitable tissues** (nerve and muscle): can rapidly change membrane potential (by altering membrane permeability to certain ions) to produce electrical signals
  - **Polarization**: membrane has potential (not 0 mV); at resting potential membrane is polarized at −70 mV in a typical neuron



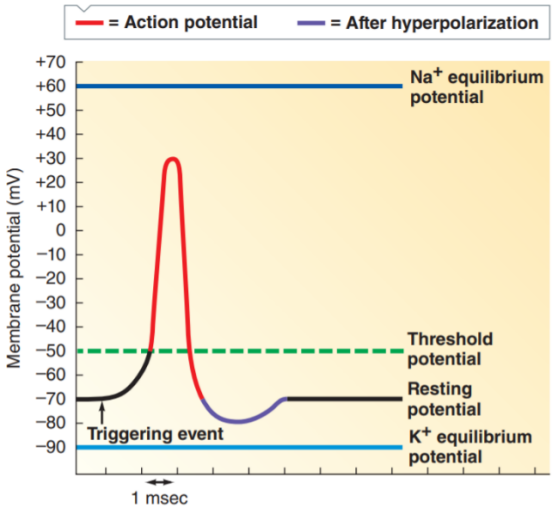
  - Generally, permeability is altered through (1) changes in electrical field (2) chemical messengers (3) stimulus (sound) (4) spontaneous change in potential
  - **Leak** (open all the time) vs **Gated** (open or closed) channels, gated can be **voltage**, **chemically**, **mechanically**, or **thermally** gated
- There are two basic forms of electrical signals: (1) **graded potentials**, which serve as short-distance signals; and (2) **action potentials**, which signal over long distances.

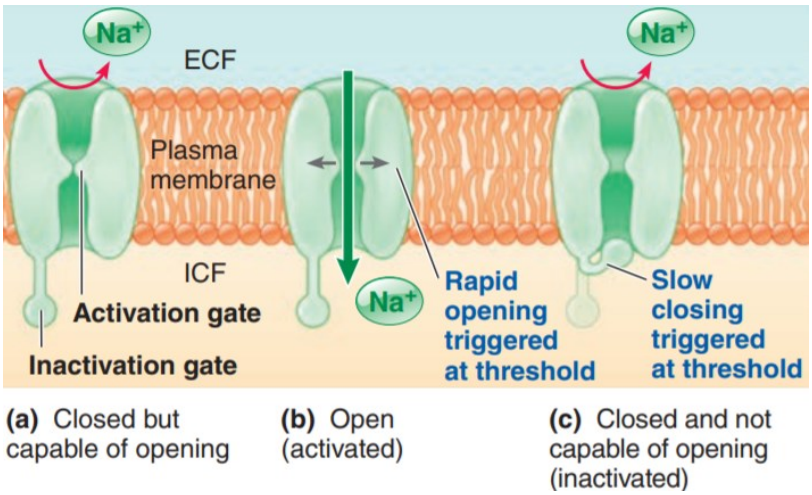
2.11 Graded potentials

- Slight change in membrane potential, often caused by opening Na channels
- Causes current and spreads to nearby areas **passively**, potential decreases with distance; signal can only travel **short distances**
- **No refractory period**, can lead to action potentials (which have refractory period)
- Ex: postsynaptic potentials, receptor potentials, end-plate potentials, pacemaker potentials, slow-wave potentials

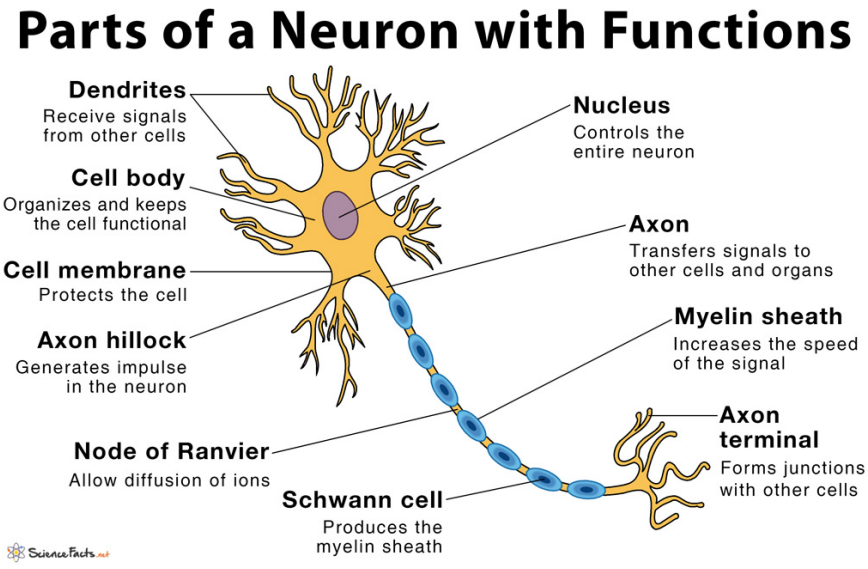
2.12 Action potentials

- Brief, rapid, large changes in membrane potential
- Controlled by voltage-gated Na ad K channels
- **Threshold potential**: all-of-none trigger, at threshold





  - (1) **rapid opening of Na activation gates**, Na enter => depolarization
    - Positive feedback loop
  - (2) **slow closing of Na inactivation gates**, halts Na entry after delay
    - Unlike variable duration of graded potential, the duration of an action potential is always the same in a give cell
  - (3) **slow opening of K gates**, K exits => repolarization and hyperpolarization
    - As potential returns, changing voltage shifts the Na channels to closed-but-capable-of-opening, ready to respond to another triggering event
    - K channels also close and the membrane channels returns to resting state
- **Restoration**
  - Long-term: Na-K pumps maintain the concentration gradients
  - Short-term: only about 1 out of 100 000 K & Na ions move, no need to restore
- **Neuron**

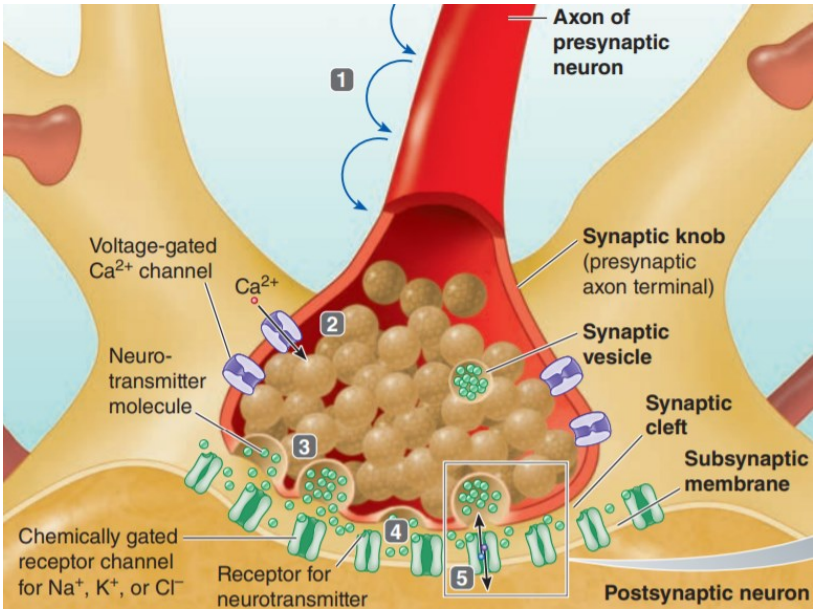


- **Input zone**: dendrite and cell body; **trigger zone**: **axon hillock**, only place action potential can initiate; **conducting zone**: axon; **output zone**: axon terminal
- Typically, regions of excitable cells where graded potentials take place do not undergo action potentials (sparse Na channels). However, graded potentials can, before dying out, trigger action potentials in adjacent portions of the membrane
- Ex: graded potentials are generated in the dendrites and cell body in response to incoming chemical signals, (sufficient magnitude when they spread to the axon hillock) they initiate an action potential at triggering zone, and is conducted along the axon and passed on to another cell at the axon terminal

- **Propagation** (within one cell, between cells is synapse)
  - Within one cell – conducting zone, current spread passively to reach threshold of nearby areas, which then triggers Na channels
    - **Contiguous** (not myelinated) or **saltatory** (myelinated, channels concentrate at node of Ranvier, current "jumps") conduction
    - one way only, **refractory period**: absolute (Na channels inactivated) vs relative (right after, Na channels capable but threshold hard to reach)
    - diameter & myelination effects speed
- Threshold is all-or-none, signal **strength determined by frequency** instead

2.14 Synapses and neuronal integration

- **Synapses**: connection between two neurons, specifically between the axon of the presynaptic neuron and the dendrite / cell body of the postsynaptic neuron



  - **Synaptic cleft**: gap between the neurons, only 0.02 um but do not touch
  - **Synaptic knob**: contains synaptic vesicles
    - **Synaptic vesicles**: release neurotransmitters
    - **Calcium channels** open when the action potential arrives, let calcium ions into the cell (causes the release of synaptic vesicles)
  - **Neurotransmitters**: binding to receptor proteins on postsynaptic neuron that trigger ion channels and changes permeability (chemically gated!)
    - **Excitatory**: trigger Na and K channels, slightly depolarize the postsynaptic neuron so its closer to threshold (rarely directly triggers AP)

        - **Inhibitory**: trigger Cl or K channels, slight hyperpolarize the postsynaptic neuron so its further away from threshold
        - Can be both excitatory and inhibitory based on the receptor proteins
    - **Neuropeptides**: large molecules released in a similar way to neurotransmitters
        - **Neuromodulators**: doesn't cause potential change but acts on the synapse (Ex. changes sensitivity to certain neurotransmitter)
    - After the transmission neurotransmitter are either diffused away, inactivated by enzymes, or reabsorbed by the presynaptic neuron
- **Grand postsynaptic potential** (GPSP): EPSP (excitatory postsynaptic potential) and IPSP (inhibitory postsynaptic potential) are additive, leading to GPSP and potentially AP
    - **Temporal summation**: same place one after another (overlaps slightly each time)
    - **Spatial summation**: different places simultaneously
    - Up to 50 different summations can be required to trigger an action potential
- Presynaptic facilitation / inhabitation: changes behaviour of presynaptic neuron (Ex. make less Ca enter)

Neurotransmitter	Ionotropic receptor	Metabotropic receptor
Amino acids		
Glutamate	Yes Excitatory	Yes (but less common)
GABA	Yes Inhibitory	Yes
Glycine	Yes Inhibitory	
Biogenic amines		
Norepinephrine	Complicated	Yes
Epinephrine		Yes
Acetylcholine	Yes Excitatory	Yes