The Cyprus International Institute for the Environment and Public Health
In collaboration with the Harvard School of Public Health

# Lecture 2

## Sherwood, Human Physiology

**Membrane Transport, Membrane Potential and Neural Communication (60-113)**

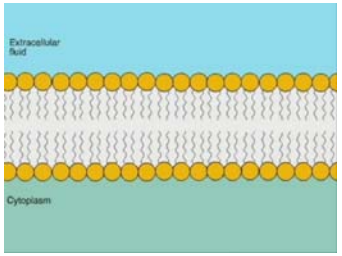
**Constantinos Pitris, MD, PhD**

**Assistant Professor, University of Cyprus**
**cpitris@ucy.ac.cy**
**http://www.eng.ucy.ac.cy/cpitris/courses/ClIPhys/**

Background Material

## Membrane Transport

- **Selective membrane permeability**
  - Lipid soluble substances (e.g. some vitamins) → high
  - Small substances ($O_2$, $CO_2$, etc) → high
  - Charged, ionic substances → none
  - Particles can also cross through substance-specific channels and carriers

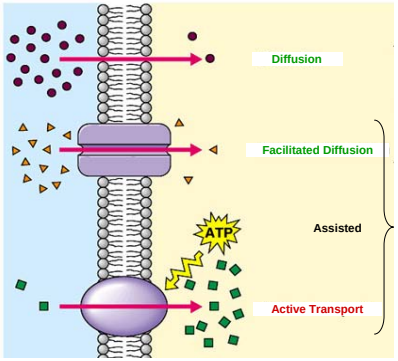





Background Material

## Membrane Transport

- **Unassisted vs. assisted transport**
  - Unassisted → permeable molecules can cross the membrane
  - Assisted →impermeable molecules must be assisted by other proteins in order to cross the membrane
- **Energy expenditure**
  - **Passive** membrane transport
    - Due to forces that require no energy expenditure
    - Can be unassisted or assisted
  - Active membrane transport
    - Require energy expenditure from the cell
    - Always assisted

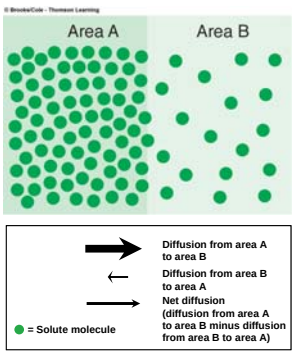





Background Material

## Unassisted Membrane Transport

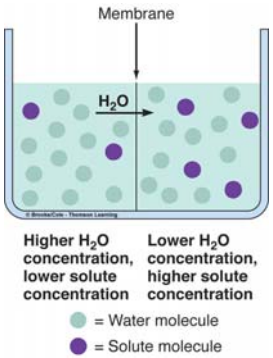
- **Unassisted transport due to**
  - Concentration gradient
  - Electrical gradient
- **Diffusion down a concentration gradient**
  - Random motion of molecules
  - Net diffusion = net motion in direction of low concentration
  - Concentrations tends to equalize → steady state
  - E.g. $O_2$ transferred by diffusion
    - Lungs → Low concentration in blood, high in air
    - Tissue → Low concentration in tissue, high in blood



Background Material

# Unassisted Membrane Transport

- **Osmosis**
  - Net diffusion of water (either through membrane or through porins)
  - Water flows to regions of lower water (i.e. higher solute) concentration → osmotic pressure
  - Tends to equalize the concentrations

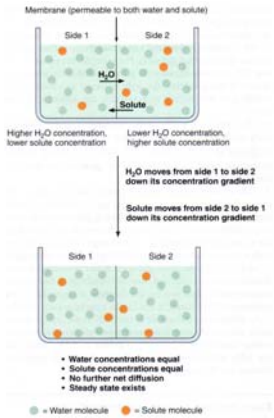




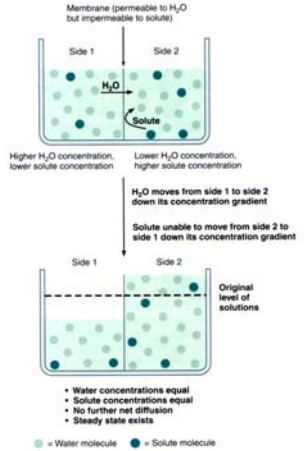

Background Material

# Unassisted Membrane Transport

- **Unequal volumes of a penetrating solute**




- **Unequal volumes of non-penetrating solute**

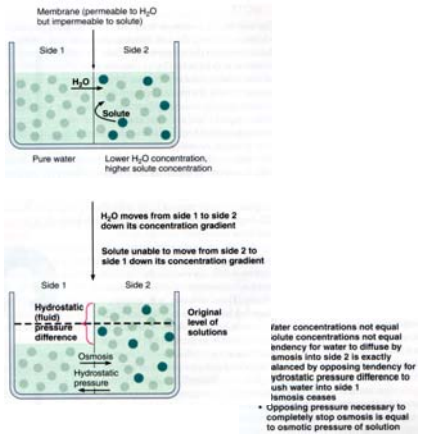





Background Material

# Unassisted Membrane Transport

- **Pure water from a non-penetrating solute**



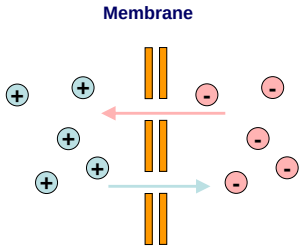

- **Tonicity of a solution**
  - Isotonic
    - Same concentration of non-penetrating solutes as the cell
    - No water movement by osmosis
    - Cell volume ~
  - Hypotonic
    - Lower concentration of non-penetrating solutes
    - Water moves in the cell
    - Cell volume ↑
  - Hypertonic
    - Higher concentration of non-penetrating solutes
    - Water moves out of the cell
    - Cell volume ↓



Background Material

# Unassisted Membrane Transport

- **Diffusion down an electrical gradient**
  - Ions diffuse down electrical gradients → to opposite charge
  - If electrical gradient exists across a membrane, permeable ions will diffuse passively

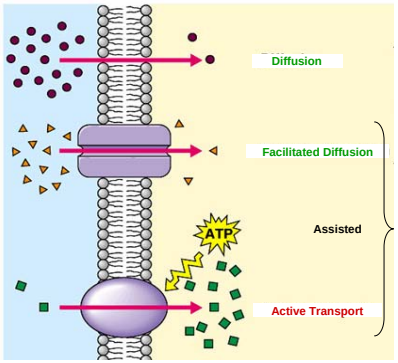



- **Combination of concentration and charge**
  - Electrochemical gradient
  - Tend to balance out (we will see this in action later)

Background Material

# Assisted Membrane Transport

- **Cells must be able to exchange larger molecules**
  - Glucose, aminoacids, waste, etc.
- **Two types of assisted transport**
  - Carrier mediated transport
    - May be passive or active
    - Small molecules
  - Vesicular transport
    - Always active
    - Very large molecules, particles

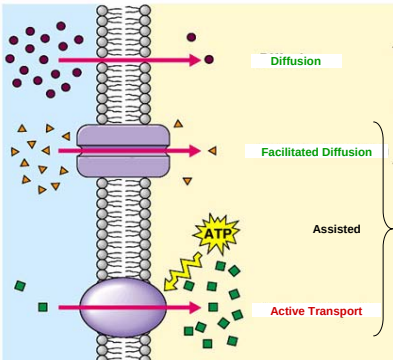





Background Material

# Assisted Membrane Transport

- **Carrier mediated transport**
  - Carriers are proteins that span the membrane
  - They change their shape to help molecules cross from one side to the other
  - Three categories
    - Facilitated diffusion
    - Active transport
    - Secondary active transport

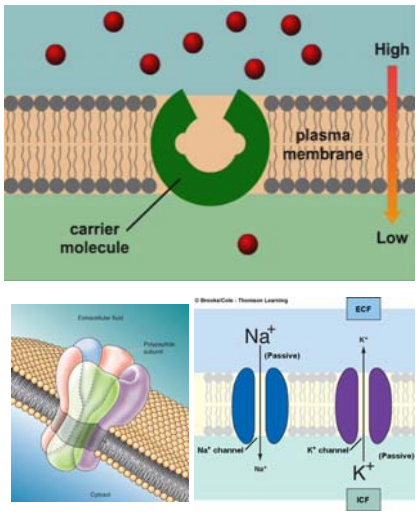





Background Material

# Assisted Membrane Transport

- **Facilitated Diffusion**
  - No energy expenditure
  - Carrier Molecules
    - Move molecules down their concentration gradient
    - Unloading on the other side
      - E.g. glucose
    - High concentration side binding is more likely →Net movement in the direction of the concentration gradient
  - Diffusion through channels
    - Membrane proteins form channels (water filled pores)
    - Diffusion of specific molecules through specific channels
      - E.g. $Na^+$ or $K^+$ channels
    - Diffusion down their electrochemical gradients (passive)
    - Can be gated (i.e. opened or closed) from external stimuli
      - Electrically gated
      - Chemically gated

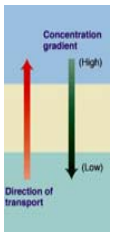


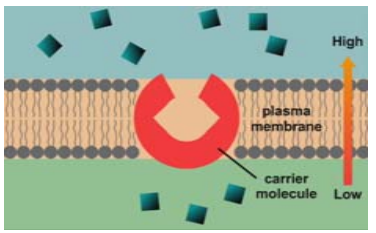



Background Material

# Assisted Membrane Transport

- **Active Transport**
  - Transport molecules <u>against</u> their concentration gradient
  - Energy expenditure
  - A.k.a. "ATPase pumps" or "pumps"
  - On the low concentration side
    - High affinity sites bind solute
    - Conformation change → flip to the other side
  - On high concentration side
    - Reduced affinity to the solute
    - Unload the solute and return to previous conformation



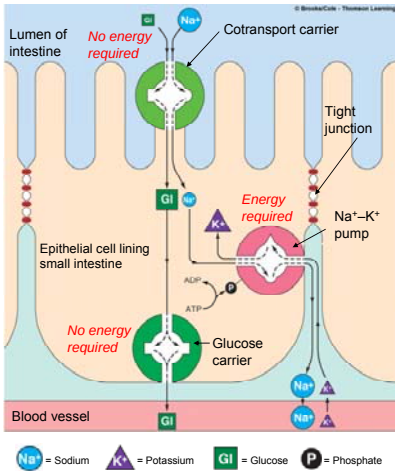




- **Examples of active pumps**
- **$H^+$-pump**
  - Transports $H^+$ into stomach
  - Against gradients of x $3\text{-}4.10^6$
- **$Na^+$-$K^+$-pump**
  - All cells, $3xNa^+$ out, $2xK^+$ in
  - Very important role!
    - Establish $Na^+$ and $K^+$ concentration gradients important for nerve and muscle function
    - Maintain cell volume by controlling solute regulation
    - Co-transport of glucose (see next)

Background Material

# Assisted Membrane Transport

- **Secondary Active Transport**
  - Intestine and kidneys must transport glucose against its concentration gradient
  - Cotransport carrier = Glucose + $Na^+$
    - Cotransport uses $Na^+$ gradient to push along glucose against its concentration gradient
  - $Na^+$-$K^+$-pump maintains $Na^+$ concentration gradient (ATP required)
  - Energy required for the overall process → secondary active transport

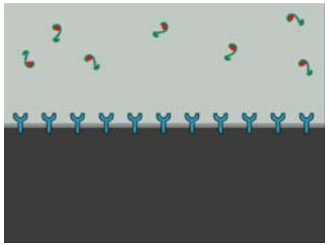





Background Material

# Assisted Membrane Transport

- **Vesicular Transport**
  - Endocytosis
  - Exocytosis
    - Opposite of endocytosis
  - Slow process for larger particles (bacteria) or larger quantities (stored hormones)
  - Membrane size must be maintained (added or retrieved)
  - See table 3-2, p.74

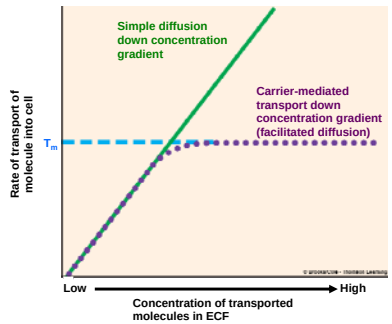




Background Material

# Assisted Membrane Transport

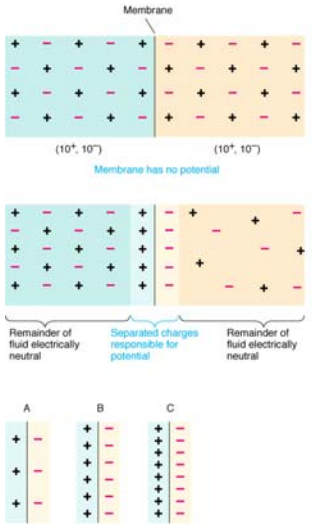
- **Important characteristics of carrier mediated transport**
  - Specificity
    - One or a few similar molecules
    - No crossing over
  - Saturation
    - There is a maximum amount of substance a set of carriers can transport in a given time → Transport maximum (Tm)
    - Number of carriers can be upregulated (e.g. insuline → ↑ glucose carriers)
  - Competition
    - If the carrier can transport more that one substance → competition between substances






# Membrane Potential

- **Opposite charges attract and similar repel**
- **Membrane potential → opposite charges across the membrane**
  - Equal number of + and – on each side → electrically neutral
  - Charges separated (more + on one side, more – on other) → electrical potential
  - Measured in V
    - More charge → ↑ V
- **Note:**
  - Only a very small number of charges is involved → majority of ECF and ICF are still neutral



# Membrane Potential

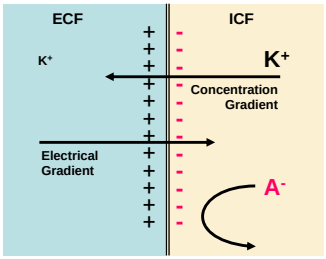
- **All cells are electrically polarized**
- **Changes in membrane potential serve as signals (nerve & muscle)**
- **Resting membrane potential**
  - Potential at steady state
  - Primarily by $Na^+$, $K^+$, and $A^-$ (negatively charged intracellular proteins)
  - Note table 3-3
    - $A^-$ found only in cells
    - $Na^+$ and $K^+$ can diffuse through channels ($K^+$>$Na^+$)
    - Concentration of $Na^+$ and $K^+$ maintained by $Na^+$-$K^+$-pump (most critical role)

| ION | Concentration (millmoles/liter) | | Relative Permeability |
|---|---|---|---|
| | Extracellular | Intracellular | |
| $Na^+$ | 150 | 15 | 1 |
| $K^+$ | 5 | 150 | 50-75 |
| $A^-$ | 0 | 65 | 0 |



# Membrane Potential

- **Resting membrane potential**
  - Effect of $K^+$ alone
    - Assume no potential and only $K^+$ and $A^-$ present
    - $K^+$ will tend to flow out
    - Net + charge in the ECF, net – charge in ICF
    - Potential opposes flow of $K^+$
    - Forces balance → no net flow
    - Equilibrium → $K^+$ equilibrium potential (calculated from Nerst equation)



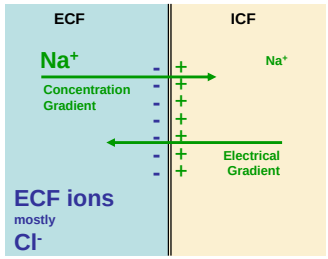

$$E = \frac{61}{z}\log\frac{C_o}{C_i} \Rightarrow E_k = \frac{61}{1}\log\frac{5mM}{150mM} = -90mV$$

  - Concentration does not significantly change since infinitesimal changes of $K^+$ are enough to set up the potential



# Membrane Potential

- **Resting membrane potential**
  - Effect of $Na^+$ alone
    - Assume no potential and only $Na^+$ and $Cl^-$ present
    - $Na^+$ will tend to flow in
    - Net + charge in the ICF, net – charge in ECF
    - Potential opposes flow of $Na^+$
    - Forces balance → no net flow
    - Equilibrium → $Na^+$ equilibrium potential (calculated from Nerst equation)



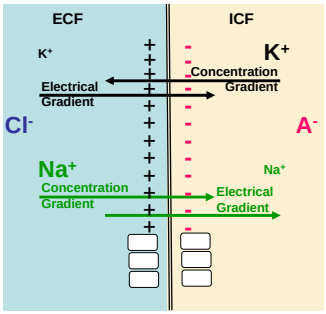

$$E = \frac{61}{z}\log\frac{C_o}{C_i} \Rightarrow E_k = \frac{61}{1}\log\frac{150mM}{15mM} = +60mV$$

    - Concentration does not significantly change since infinitesimal changes of $Na^+$ are enough to set up the potential



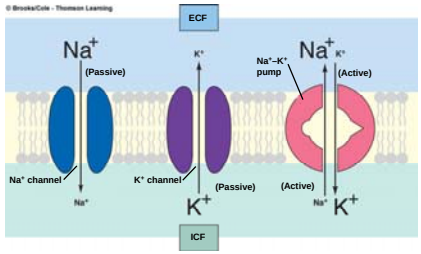
# Membrane Potential

- **Resting membrane potential**
  - Concurrent effects
  - Both $K^+$ and $Na^+$ present
  - The higher the permeability the greater the tendency to drive the membrane potential to its equilibrium value
  - $Na^+$ neutralizes some of the $K^+$ potential but not entirely
    - $K^+$ permeability is much higher
  - Resting membrane potential = -70mV



# Membrane Potential

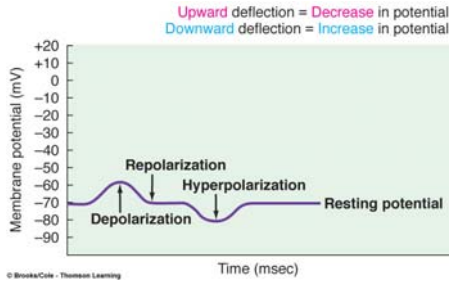
- **Balance of passive leaks and active pumping**
  - At -70 nm both $K^+$ and $Na^+$ continue to flow
  - $Na^+$-$K^+$-pump maintains the concentrations
  - Implication: cells need energy continuously just to maintain their membrane potential






# Excitable Tissues

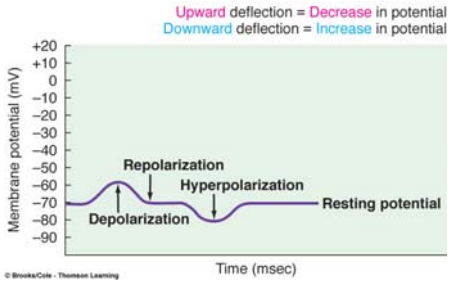
- **Nerve and muscle are excitable tissue**
  - Change their membrane potential to produce electrical signals
  - Neurons → messages
  - Muscle → contraction
- **Membrane potential changes**
  - Polarization
    - When a potential (either + or -) exists across a membrane
  - Depolarization
    - Reduction of the magnitude of potential (e.g. -70 mV → -50 mV)
  - Repolarization
    - Return to resting potential
  - Hyperpolarization
    - Increase in the magnitude of the potential (e.g. -70 mV → -90 mV)






# Excitable Tissues

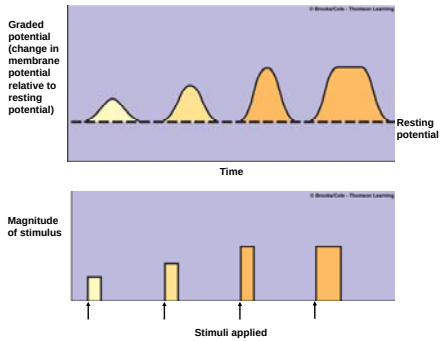
- **Changes are triggered by**
  - Change of the local electrical field
  - Interaction with chemical messenger and surface receptor
  - Stimulus (e.g. sound, light, etc)
  - Spontaneous change of potential by inherent ion leaks
- **Changes are caused by movement of ions**
  - Leak channels
    - Open all the time
  - Gated channels
    - Can be open or closed (conformation change)
    - Types
      - Voltage gated
      - Chemically gated
      - Mechanically gated
      - Thermally gated
- **Electrical signals**
  - Graded Potentials
  - Action Potentials





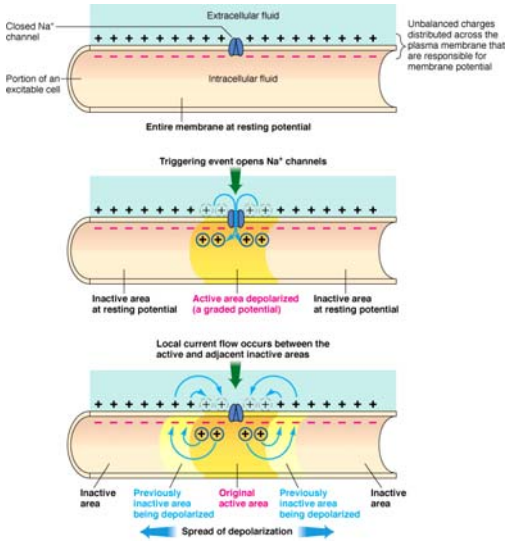

# Graded Potentials

- **Local changes in membrane potential**
  - Confined to a small area, the ***Active Area***
  - Remaining cell is still at resting potential (***Inactive Area***)
  - Triggered by specific events
    - E.g. sensory stimuli, pacemaker potentials, etc
  - Gated channels (usually Na+ open)
  - Magnitude and duration proportional to triggering event



# Graded Potentials

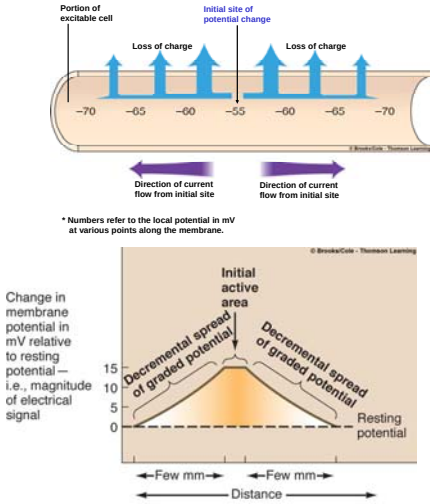
- **Propagate to adjacent areas**
  - Movement of ions = current
  - Current spreads in the ECF and ICF (low resistance) but not through the membrane (high resistance)
  - Depolarizes adjacent regions
  - Graded potentials propagate






# Graded Potentials

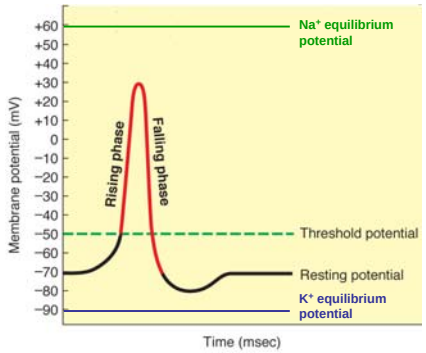
- **Graded potentials die out over short distances**
  - Loss of charge
  - Magnitude decreases as it moves away from the point of origin
  - Completely disappear with a few mm






# Action Potentials

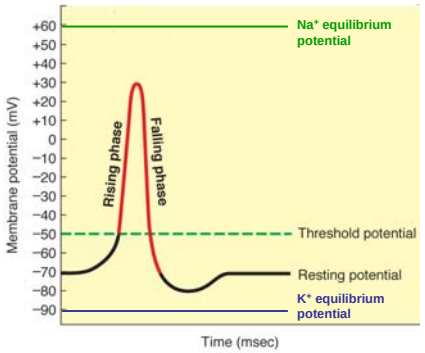
- **Large (~100 mV) changes in the membrane potential**
  - A.k.a *spikes*
  - Can be initiated by graded potentials
  - Unlike graded potentials action potentials propagate
  - Transmit information






# Action Potentials

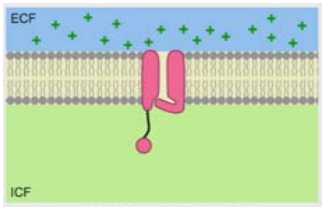
- **Changes during an action potential**
  - Gradual depolarization to threshold potential (-50 to -55 mV)
    - If not reached no action potential will occur
  - Rapid depolarization (+30 mV)
    - Portion between 0 and 30 mV is called an *overshoot*
  - Rapid repolarization leading to hyperpolarization (-80 mV)
  - Resting potential restored (-70 mV)
- **Constant duration and amplitude for given cell type ("all-or-none")**
  - E.g. Nerves → 1 msec



# Action Potentials

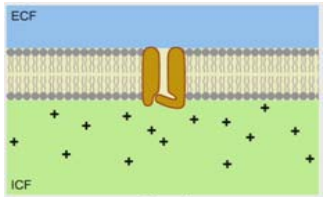
- **APs are a result of changes in ion permeability**
  - Voltage-gated channels
    - Proteins which change conformation depending on potential
    - Allow passage of ions
    - Voltage-gated $Na^+$ channels
      - Activation (immediate) and inactivation gates (delayed)
    - Voltage-gated $K^+$ channels
      - Activation gate (delayed)

**Voltage-gated $Na^+$ channels**



Closed but capable of opening

**Voltage-gated $K^+$ channels**

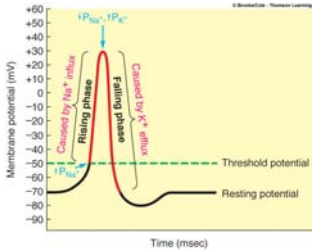


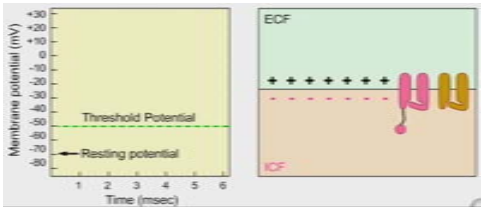
Closed



# Action Potentials

| Time | Event | Potential |
|---|---|---|
| 0 msec | Resting state<br>All channels are closed Graded potential arrives<br>Begins depolarization | - 70 mV |
| 2 msec | Threshold reached<br>Activation gates of Na+ channels open<br>Activation gates of K+ channels begin to open slowly<br>Inactivation gates of Na+ channels begin to close slowly | - 50 mV |
| 2.5 msec | Peak potential reached<br>Inactivation gates of Na+ channels are now closed<br>Activation gates of K+ channels are now open | 30 mV |
| 3.75 msec | Hyperpolarized state<br>Activation gates of K+ channels close | - 80 mV |
| 5 msec | Resting state<br>Na+-K+-pump restores resting potential<br>Na+ channels are reset to close but active | -70 mV |

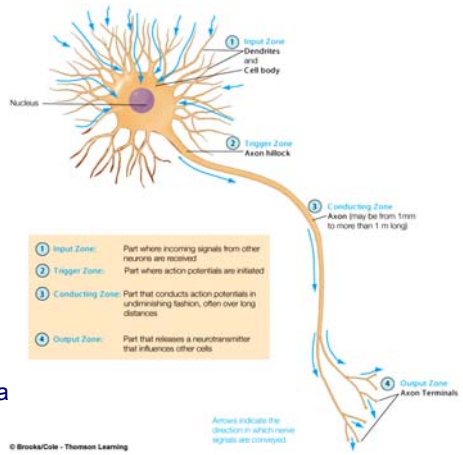





# Action Potentials

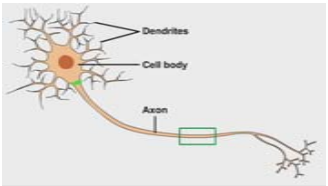
- **Neuron structure**
  - Input Zone
    - Dendrites (up to 400 000)
    - Cell Body
    - Have receptors which receive chemical signals
  - Conduction zone
    - Axon or nerve fiber (axon hillock to axon terminals) <1 mm to >1m
  - Output zone
    - Axon terminal
- **Input**
  - Graded Potentials
  - Generated in the dendrites as a response to chemical signals
  - Can trigger action potentials in the axon

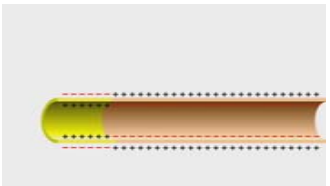





# Action Potentials

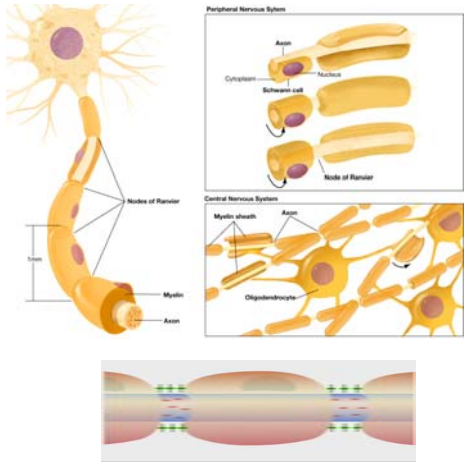
- **AP Propagation**
  - APs initiated at the axon hilloc
    - More voltage-gated channels → lower threshold
  - Once initiated the AP travels the entire axon
    - Contiguous conduction
    - Saltatory conduction
  - Contiguous conduction
    - Flow of ions → depolarization of adjacent area to threshold
    - As AP is initiated in adjacent area, the original AP is ending with repolarization
    - The AP itself does not travel, it is regenerated at successive locations (like “wave” in a stadium)



# Action Potentials

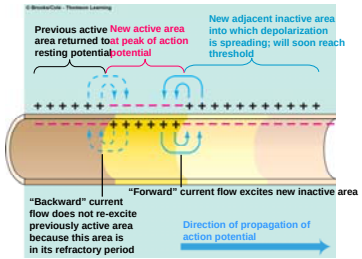
- Saltatory Propagation
  - Some neurons are myelinated
    - Covered with myelin (lipid barrier)
    - Formed by oligodendrocytes (CNS) and Schwann cells (PNS)
    - No ion movement across myelinated areas
  - Nodes of Ranvier
    - Areas between myelin sheaths
    - Ions can flow → APs can form
  - Local current can generate AP at the next node
  - APs "jump" from node to node → information travels 50x faster, less work by pumps to maintain ion balance
  - Loss of myelin can cause serious problems
    - E.g. multiple sclerosis

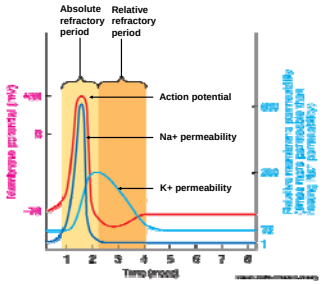





# Action Potentials

- **Refractory Period**
  - APs do not travel backwards
    - Local currents do not regenerate an AP in the previously-active-now-inactive area
  - Certain time must pass before a second AP can be triggered → ***refractory period***
  - Absolute refractory period
    - During an AP
    - No APs can be triggered
  - Relative refractory period
    - $Na^+$ channels are mostly inactive
    - $K^+$ channels are slow to close
    - After an AP → second AP can be triggered only be exceedingly strong signals
  - Refractory period sets an upper limit to the frequency of APs →~2.5 KHz

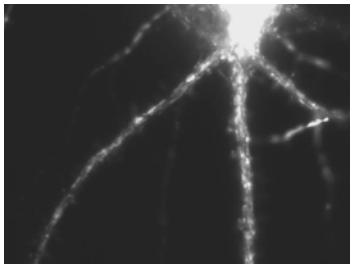





# Action Potentials

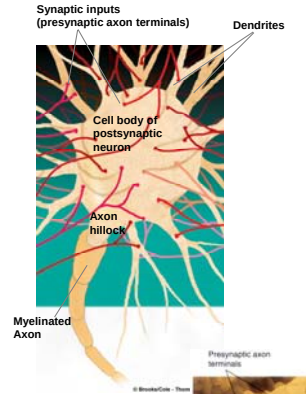
- **Characteristics of APs**
  - How does strength vary?
    - Always the same! → All-or-None Law
    - Does not decrease during propagation
  - How are stronger stimuli recognized?
    - Faster generation of APs → ↑Frequency
    - More neurons fire simultaneously
  - What determines the speed of APs?
    - Myelination
    - Neuron diameter (↑ diameter →↓ Resistance to local current → ↑ Speed)
    - Large myelinated fibers: 120 m/sec (432 km/hr) → urgent information
    - Small unmyelinated fiber: 0.7 m/sec (2.5 km/hr) → slow-acting processes
    - Without myelin the diameter would have to be huge! (50 x larger)

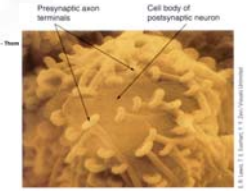




# Synapses and Integration

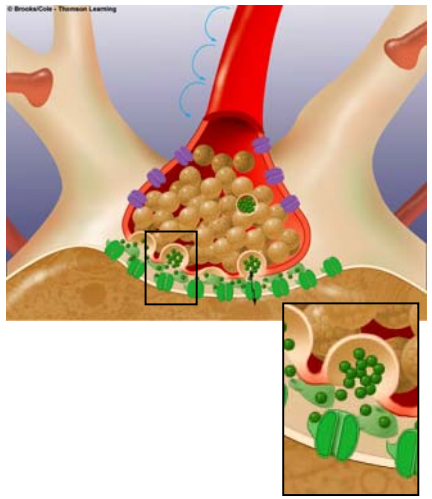
- **A neuron innervates (terminates or supplies) on**
  - Other neurons, Muscle, Gland
- **Synapse**
  - A junction between two neurons
    - Presynaptic neuron
      - Synaptic knob
      - Synaptic vesicles with neurotransmitter (chemical messenger molecule)
    - Synaptic Cleft
    - Postsynaptic neuron
      - Subsynaptic membrane
  - Most inputs on the dendrites
  - No direct ion flow → Chemical signaling
  - One-directional signaling



# Synapses and Integration

- **Synaptic Signaling**
  - AP reaches the synaptic knob
  - Voltage-gated $Ca^{2+}$ channels open
  - $Ca^{2+}$ flows into the synapse from the ECF
  - Ca induces exocytosis of vesicles and release of neurotransmitter
  - Neurotransmitter diffuses across the synaptic cleft to the subsynaptic membrane and binds to specific receptors
  - Binding triggers opening of ion channels
    - Each neuron releases one specific neurotransmitter
    - Many different neurotransmitters exist
    - Cause permeability changes of different ions
    - Can be excitatory or inhibitory synapses






# Synapses and Integration

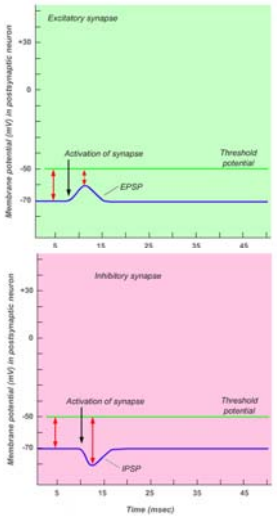
- **Neurotransmitters and Receptors**
  - Variety of neurotransmitters
  - Can bind to variety of receptors
  - Each particular synapse releases one specific neurotransmitter (very rarely two)
  - Each neurotransmitter-receptor combination produces the same response
    - Glutamate →EPSPs in the brain
    - γ-Aminobutyric Acid (GABA) → IPSPs in the brain
  - Neurotransmitters combined with different receptors can produce different responses
    - Norepinephrine → varied responses depending on receptor
- **Neurotransmitter clearing**
  - Removal or inactivation to stop the end the signal
    - Inactivation by specific enzymes within the subsynaptic membrane
    - Reuptake back in the axon → recycling

| Some Common Neurotransmitters | |
|---|---|
| Acetylcholine | Histamine |
| Dopamine | Glycine |
| Norepinephrine | Glutamate |
| Epinephrine | Aspartate |
| Serotonin | Gamma-aminobutyric acid (GABA) |



# Synapses and Integration

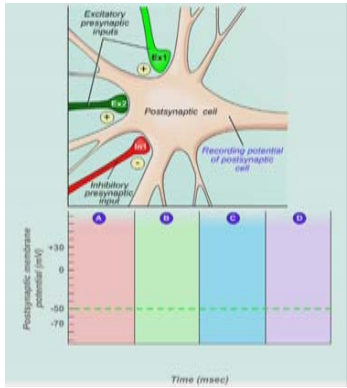
- **Excitatory Synapses**
  - Open non-specific cation channels (both $Na^+$ and $K^+$ can pass through)
  - More $Na^+$ flows into the cell than $K^+$ flows out
    - Both the chemical and electrical gradients favor Na movement
  - Net result → ***Excitatory Postsynaptic Potential*** (a small depolarization)
  - Usually one EPSP is not enough to trigger an AP
  - Membrane is now more excitable
- **Inhibitory Synapses**
  - Different neurotransmitters
  - Open either $K^+$ or $Cl^-$ channels
  - K+ efflux or Cl- influx → ***Inhibitory Postsynaptic Potential*** (a small hyperpolarization)
- **Synaptic Delay**
  - 0.5 to 1 msec
  - Travel through more synapses → ↑Total reaction time





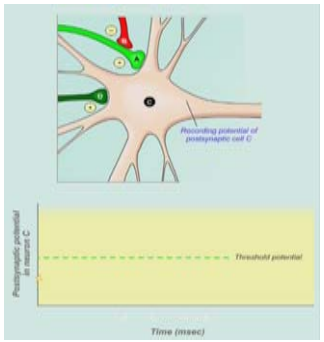

# Synapses and Integration

- **Grand Postsynaptic Potential (GPSP)**
  - EPSPs and IPSPs are graded potentials and can be summed
  - About 50 EPSPs are required to initiate AP
  - Temporal Summation
    - EPSPs occurring very close in time can be summed
    - E.g. repeated firing of pre-synaptic neuron because of a persistent input
  - Spatial Summation
    - EPSPs from different adjacent synapses can be summed
  - Concurrent EPSPs and IPSPs
    - Cancel each other (more or less) depending on amplitude and location



# Synapses and Integration

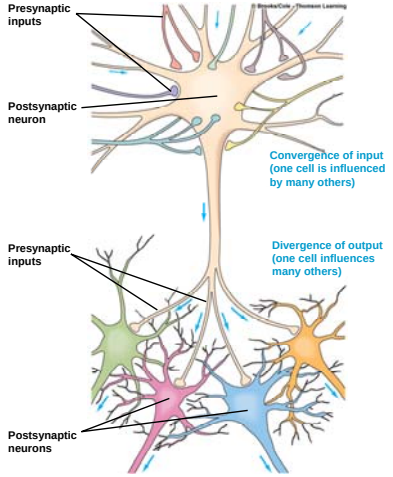
- **Variation in synaptic activity**
  - Neuromodulation
    - Neuromodulators released by neuron
    - Large molecules which fine-tune a neuron's response
      - Change neurotransmitter production or release
      - Change number of receptors
      - Etc
    - Effect are long term (days, months or years)
  - Pre-synaptic inhibition or Pre-synaptic facilitation
    - Pre-synaptic terminal innervated by modulatory axon terminal
    - Modulatory neuron can inhibit or facilitate the action of a neuron
      - Changing amount of $Ca^{2+}$ entering
    - Does not have any effect on the post-synaptic neuron






# Synapses and Integration

- **Post-synaptic Integration**
  - APs are initiated depending on a combination of inputs
  - Neuron is a complex computational device
    - Synapses = inputs
    - Dendrites = processors
    - Axons/APs = output
  - Signaling and frequency of APs is a result of integration of information from different sources
  - Information not significant enough is not passed at all
  - Neurons are integrated into complex networks ($10^{11}$ neurons and $10^{14}$ synapses in the brain alone!)
    - Converging
    - Diverging

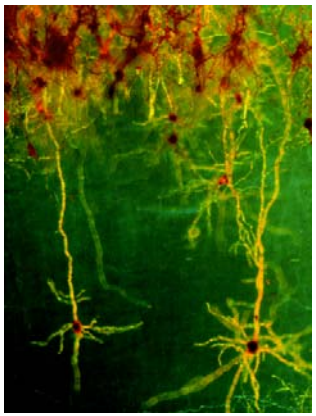



Arrows indicate direction in which information is being conveyed.



# Synaptic Plasticity & Learning

- **Short- and long-term changes in synaptic function**
- **Posttetanic Potentiation**
  - Enhancement lasts up to 60 seconds
  - Accumulation of Ca2+
- **Habituation**
  - The stimulus gradually disappears
  - Decreased intracellular Ca2+
- **Sensitization**
  - Habituated response paired once or several times with a noxious stimulus
- **Long-Term Potentiation**
  - Rapidly developing persistent enhancement of the postsynaptic potential
  - plays a role in memory
- **Long-Term Depression**
  - LTD is the opposite of LTP





# Synapses and Integration

- **Effects of drugs and diseases**
  - Drug actions may include
    - Altering the synthesis, axonal transport, storage, or release of a neurotransmitter
    - Modifying the neurotransmitter interaction with the postsynaptic receptor
    - Influence neurotransmitter reuptake or destruction
    - Replace a neurotransmitter with a substitute either more or less powerful
  - Examples
    - Cocaine → blocks reuptake of neurotransmitter dopamine → pleasure pathways remain "on"
    - Tetanus toxin → prevents release of inhibitory neurotransmitter GABA → muscle excitation unchecked → uncontrolled muscle spasms
    - Strychnine → blocks the receptor of inhibitory neurotransmitter glycine → convulsions, muscle spasticity

# Next Lecture …

## Sherwood, Human Physiology

**The Central Nervous System**

**(131-157, 163-166, 168-179)**

**Excluded**: molecular mechanisms of memory, habituation, potentiation, permanent synaptic connections, sleep