PHYSIO

FIRST LECTURE

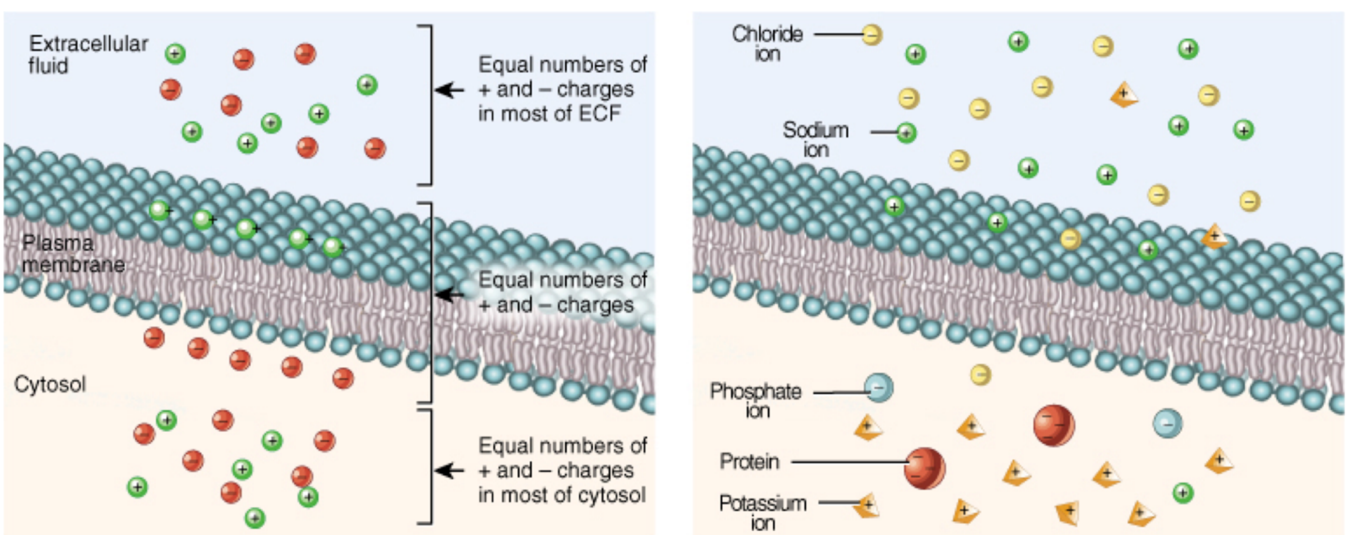
Dr. RAKAN HADDAD

Action Potential

- The cell membrane is a phospholipid bilayer that acts as a selective barrier to substances around it (whether from the inside or the outside of a cell) this bilayer tends to separate the intracellular fluid from the extracellluler fluid as they differ from each other in ion concentrations and whatever substances/ions/molecules present there.

- The membrane being selective means that it allows certain ions to pass throughout it by either the membrane itself by simple diffusion or by carrier-mediated diffusion, all that allows for specific molecules and ions to move throughout the membrane easier than others.

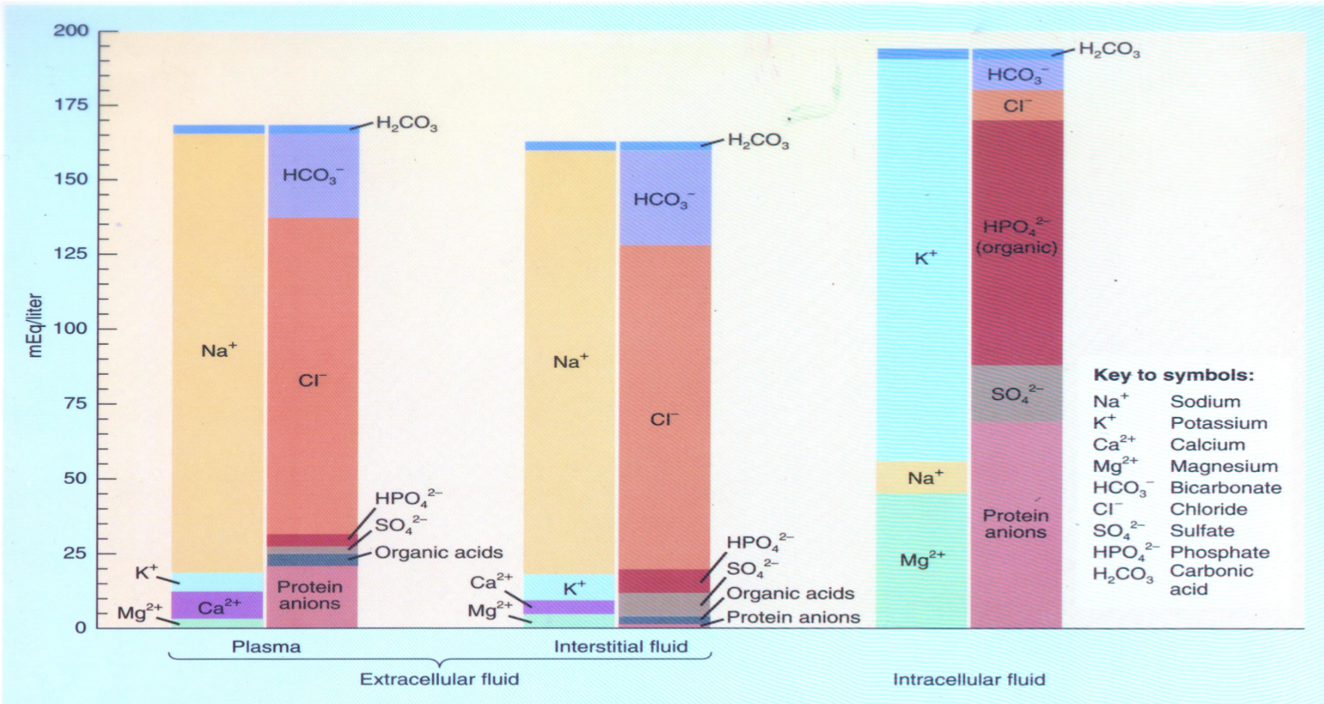
- We also need to understand that the cell membrane is special… How so? When we go deeper into the cell (away from the membrane) the number of cations and anions are equal! Same thing outside and away from the membrane. BUT when we look at the cell membrane itself the intracellular part has a specific charge different from the extracellular part of the cell membrane and that here is what makes the cellular membranes so special! They allow certain charges to dominate each part of the bilayer.



(a) Distribution of charges (b) Distribution of ions

- As we can see from the picture above, the area near the membrane from the inside is a negatively charged area while on the outside exactly its positively charged.

- So what exactly are those ions that create this **<u>CHARGE DIFFERENCE = MEMBRANE POTENTIAL</u>**?
- Intracellularly we would tend to find high concentrations of: K+ / Anionic Proteins / Phosphate ions. Extracellularly we would find high concentrations of: Na+ / Cl-…



Comparison of Electrolyte and Protein Anion Concentrations in the Body Fluid Compartments,

Concentration and Permeability of Ions Responsible for Membrane Potential

Ion	Extracellular Concentration*	Intracellular Concentration*	Relative Permeability
Na+	150	15	1
K+	5	150	25–30
A−	0	65	0

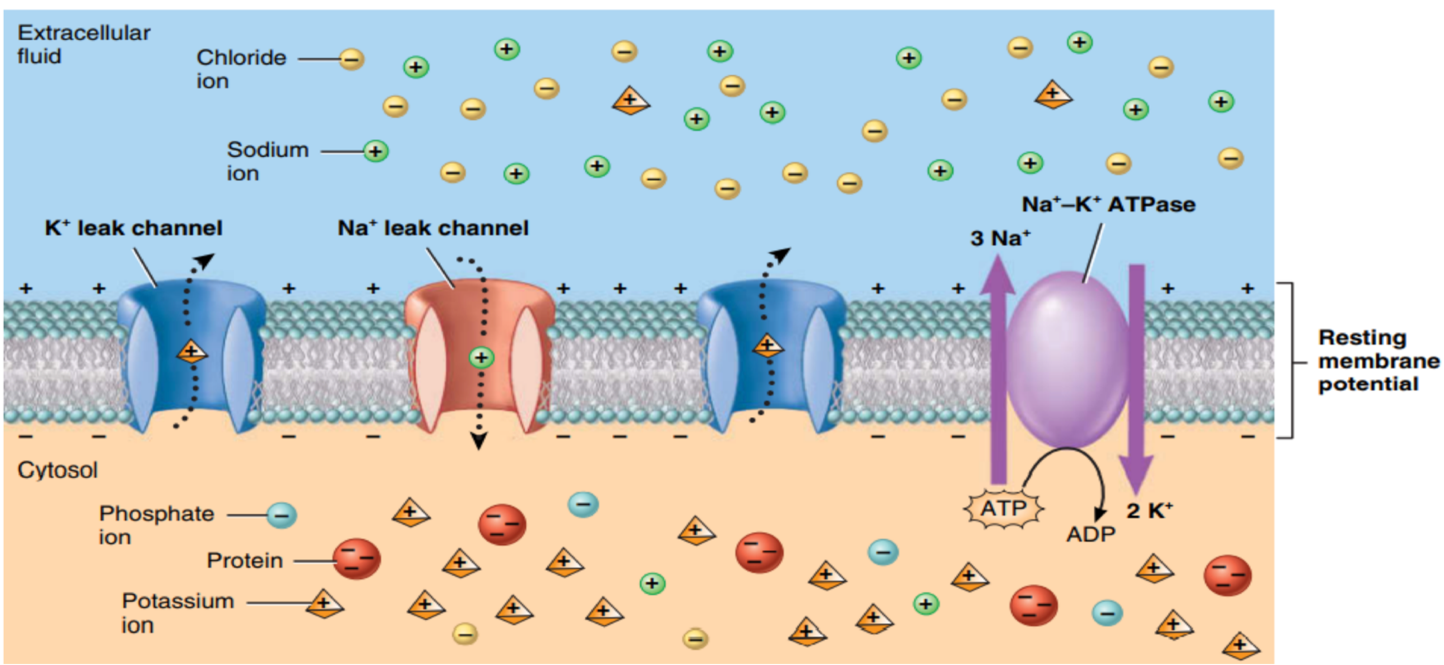
*Concentration expressed in millimoles per liter, mM

- After studying these pictures, we can now understand how a gradient forms across the membrane: As we said the cell membrane is selectively permeable allowing the maintenance of different concentrations of certain substancs on either side of the plasma membrane and it also creates a charge gradient allowing it to "typically" be (-) intracellularly and (+) extracellulary (the membrane bilayer sides). The charge gradient that forms is termed as the membrane potential.

- So now that we created this membrane potential… how do we determine it as a value? Here we need to search for three things: concentration gradient for an ion / charge of the ion / permeability for the ions.

- Now lets learn another term… RESTING POTENTIAL: Its basically the resting membrane potential of the cell membrane… DUH? What do we mean by resting tho? That the cell is in a calm state and it didn't receive any stimulus yet. The membrane with its two sides creates a charge difference as its seperating its negative side (inside) from the positive side (outside). We can measure this difference in millivolts or volts and the greater the charge difference becomes the greater the membrane potential value is. I will repeat again that this build-up of charge on both membrane sides is only near the membrane as the cytosol and the ECF away from the membrane contain equal positive and negative charges.

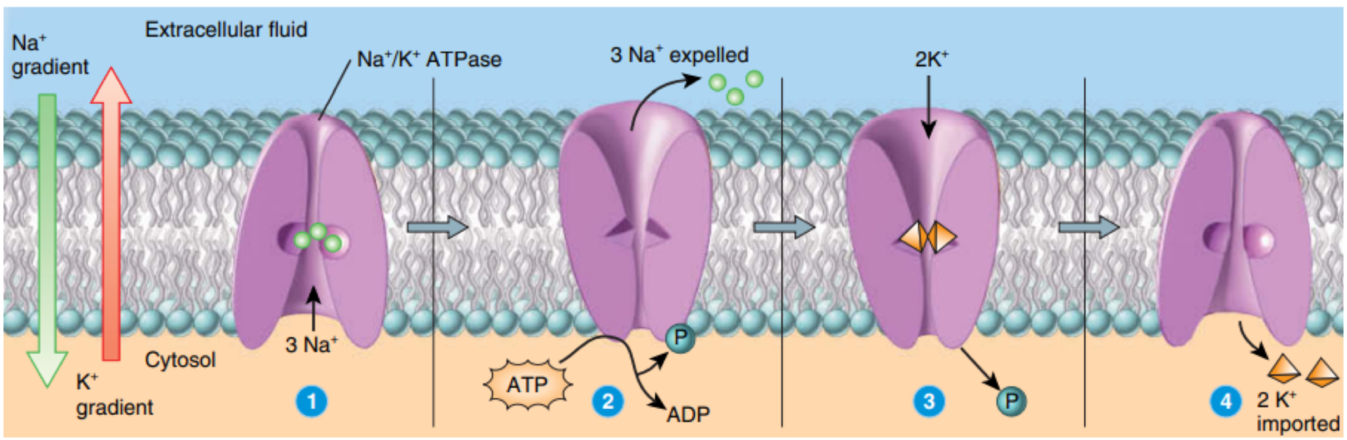
Resting membrane potential



- From the diagram below we can view the cell membrane and some important proteins in the membrane and we can easily tell that there are MORE K+ channels than there is for Na+ and this simply means that the membrane is more permeable to K+ allowing it to move easily throughout it. As we learned before these ions move across a concentration gradient and knowing that K+ has higher intracellular concentration, it tends to move outside the cell causing the net positive charges number to drop on the inside making the internal side of the membrane more negative. We would also expect the resting membrane potential to be really close to the K+ potential as it's the most important effector on the potential due to its high permeability. (the more K+ exits the more negative the intracellular part becomes and the more positive the extracellular part is. Na+ has low perm. ➔ no effect on potential.

- In the picture above and below we can also see the Na+/K+ pump (Na+/K+-ATPase) that needs ATP to function,,, and what its doing is simply moving these ions AGAINST their concentration gradients allowing for 3Na+ ions to exit and 2K+ ions to enter, basically its also affecting the membrane potential. Whats happening here is that this pump is always working on restoring the gradient by bringing back the potassium ions that leaked out as well as throwing out the sodium ions that leaked in, BUT the potassium ions will leak again moving down their [ ] gradient. This pump is **electrogenic** (contributes to the –ve charge)

Na+/ K+ pump



- And now yet another factor contributing to the resting membrane potential and its negativity is the inability of most the anions to leave the cell as they are usually too large or are interacting with cytosolic molecules like Phosphate groups and their interactions in molecules like ATP, or the large proteins.

- To Summarize: Membrane potential (resting) is formed due to a charge difference across the cell membrane, and this potential mainly depends on K+ leakiness as the membrane is permeable to it. In addition to the K+ leakiness there are other factors like Na+/K+ pump and the inability of anionic molecules to cross the membrane.

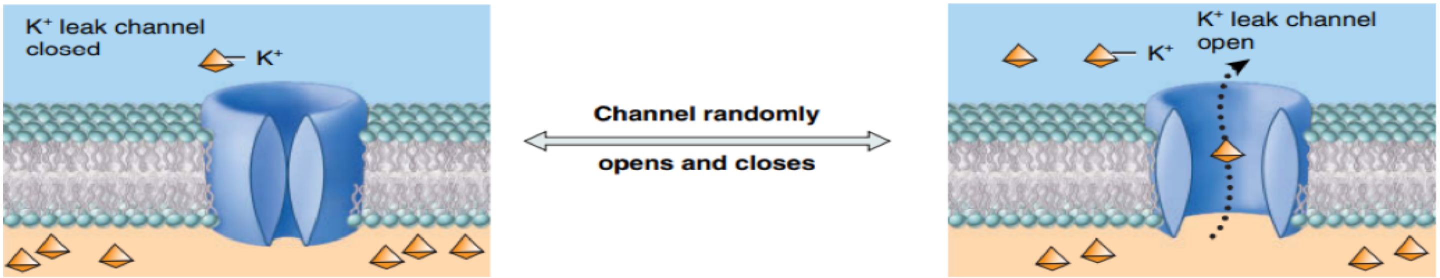
- So now… How about we discuss an important type of cells? **EXCITABLE CELLS:** An excitable cell is one that can be excited electrically meaning that they respond to stimuli by producing electric signals that we will call **ACTION POTENTIAL.**
- These cells, such as neurons and muscle fibers, generate rapidly changing electrochemical impulses at their membranes and these impulses are used to transmit signals along their membranes.
- There are three important potentials one should know:
  1) Resting Potential: no stimulus.
  2) Graded Potential: weak stimulus.
  3) Action Potential: Strong stimulus.

- Also we need to be familiar with four types of very important ion channels:
  a) Leaky Channels: Channels randomly open and close, related to permeability so we would expect more for K+ than for Na+ causing the resting membrane potential that we already explained.
  b) Ligand-Gated Channels:Depends on a chemical stimulus (hormone/neurotransmitter) for them to open such as when Ach binds to its receptors allowing for Ligand-Gated Na+ channels to open.
  c) Mechanically-Gated Channels: Depends on conformational change to the channel opening it up for the passage of ions. e.g: activation gates & inactivation gates for Na+.
  d) Voltage-Gated Channels: Depends on membrane voltage so a change in the voltage can either open or close the channel depending on the ions it allows the passage of.

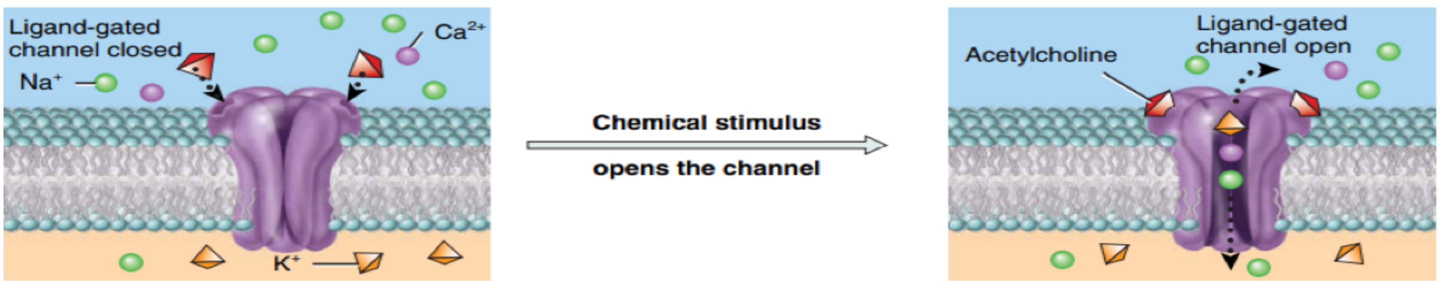
➔ Lets take an example on how all these channels work together: Imagine with me, a normal cell membrane at rest with the leaky channels acting as they always would, then suddenly Ach starts binding to RECEPTORS on the cell meaning that the LIGAND found its place which will cause ligand-gated Na+ channels to open -> Na+ starts entering the cell CHANGING the charge difference and making it more positive on the inside and as a result VOLTAGE-gated channels will start to open creating this positive feedback system that will cause more channels to open. The mechanically gated channels will also undergo conformational changes due to the stimulus binding. So here we learn that everything works together!

… Look at pics below for more info on these channels.

Ion channels in excitable cells

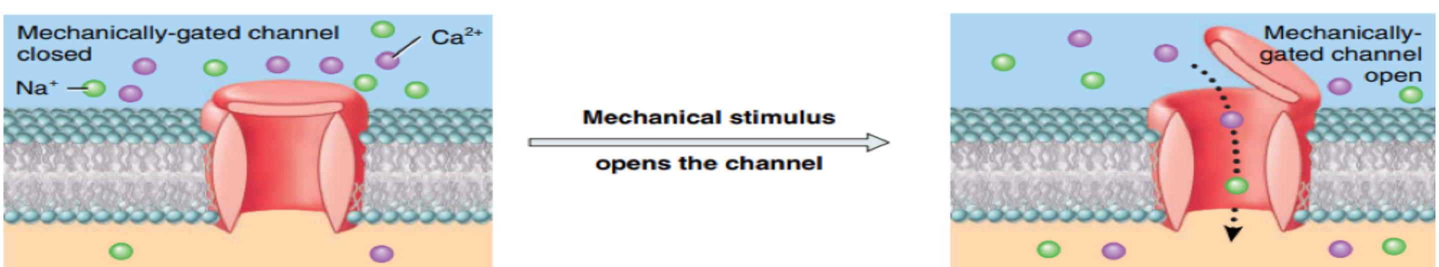


(a) Leak channel

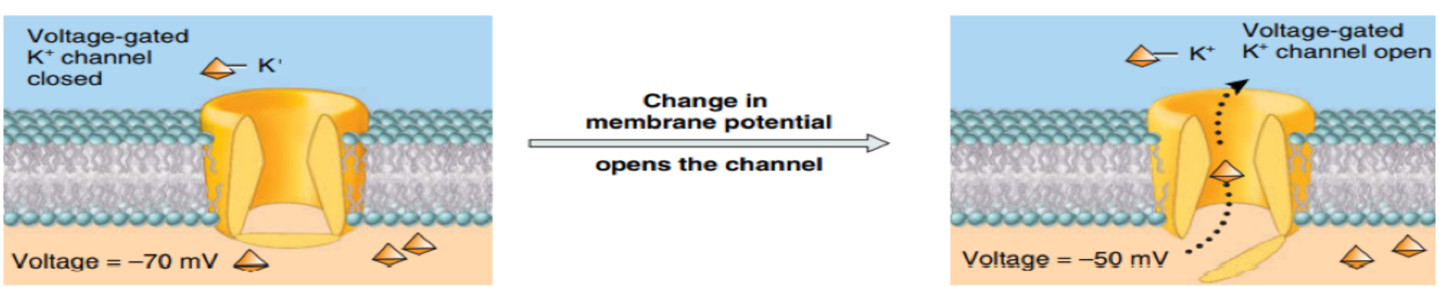


(b) Ligand-gated channel

Ion channels in excitable cells



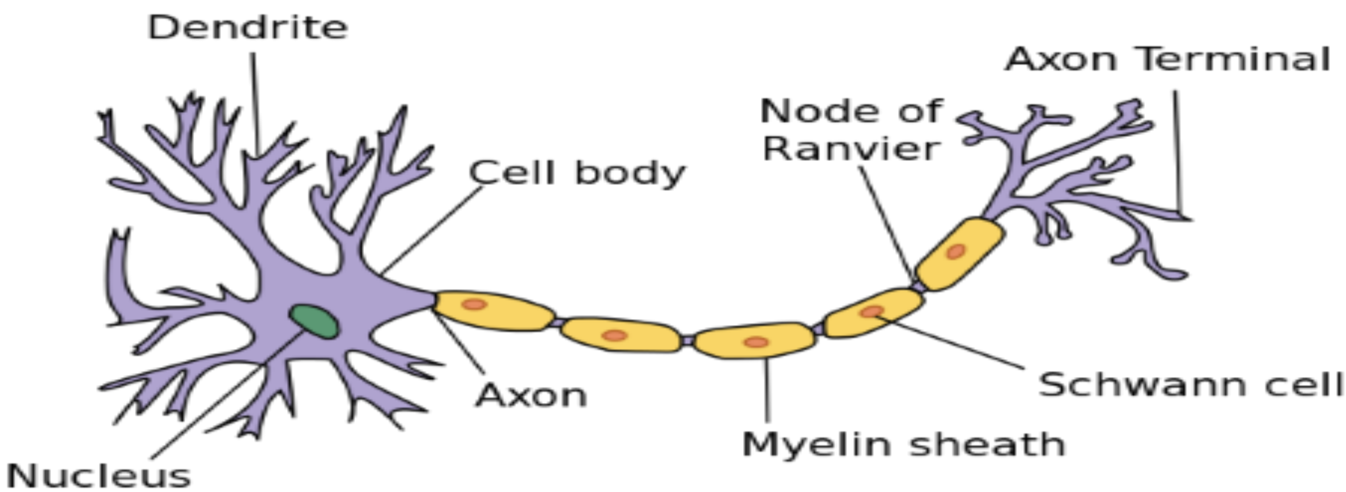
(c) Mechanically-gated channel



(d) Voltage-gated channel

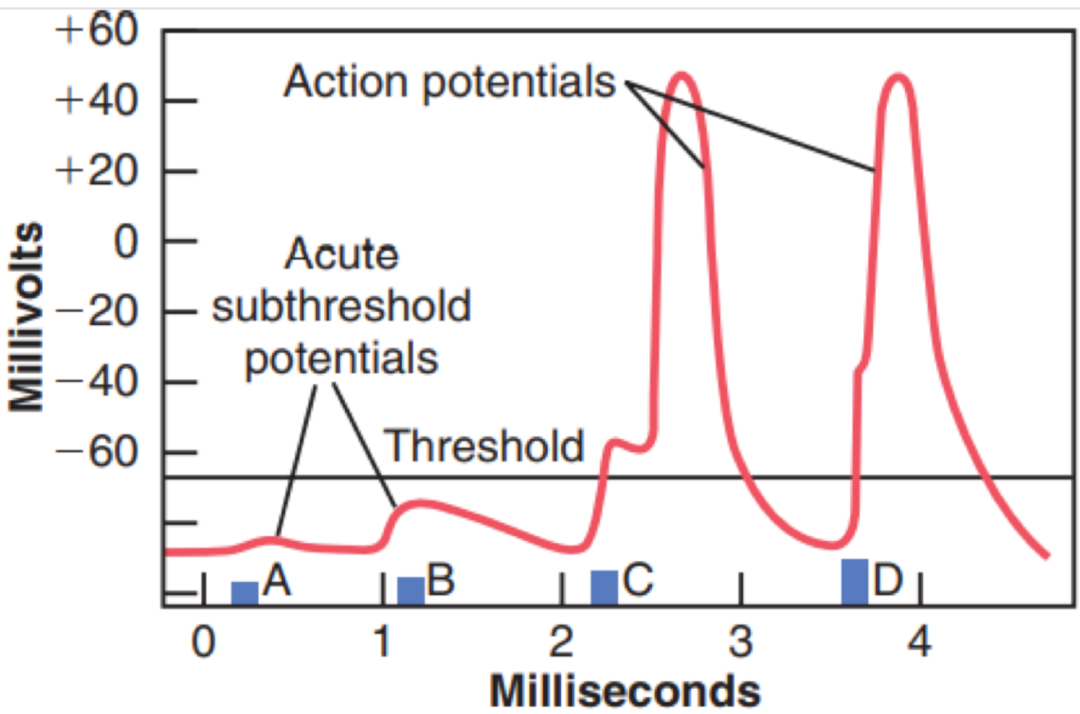
- Now for excitable cells such as a neurons… They have the ability to communicate with one another using two types of electrical signals:
  1) Graded Potential: short distance communication.
  2) Action Potential: long distance communication within the body.

- A neuron consists of very important parts: Dendrites/ Cell Body/ Axon Hillock/ Axon/ Axon terminals/ and on some neurons Shwann Cells or myleinated sheath which allows faster conduction.



- To calculate an ions potential we use nernst equation and when we do so for all ions near the cell membrane we can then use goldsman equation to calculate the full membrane potential.
- An Action Potential is formed when a stimulus strong enough to reach the **threshold** arrives to the excitable cell. Threshold is basically the limit that a stimulus needs to reached and that if reached will create the action potential.
- A Graded Potential simply cant reach this threshold BUT multiple stimuli can arrive causing summation and it might cause it to reach the threshold.
- Refractory Periods are periods in which an excitable cell cant receive or deal with stimuli and its of two types:
  1) Absolute RP: The cell would never be able to get excited no matter how strong a stimuli is.
  2) Relative RP: The cell can get excited if a a really strong stimuli (stronger than the previous one) arrives to stimulate the cell.

  ➔check the table and the image below



Graded potential vs Action potential

CHARACTERISTIC	GRADED POTENTIALS	ACTION POTENTIALS
Origin	Arise mainly in dendrites and cell body.	Arise at trigger zones and propagate along axon.
Types of channels	Ligand-gated or mechanically-gated ion channels.	Voltage-gated channels for Na^+ and K^+.
Conduction	Decremental (not propagated); permit communication over short distances.	Propagate and thus permit communication over longer distances.
Amplitude (size)	Depending on strength of stimulus, varies from less than 1 mV to more than 50 mV.	All or none; typically about 100 mV.
Duration	Typically longer, ranging from several milliseconds to several minutes.	Shorter, ranging from 0.5 to 2 msec.
Polarity	May be hyperpolarizing (inhibitory to generation of action potential) or depolarizing (excitatory to generation of action potential).	Always consist of depolarizing phase followed by repolarizing phase and return to resting membrane potential.
Refractory period	Not present; summation can occur.	Present; summation cannot occur.

- Finally, lets study how the action potential is formed and how the cell is able to return to its original state after so… :

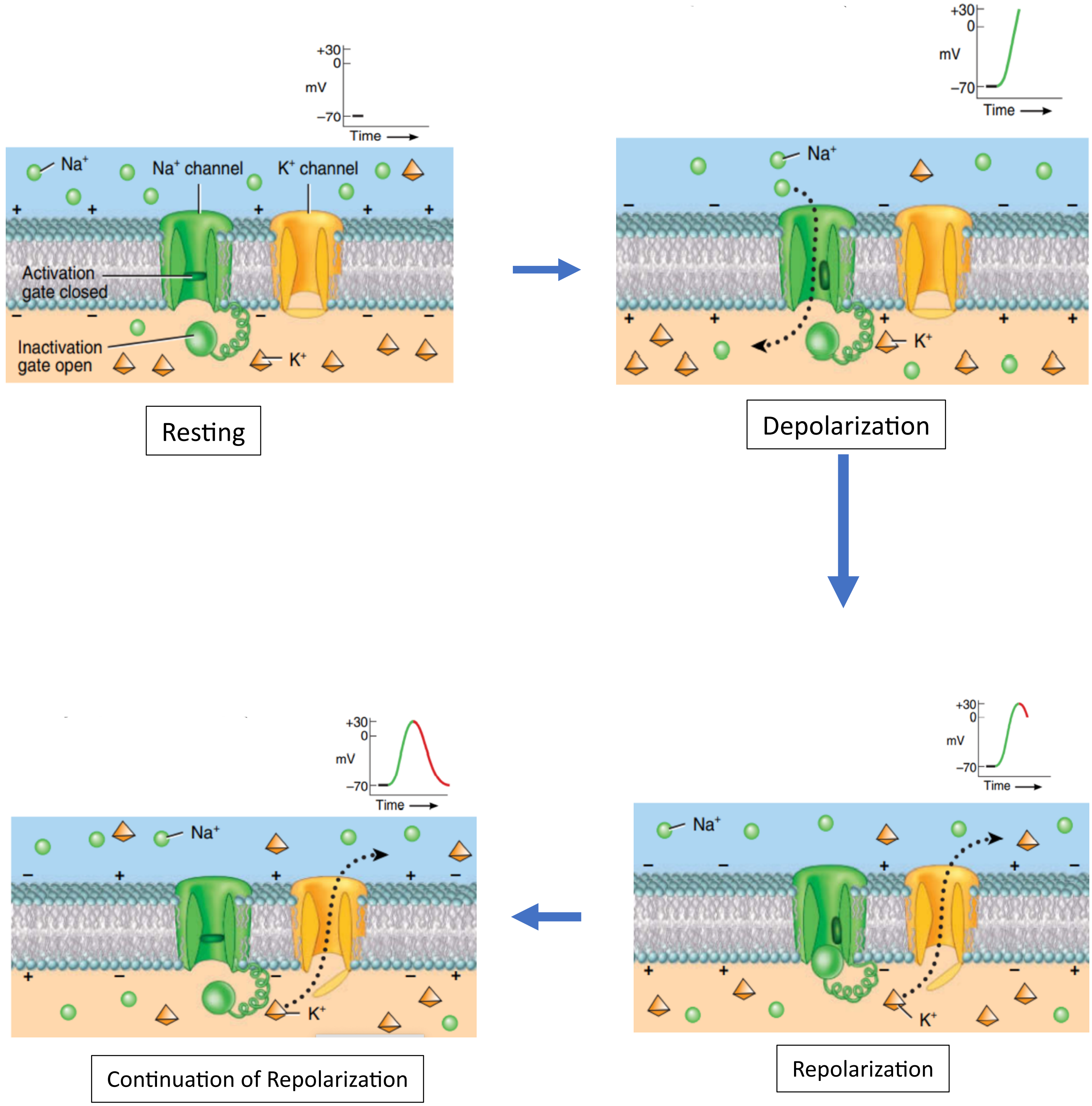
1) Resting State: All Voltage-Gated Channels for Na+ and K+ are closed. Leaky channels are doing their thing the resting membrane potential is maintained as normal. Activation gate of mechanical gated channels is closed, inactivation gate is open (no ion movement as both need to be opened to allow for anything to move)

2) Depolarizing Phase: When the membrane potential reaches the threshold what happens is activation gates of mechanical gated channels of Na+ open up allowing and for only a short amount of time Na+ to enter the cell causing the buildup of positive charges along the inside surface of membrane and it becomes depolarized.

3) Repolarization Phase: The inactivation gates close here so no more movement of sodium and because the inactivation gates are difficult to open at this time its considered the absolute regractory period. When this occurs the K+ channels open up allowing for the exit of K+ making the inside surface negative and the negative charges starts to buildup along the inside surface of the membrane and it will help in returning to resting potential.

4) After-Hyperpolarization (continued repolarization): K+ outflow continues due to increased permeability (more than at resting state) as more K+ channels were opened now and this causes an undershoot making the potential even more negative than the resting membrane potential. K+ outflow allows for membrane to return to rest.

- ⇨ In the last part of phase 3 and in all of phase 4 the inactivation gates of Na+ channels open BUT activation gates are closed and this is where the relative refractory period takes place as a strong stimulus can definetly re-excite the cell before it rests.
- ⇨ The re-establishment of the membrane potential is done by the help of: Na+/K+ pump as it gets rid of any extra Na+ intracellularly, this pump needs ATP so the recharging of the nerve is an active metabolic process. Also keep in mind the K+ channels that open allow it to repolarize and return to the negative potential and eventually resting membrane potential will be achieved after the hyperpolarization.
- ⇨ Look at pics below for further understanding…


+30
0
mV
–70
Time
Na+
Na+ channel
K+ channel
Activation gate closed
Inactivation gate open
K+
Resting
Depolarization
Repolarization
Continuation of Repolarization

Action Potential

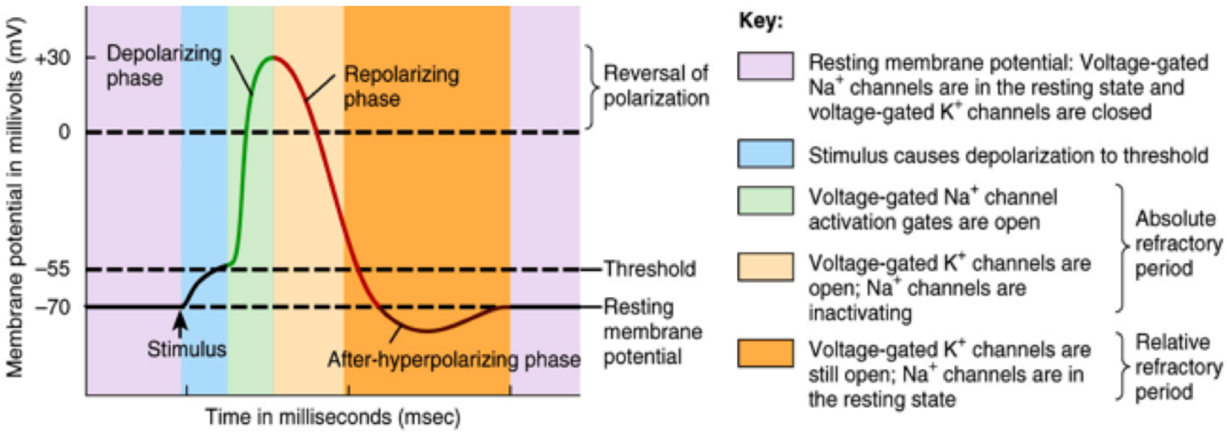


Figure 12.19 Tortora - PAP 12/e