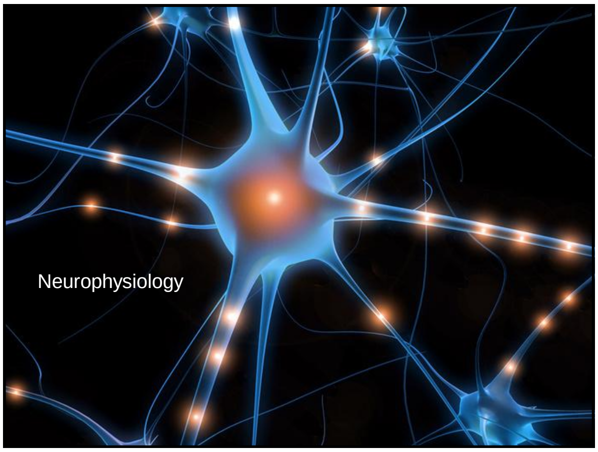
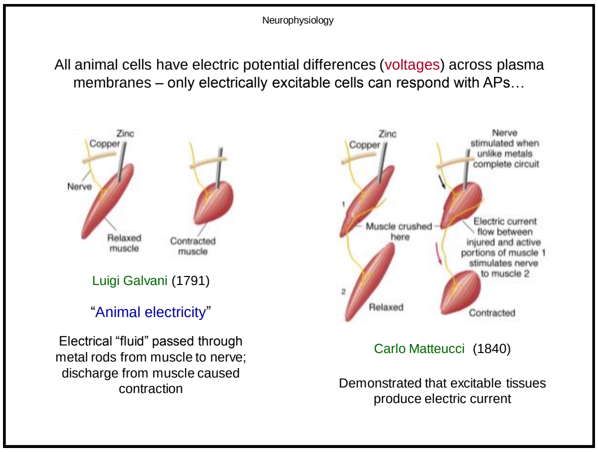


Neurophysiology



Neurophysiology

All animal cells have electric potential differences (voltages) across plasma membranes – only electrically excitable cells can respond with APs…

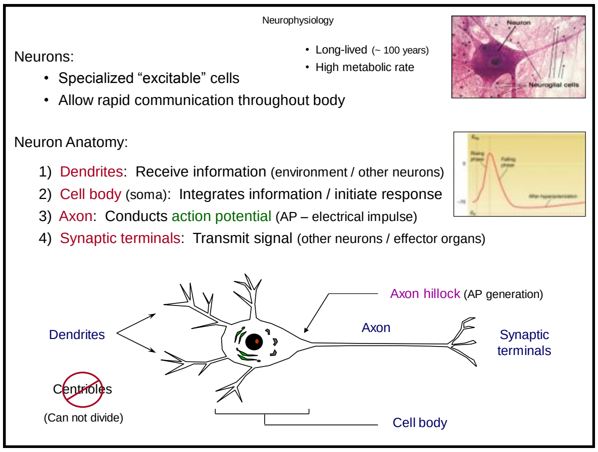
Luigi Galvani (1791)

"Animal electricity"

Electrical "fluid" passed through metal rods from muscle to nerve; discharge from muscle caused contraction

Carlo Matteucci (1840)

Demonstrated that excitable tissues produce electric current



Neurophysiology

Neurons:
- Specialized "excitable" cells
- Allow rapid communication throughout body

- Long-lived (~ 100 years)
- High metabolic rate

Neuron Anatomy:

1) Dendrites: Receive information (environment / other neurons)
2) Cell body (soma): Integrates information / initiate response
3) Axon: Conducts action potential (AP – electrical impulse)
4) Synaptic terminals: Transmit signal (other neurons / effector organs)

Axon hillock (AP generation)

Dendrites

Axon

Synaptic terminals

~~Centrioles~~

(Can not divide)

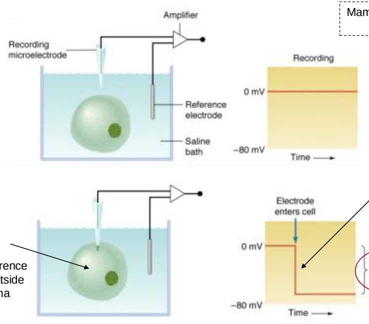
Cell body

How do we generate a membrane potential in a living cell?

Membrane Potential:

- Voltage difference between cytosol of a cell and the extracellular medium

Mammalian neurons: - 90 mV



Downward deflection = Negative inside potential

Isopotential

Entire potential difference between inside / outside localized to plasma membrane

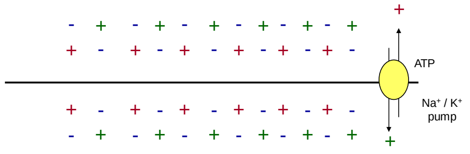
(- 20 to - 100 mv)

Need to develop unequal charge distribution across cell membrane…

HOW?

Develop unequal distribution of ions!

+ = Na^+
+ = K^+
- = Cl^-
Proteins$^-$



Step 1: Make [ion species] inside cell different from [ion species] outside cell

- Na^+ / K^+ pump (active transport)

Need to develop unequal charge distribution across cell membrane…

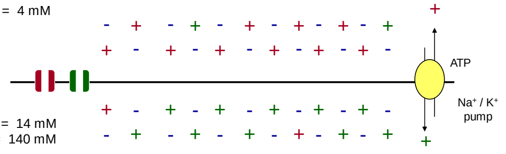
Concentration gradient established

Na^+ = 142 mM
K^+ = 4 mM

HOW?

Develop unequal distribution of ions!

+ = Na^+
+ = K^+
- = Cl^-
Proteins$^-$

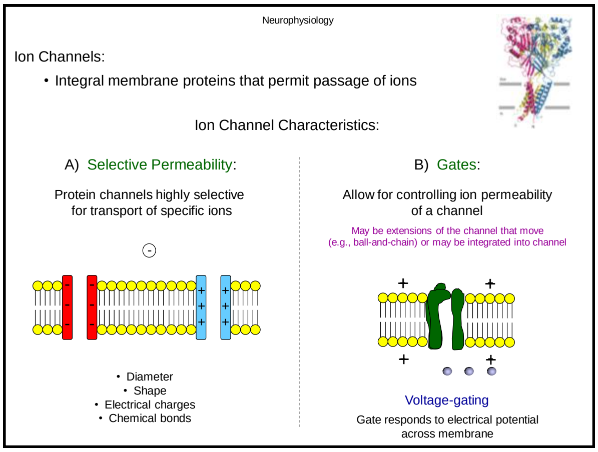


Na^+ = 14 mM
K^+ = 140 mM

Step 1: Make [ion species] inside cell different from [ion species] outside cell

- Na^+ / K^+ pump (active transport)

Step 2: Put selectively permeable ion channels into membrane



Ion Channels:

- Integral membrane proteins that permit passage of ions

Ion Channel Characteristics:

A) Selective Permeability:

Protein channels highly selective for transport of specific ions

- Diameter
- Shape
- Electrical charges
- Chemical bonds

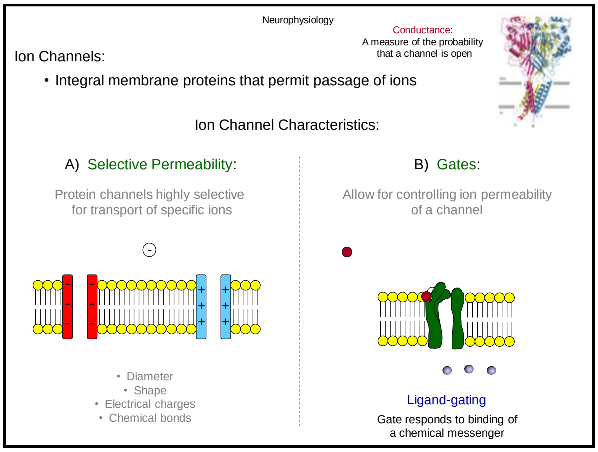
B) Gates:

Allow for controlling ion permeability of a channel

May be extensions of the channel that move (e.g., ball-and-chain) or may be integrated into channel

Voltage-gating

Gate responds to electrical potential across membrane



Conductance:
A measure of the probability that a channel is open

Ion Channels:

- Integral membrane proteins that permit passage of ions

Ion Channel Characteristics:

A) Selective Permeability:

Protein channels highly selective for transport of specific ions

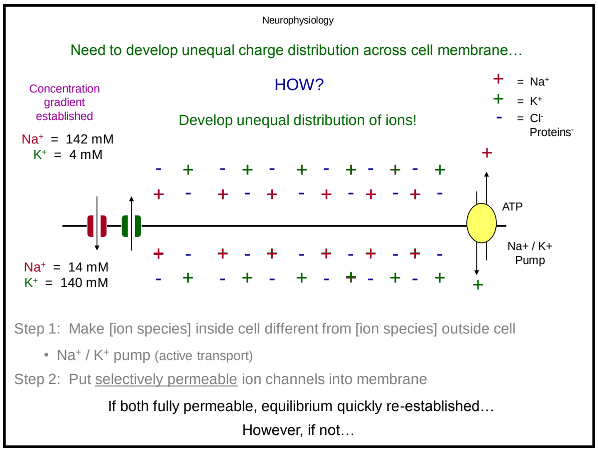
- Diameter
- Shape
- Electrical charges
- Chemical bonds

B) Gates:

Allow for controlling ion permeability of a channel

Ligand-gating

Gate responds to binding of a chemical messenger



Need to develop unequal charge distribution across cell membrane…

HOW?

Develop unequal distribution of ions!

Concentration gradient established

Na⁺ = 142 mM
K⁺ = 4 mM

Na⁺ = 14 mM
K⁺ = 140 mM

Step 1: Make [ion species] inside cell different from [ion species] outside cell

- Na⁺ / K⁺ pump (active transport)

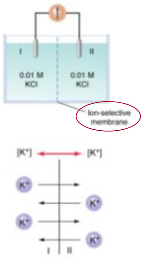
Step 2: Put selectively permeable ion channels into membrane

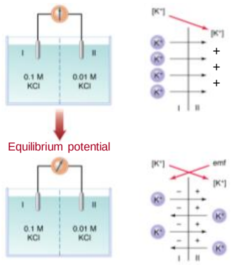
If both fully permeable, equilibrium quickly re-established…

However, if not…

Equilibrium Potential:

Diffusional potential:
Potential difference generated
across a membrane when a charged
solute diffuses down its [gradient]





Electrochemical
equilibrium

Requires only small amount
of ions to cross membrane

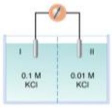
Equilibrium Potential:

Nernst Equation: Allows for calculating the equilibrium potential of single ions

$$E_X = \frac{-2.3\,RT}{zF}\log\frac{[X]_{in}}{[X]_{out}}$$

(Derived from Ideal Gas Laws)

E_x = Equilibrium potential for ion X (V)
R = Gas constant
F = Faraday constant
T = Absolute temperature (K)
Z = charge on each ion
[X] = concentrations of ions on each side of membrane



$$E_X = \frac{-60\text{ mV}}{z}\log\frac{[X]_{in}}{[X]_{out}}$$

$$E_X = \frac{-60}{1}\log\frac{0.1}{0.01} = -60\text{ mV}$$

Need to develop unequal charge distribution across cell membrane…

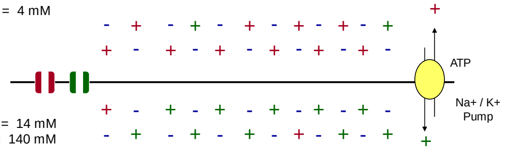
HOW?

Develop unequal distribution of ions!

Concentration
gradient
established

+ = Na^+
+ = K^+
- = Cl^-
Proteins$^-$

Na^+ = 142 mM
K^+ = 4 mM



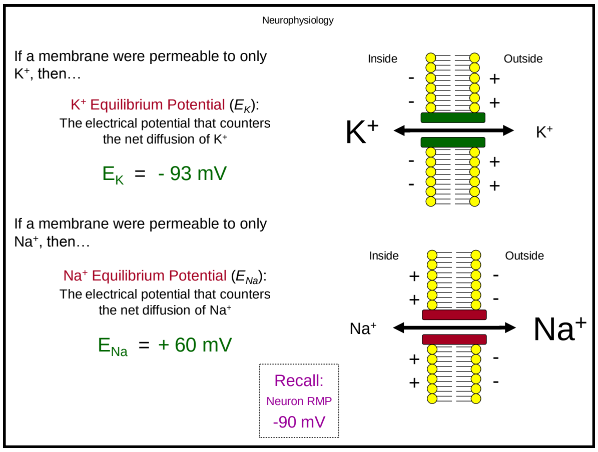
Na^+ = 14 mM
K^+ = 140 mM

Step 1: Make [ion species] inside cell different from [ion species] outside cell

- Na^+ / K^+ pump (active transport)

Step 2: Put selectively permeable ion channels into membrane

Which ion is more permeable?



If a membrane were permeable to only K^+, then…

K^+ Equilibrium Potential (E_K):
The electrical potential that counters the net diffusion of K^+

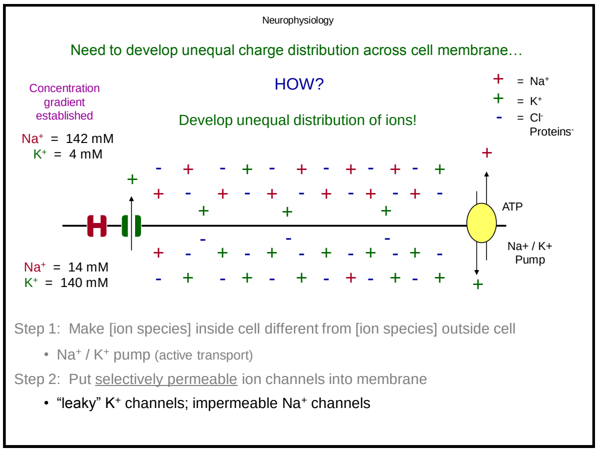
E_K = - 93 mV

If a membrane were permeable to only Na^+, then…

Na^+ Equilibrium Potential (E_{Na}):
The electrical potential that counters the net diffusion of Na^+

E_{Na} = + 60 mV

Recall:
Neuron RMP
-90 mV



Need to develop unequal charge distribution across cell membrane…

HOW?

Develop unequal distribution of ions!

Concentration gradient established

Na^+ = 142 mM
K^+ = 4 mM

Na^+ = 14 mM
K^+ = 140 mM

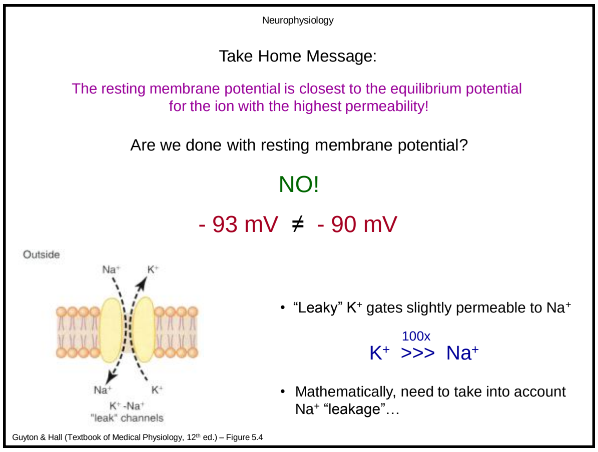
+ = Na^+
+ = K^+
- = Cl^-
Proteins$^-$

Step 1: Make [ion species] inside cell different from [ion species] outside cell

- Na^+ / K^+ pump (active transport)

Step 2: Put selectively permeable ion channels into membrane

- "leaky" K^+ channels; impermeable Na^+ channels



Take Home Message:

The resting membrane potential is closest to the equilibrium potential for the ion with the highest permeability!

Are we done with resting membrane potential?

NO!

- 93 mV ≠ - 90 mV

- "Leaky" K^+ gates slightly permeable to Na^+

$K^+ \overset{100x}{>>>} Na^+$

- Mathematically, need to take into account Na^+ "leakage"…

Guyton & Hall (Textbook of Medical Physiology, 12th ed.) – Figure 5.4

X = K^+
Y = Na^+
Z = $\cancel{Cl^-}$

P = permeability constant

Equilibrium Potential:

Goldman Equation: Allows for calculating the equilibrium potential for multiple ions

$$E_{X,Y,Z} = \frac{-60}{z} \log \frac{P_X[X]_{in} + P_Y[Y]_{in} + P_Z[Z]_{in}}{P_X[X]_{out} + P_Y[Y]_{out} + P_Z[Z]_{out}}$$

$$E_{Na,\,K} = \frac{-60}{z} \log \frac{1\,[K^+]_{in} + 0.01\,[Na^+]_{in}}{1\,[K^+]_{out} + 0.01\,[Na^+]_{out}}$$

Mammalian Neuron:

$$E_{Na,\,K} = -60 \log \frac{1\,(140) + 0.01\,(14)}{1\,(4) + 0.01\,(142)}$$

Na^+ = 142 mM
K^+ = 4 mM

Na^+ = 14 mM
K^+ = 140 mM

$$E_{Na,\,K} = -85\text{ mV}$$

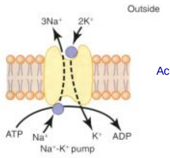
Take Home Message II:

The resting membrane potential must take into account all ion species that are able to cross the membrane!

Are we done with resting membrane potential?

NO!

$-85\text{ mV} \neq -90\text{ mV}$



Accounts for ~ - 5 mV toward RMP…

Remember:
Na^+ / K^+ pump is electrogenic
(3 +'s out / 2 +'s in)

$-90\text{ mV} = -90\text{ mV}$

Guyton & Hall (Textbook of Medical Physiology, 12th ed.) – Figure 5.4

Action Potential:

- Rapid changes in membrane potential that spread along a nerve / muscle fiber membrane

Characteristics of Action Potentials:

1) Stereotypical size / shape:

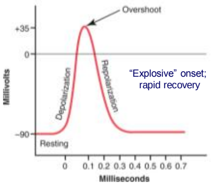
Each normal action potential for a given cell looks identical

2) Propagation:

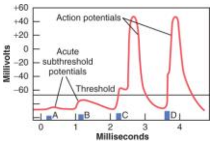
An action potential at one site triggers action potentials at adjacent sites

3) All-or-none response:

If a cell is excited above a certain point, then the occurrence of an action potential is inevitable.



"Explosive" onset; rapid recovery



Threshold (~ - 60 mV):
Intensity of stimulation required to elicit an action potential

Guyton & Hall (Textbook of Medical Physiology, 12th ed.) – Figure 5.6 / 5.8

Neurophysiology

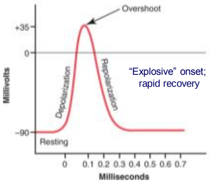
Action Potential:

- Rapid changes in membrane potential that spread along a nerve / muscle fiber membrane

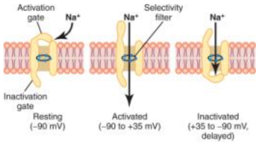
Ionic Basis of Action Potential:

1) Depolarization:

- Neutralization of membrane via influx of Na^+ ions
  - Overshoot: Excess of (+) ions entering (only occurs in large neurons…)
- Voltage-gated sodium channels
  - Two gates (activation / inactivation)
    - Activation = rapid onset
    - Inactivation = slow onset



"Explosive" onset; rapid recovery



℞ Tetrodotoxin (toxin) and lidocaine (local anesthetic) block voltage-gated sodium channels

Guyton & Hall (Textbook of Medical Physiology, 12th ed.) – Figure 5.6 / 5.7

Neurophysiology

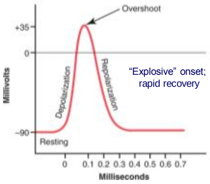
Action Potential:

- Rapid changes in membrane potential that spread along a nerve / muscle fiber membrane

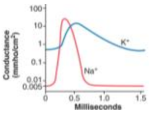
Ionic Basis of Action Potential:

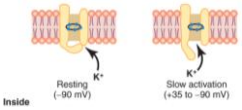
2) Repolarization:

- Re-establishment of polarity via efflux of K^+ ions
- Voltage-gated Potassium Channels
  - Single gate; delayed activation



"Explosive" onset; rapid recovery





Guyton & Hall (Textbook of Medical Physiology, 12th ed.) – Figure 5.6 / 5.7 / 5.10

Neurophysiology

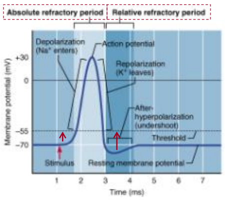
Action Potential:

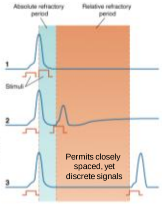
- Rapid changes in membrane potential that spread along a nerve / muscle fiber membrane

Ionic Basis of Action Potential:

3) Refractory period:

- Absolute: (~ 0.5 ms)
  - Na^+ inactivation gate will not reopen until cell nears RMP
- Relative: (~ 1 ms)
  - Excess of (+) ions leaving (undershoot) results in brief increase in polarity of cell
    - Stronger stimulus needed to reach threshold
    - All-or-none property of AP not applicable

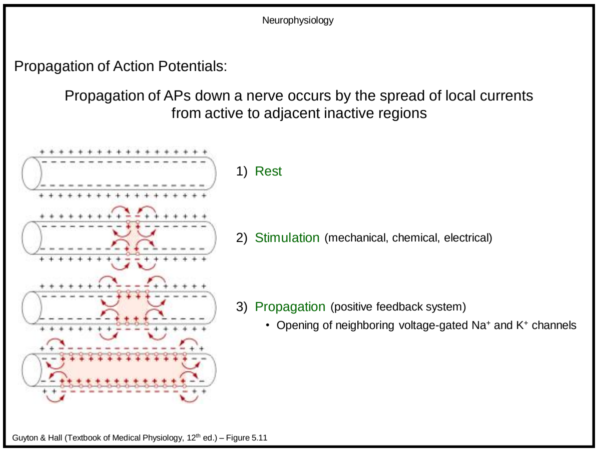




Permits closely spaced, yet discrete signals

"Toilet" analogy

Guyton & Hall (Textbook of Medical Physiology, 12th ed.) – Figure 5.12



Propagation of Action Potentials:

Propagation of APs down a nerve occurs by the spread of local currents from active to adjacent inactive regions

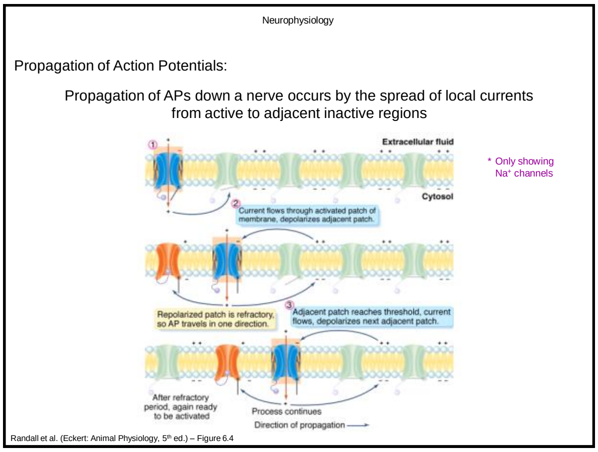
1) **Rest**

2) **Stimulation** (mechanical, chemical, electrical)

3) **Propagation** (positive feedback system)

- Opening of neighboring voltage-gated Na^+ and K^+ channels

Guyton & Hall (Textbook of Medical Physiology, 12th ed.) – Figure 5.11



Propagation of Action Potentials:

Propagation of APs down a nerve occurs by the spread of local currents from active to adjacent inactive regions

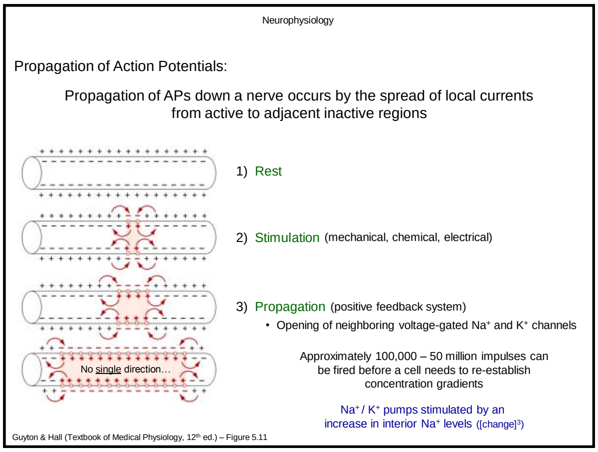
② Current flows through activated patch of membrane, depolarizes adjacent patch.

Repolarized patch is refractory, so AP travels in one direction.

③ Adjacent patch reaches threshold, current flows, depolarizes next adjacent patch.

* Only showing Na^+ channels

Randall et al. (Eckert: Animal Physiology, 5th ed.) – Figure 6.4



Propagation of Action Potentials:

Propagation of APs down a nerve occurs by the spread of local currents from active to adjacent inactive regions

1) **Rest**

2) **Stimulation** (mechanical, chemical, electrical)

3) **Propagation** (positive feedback system)

- Opening of neighboring voltage-gated Na^+ and K^+ channels

Approximately 100,000 – 50 million impulses can be fired before a cell needs to re-establish concentration gradients

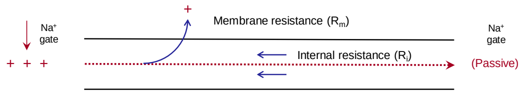
Na^+ / K^+ pumps stimulated by an increase in interior Na^+ levels ([change]^3)

Guyton & Hall (Textbook of Medical Physiology, 12th ed.) – Figure 5.11

Johannes Müller
1830's
"Speed of light"

Conduction Velocity:

AP propagation speeds vary among neurons and are dependent on neuron structure



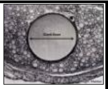
+
Membrane resistance (R_m)
Na^+ gate
Na^+ gate
Internal resistance (R_i)
+ + +
(Passive)

Signal decays with distance from source:

- Cytoplasm resists electrical signal flow
- Plasma membrane not 100% impermeable

$$\lambda = \sqrt{\frac{R_m}{R_i}}$$

Length Constant (λ)
Distance over which signal shows 63% drop in amplitude



Problem?

Conduction Velocity:

AP propagation speeds vary among neurons and are dependent on neuron structure

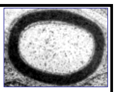
Speed that membrane ahead of active area brought to threshold = Speed of AP propagation

Greater the length constant (λ) = Farther local current can flow = More rapidly membrane ahead depolarizes

R_m = membrane resistance; R_i = internal resistance

$$\lambda = \sqrt{\frac{R_m}{R_i}} \longrightarrow \uparrow \text{Diameter} = \downarrow R_i = \uparrow \lambda$$

squids / arthropods / annelids / teleosts



Schwann cell (PNS)
Oligodendrocyte (CNS)

Conduction Velocity:

AP propagation speeds vary among neurons and are dependent on neuron structure

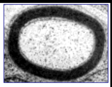
Speed that membrane ahead of active area brought to threshold = Speed of AP propagation

Greater the length constant (λ) = Farther local current can flow = More rapidly membrane ahead depolarizes

R_m = membrane resistance; R_i = internal resistance

$$\lambda = \sqrt{\frac{R_m}{R_i}} \longrightarrow \uparrow \text{Insulation} = \uparrow R_m = \uparrow \lambda$$

↑
Myelination

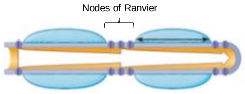


Myelin (↑) membrane resistance ~ 5000x

Conduction Velocity:

Can we simply myelinate the entire axon?

NO – Breaks in the myelin sheath are necessary to regenerate APs...

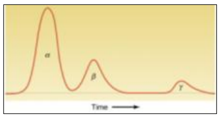


Nodes of Ranvier:
Interruptions in myelin sheath
(Location of voltage-gated ion channels)

Saltatory Conduction
(↓) time… (~ 100 m / sec)
(↓) energy usage

Conduction Velocity:

AP propagation speeds vary among neurons and are dependent on neuron structure



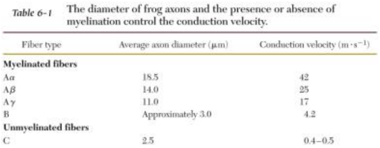


Table 6-1 The diameter of frog axons and the presence or absence of myelination control the conduction velocity.

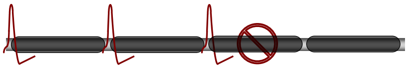
Fiber type	Average axon diameter (μm)	Conduction velocity ($m \cdot s^{-1}$)
Myelinated fibers		
Aα	18.5	42
Aβ	14.0	25
Aγ	11.0	17
B	Approximately 3.0	4.2
Unmyelinated fibers		
C	2.5	0.4–0.5

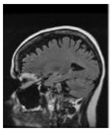
Randall et al. (Eckert: Animal Physiology, 5th ed.) – Figure 6.8 / Table 6.1

Pathophysiology:

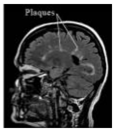
Difficult diagnosis:
Non-stereotypic symptoms
Transient symptoms

Multiple sclerosis is a disease characterized by demyelination of the neurons in the central nervous system





Healthy brain



Brain with damage caused by MS

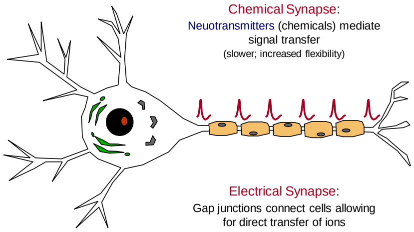
About 1 person per 1000 in the USA is thought to have the disease

- Female-to-male ratio = 2:1
- Highest incidence in individuals of northern European descent

How Do Neurons Communicate Together?

Sir Charles Sherrington (early 1900's)

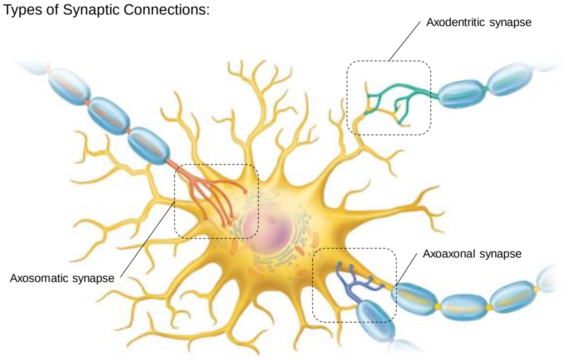
Synapse (*Gr* – "to clasp") : Point of junction between neighboring neurons or a neuron and effector organ



Chemical Synapse:
Neuotransmitters (chemicals) mediate signal transfer
(slower; increased flexibility)

Electrical Synapse:
Gap junctions connect cells allowing for direct transfer of ions
(allows for rapid, coordinated signaling)

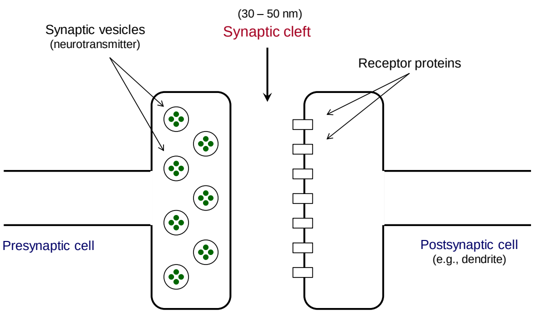
Types of Synaptic Connections:



Marieb & Hoehn (Human Anatomy and Physiology, 12th ed.) – Figure 11.16

Events at a Chemical Synapse:

Synaptic delay:
Time required for chemical neurotransmission to occur
(0.3 – 5.0 ms; rate-limiting)



(30 – 50 nm)
Synaptic cleft

Synaptic vesicles
(neurotransmitter)

Receptor proteins

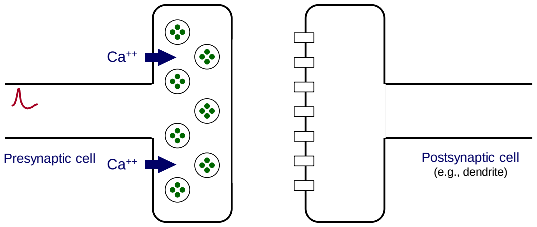
Presynaptic cell

Postsynaptic cell
(e.g., dendrite)

Neurophysiology

Events at a Chemical Synapse:

1) Action potential arrives at synaptic terminal
2) Ca^{++} voltage gates open; Ca^{++} enters cell
3) Synaptic vesicles fuse with plasma membrane



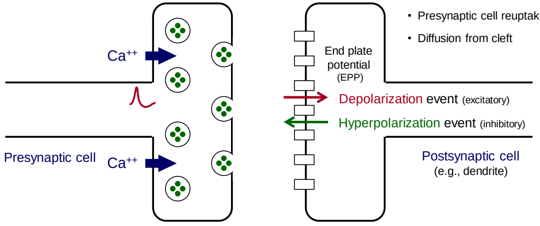
Neurophysiology

Neurotransmitter release is quantal

(minimum amount = 1 synaptic vesicle content)

Events at a Chemical Synapse:

1) Action potential arrives at synaptic terminal
2) Ca^{++} voltage gates open; Ca^{++} enters cell
3) Synaptic vesicles fuse with plasma membrane
4) Neurotransmitter released into synaptic cleft (exocytosis)
5) Neurotransmitter binds with post-synaptic receptors
6) Neurotransmitter removal
   - Enzyme degradation
   - Presynaptic cell reuptake
   - Diffusion from cleft



End plate potential (EPP)

Depolarization event (excitatory)

Hyperpolarization event (inhibitory)

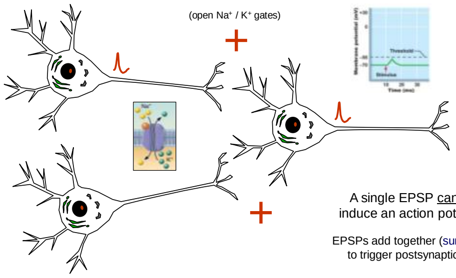
Neurophysiology

Synaptic Integration:

Miniature end plate potential (MEPP):
Smallest possible change in membrane potential
(one quantral of neurotransmitter)

Neuron activity depends on a balance of excitatory and inhibitory input:

EPSP
(Excitatory Postsynaptic Potential)

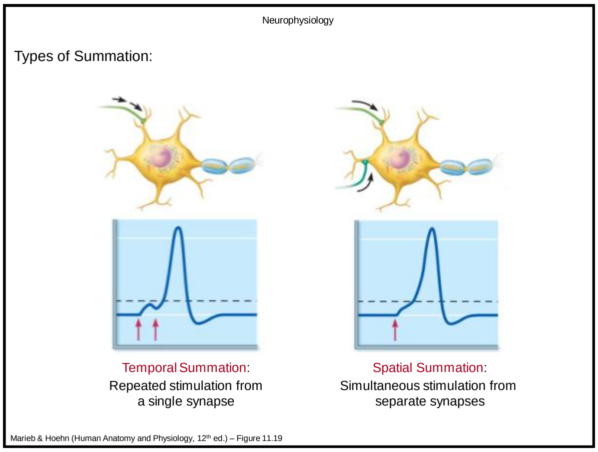


(open Na^+ / K^+ gates)

A single EPSP cannot induce an action potential

EPSPs add together (summate) to trigger postsynaptic cell

Marieb & Hoehn (Human Anatomy and Physiology, 12th ed.) – Figure 11.18 / Table 11.2



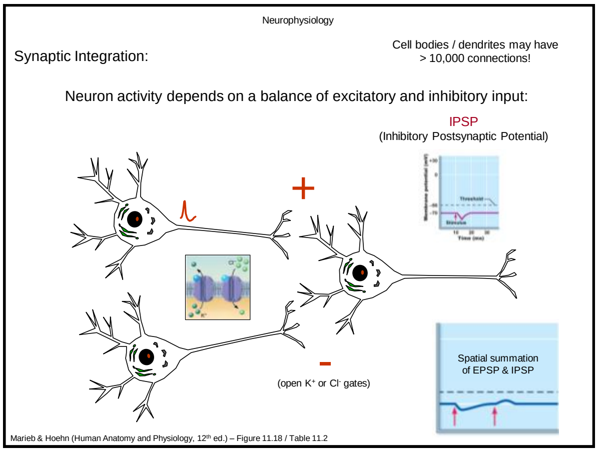
Neurophysiology

Types of Summation:

Temporal Summation: Repeated stimulation from a single synapse

Spatial Summation: Simultaneous stimulation from separate synapses

Marieb & Hoehn (Human Anatomy and Physiology, 12th ed.) – Figure 11.19



Neurophysiology

Synaptic Integration:

Cell bodies / dendrites may have > 10,000 connections!

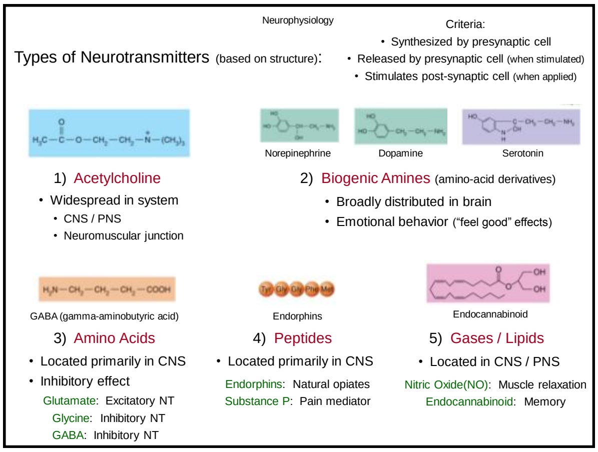
Neuron activity depends on a balance of excitatory and inhibitory input:

IPSP (Inhibitory Postsynaptic Potential)

(open K^+ or Cl^- gates)

Spatial summation of EPSP & IPSP

Marieb & Hoehn (Human Anatomy and Physiology, 12th ed.) – Figure 11.18 / Table 11.2



Neurophysiology

Types of Neurotransmitters (based on structure):

Criteria:
- Synthesized by presynaptic cell
- Released by presynaptic cell (when stimulated)
- Stimulates post-synaptic cell (when applied)

Norepinephrine | Dopamine | Serotonin

1) Acetylcholine
- Widespread in system
  - CNS / PNS
  - Neuromuscular junction

2) Biogenic Amines (amino-acid derivatives)
- Broadly distributed in brain
- Emotional behavior (“feel good” effects)

GABA (gamma-aminobutyric acid)

Endorphins

Endocannabinoid

3) Amino Acids
- Located primarily in CNS
- Inhibitory effect

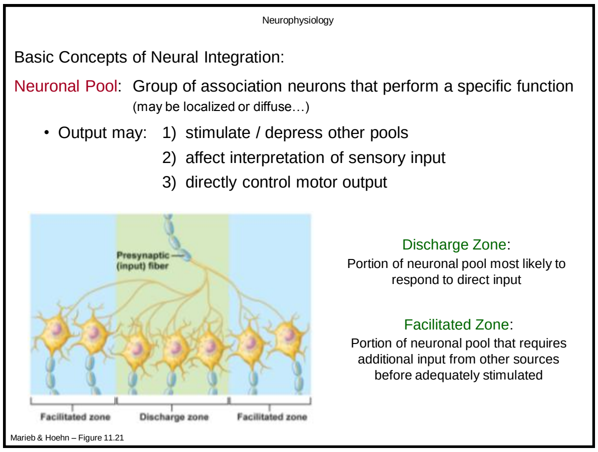
Glutamate: Excitatory NT
Glycine: Inhibitory NT
GABA: Inhibitory NT

4) Peptides
- Located primarily in CNS

Endorphins: Natural opiates
Substance P: Pain mediator

5) Gases / Lipids
- Located in CNS / PNS

Nitric Oxide(NO): Muscle relaxation
Endocannabinoid: Memory



Neurophysiology

Basic Concepts of Neural Integration:

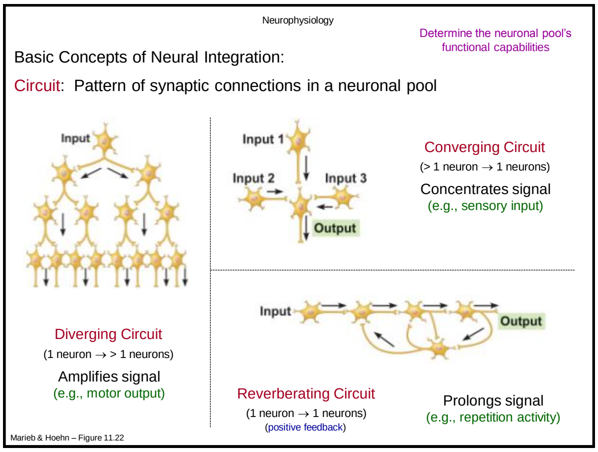
Neuronal Pool: Group of association neurons that perform a specific function (may be localized or diffuse…)

- Output may:
  1) stimulate / depress other pools
  2) affect interpretation of sensory input
  3) directly control motor output

Discharge Zone: Portion of neuronal pool most likely to respond to direct input

Facilitated Zone: Portion of neuronal pool that requires additional input from other sources before adequately stimulated

Marieb & Hoehn – Figure 11.21



Neurophysiology

Determine the neuronal pool's functional capabilities

Basic Concepts of Neural Integration:

Circuit: Pattern of synaptic connections in a neuronal pool

Converging Circuit
(> 1 neuron → 1 neurons)
Concentrates signal
(e.g., sensory input)

Diverging Circuit
(1 neuron → > 1 neurons)
Amplifies signal
(e.g., motor output)

Reverberating Circuit
(1 neuron → 1 neurons)
(positive feedback)

Prolongs signal
(e.g., repetition activity)

Marieb & Hoehn – Figure 11.22