Yesterday's lecture was an introduction for the cardiovascular system. Today we will talk about the cardiac muscle physiology because if you know how the cardiac muscle works you will know as a generalization how the heart works.

Objectives of the lecture:

- To distinguish the cardiac muscle cell microstructure. We'll take that in anatomy but we'll go over the important parts related to physiology.
- Describe cardiac muscle action potential. This is very important.
- Point out the functional importance of the action potential, because the action potential of the cardiac muscle differs from that of skeletal muscle action potential.
- Follow the cardiac muscle mechanism of contraction. It's similar to that of skeletal muscle but with some little differences that we'll go over during the lecture.
- Delineate cardiac muscle energy sources. The skeletal muscle uses Glucose as an energy source while the cardiac muscle uses Fatty acids as its major source.
- Outline the intracellular calcium homeostasis.
  Totally different than that (calcium homeostasis) of skeletal muscle (different pumps, Sodium-Calcium exchanger…). The calcium pump of the cytoplasmic reticulum is the same like the skeletal muscle.
- Explain the relationship between muscle length and tension of cardiac muscle (Frank-Starling law of the heart).

Last time in our introduction lecture we said that in the cardiovascular system we have the cardiac part and the vascular part. We'll start now with the cardiac part.

According to slide #4, the heart has 3 layers: Endocardium, myocardium and pericardium. The innermost layer is called **Endocardium**.
Endocardium is the epithelial layer of the heart (Note: the epithelial layer of the vessels is called endothelium).
Endocardium has many functions other than protection and forming the epithelial layer, for example:

1. It secretes certain substances that control blood flow to the heart and to the tissue. This substance is called nitric oxide or Endothelial cell derived relaxing factor (an old naming).
2. It also secretes another substance that causes local vasoconstriction. This substance is called Endothelin

So the Endocardium (epithelium) is not ONLY an epithelial layer like the other epithelium layers anywhere else.

The major layer of the heart is the myocardium.

The myocardium in the heart isn't like the skeletal muscle, the skeletal muscle is spindle in shape and the cells of the skeletal muscle are separated from each other and the cell's length might be in millimeters or meters, it depends, it runs from the origin to the insertion. But in the myocardium, cells run haphazardly, they're overlapping, they intermingle with each other. They are rectangular in shape, and they're connected to each other. We'll talk about those details later on.

The last layer is called **Pericardium**, the pericardium has two layers: Visceral pericardium and Parietal pericardium. In between them there's a space that's called the Pericardial cavity/space. In this space there's a fluid "proteins fluid". This protein has certain amount that might range from 50 to 100 ml not more than that.
This pericardial fluid is very important, since it acts as a shock absorber and it protects the heart from the injuries that might occur because of certain movements. But this fluid shouldn't increase more than its normal range, if it increases more and more it will limit the filling of the heart. (Note: We know that the main job of the heart is to pump the blood).

What's pumped out of the right or the left ventricle per minute of the heart is called Cardiac output. And this blood is what supplies the tissues with oxygen.

What's pumped out of the heart EQUALS what's coming into the heart.
Meaning that "What comes, goes" → "what comes" is called filling.
The pericardium space limits the filling so if we put too much fluid in the space there will be a limit to the filling → the filling might reach zero →so the cardiac output will equal zero → which leads to death!!

This condition where the pericardial fluid has increased too much to the extent that it limits the filling too much is called Cardiac tamponade.
Car accidents → bleeding in pericardium → too much fluid (blood) → as if the person is suffocating since there's no cardiac output, no oxygenation so as if the person is hungry for air. If we diagnose this condition, the treatment is to relieve this cardiac tamponade. How? By putting a needle, a knife, anything sharp in the pericardium. This way we relieve the cardiac temponade and the person is breathing again. Even if the needle or the knife wasn't sterile it's okay, at least we saved the patient's life since it's our priority in such cases, then we can treat him afterwards with antibiotics or antiviral treatments for any infection that may have risen from the contaminated material we used to save the person's life. So the most important thing is to relieve this fluid, take it out!

Note: Dextrocardia means that the heart in on the right side of the body. (Dextro (D) means right while levo (L) means left)… this was the answer of a question one of the students asked,

but the doctor said that mostly we deal with the patient in this emergency case as a normal case (the heart is on the left) because in order to discover a Dextrocardia case we need a stethoscope at least and sometimes we discover this case when doing ECG.

Now we'll get back to our subject, the cardiac muscle. We said earlier that the cardiac muscle cells are rectangular in shape (NOT spindle in shape), they are intermingled with each other, they're connected to each other by desmosomes, and in between those desmosomes we have gap junctions that connect one cell to the other. (check the figure in slide #5).
 The gap junctions are low electrical resistance areas, which means that if there's any potential change in one of the cells, this potential change spreads to the other cells very fast to the extent that if there's an action potential in one of the cells, the action potential will spread to ALL cells that are connected with these gap junctions at the same time. And this is very important, if these cells depolarizes at the same time it means that they will contract simultaneously (at the same time)… and this is very important for the heart to have a simultaneous contraction because if a part of the heart was contracted and another part was relaxed the force that's formed by the contraction is going to be relieved by the relaxation and thus no force will emerge! For example if the left ventricle contracted and the right ventricle relaxed, the force coming from the left side contraction will go to the right side and no blood comes out of the ventricles! But if both ventricles contracted at the same time the blood has no other option but to get out of the ventricles, so this is very important that the ventricles contract at the same time. This is what we call an Effective pump. Otherwise if you have one cell that is contracted and another one that is relaxed, we call this Fibrillation which means that each fiber contracts by itself.
Ventricular fibrillation is a LETHAL condition unless we do a DC shock (Direct Current Shock) to turn this ventricular fibrillation into a normal ventricular depolarization. That's why the Effective pump (depolarization of the whole muscle cells) is very important.

Now, the muscles of the atria are separated from the ventricular muscles by the Atrioventricular septum.

The atrial muscles themselves are connected to each other.
The ventricular muscles are also connected to each other.

| This is what is called Syncytium |

So we have two syncytia, atrial syncytium and ventricular syncytium.
We have two pumps, atrial pump and ventricular pump.
Thus both atria contract simultaneously, and both ventricles do as well.

Then, the doctor pointed out the structures in slide #5 starting with the sarcomere, Z- lines, gap junctions, desmosomes and the sarcoplasmic reticulum.

The plasma membrane of the muscle is called → the <u>Sarcolemma (SL)</u>.
The endoplasmic reticulum of the muscles → <u>Sarcoplasmic reticulum (SR).</u>
The cytoplasm of the muscles → <u>Sarcoplasm.</u>

MAGNIFIED VIEW OF CARDIAC MUSCLE CELLS
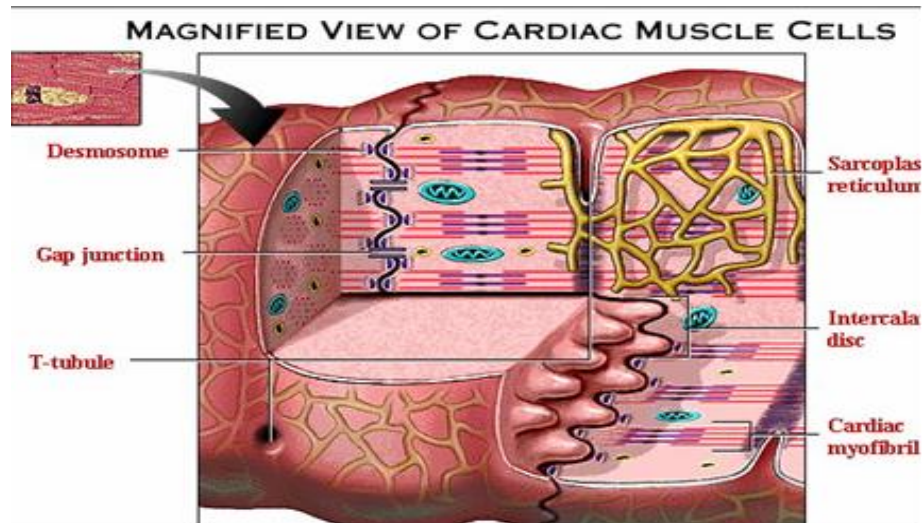
Our reference point is the skeletal muscle and thus we want to see how the cardiac muscle differs from the skeletal muscle:

- Both cells have sarcolemma. The sarcolemma has invaginations inside the cells that are called transverse tubules; those tubules are slender, thinner and longer in skeletal muscle, while in the cardiac muscle they're wider and shorter. The other difference is that the transverse tubule in the cardiac muscle is located on the Z-lines, while the transverse tubule in the skeletal muscle is located in between the Z-lines, in the I-band. Which means that <u>there's one Transverse tubule per sarcomere for the cardiac muscle while there are 2 transverse tubules per sarcomere in the skeletal muscle.</u>
- The SR of the skeletal muscle is well developed (remember that the function of the SR is to store Calcium that needs to be released to the sarcoplasm to initiate contraction). So in the skeletal muscle the SR is well developed so it stores a lot of calcium. The calcium that is released from the SR is enough to initiate contraction. While the SR of the cardiac muscle is less developed, this means that its storage of calcium is much less than the skeletal muscle. NOTE: if the SR storage of calcium is little, this means that the heart needs another source for Calcium beside the SR. The other source is the extracellular fluid (interstitial fluid/the internal environment).
- The Mitochondria:
  the heart is always contracting (involuntary contraction), it never stops while the skeletal muscle only contracts when used (voluntary). This means that the heart always

needs a lot of energy. The energy source is the mitochondria, thus there are lots of mitochondria in the cardiac muscle as compared to the skeletal muscle.

- In skeletal muscles there are more nuclei than in cardiac muscle.
- Sarcomere (The distance between two Z-lines). In each fiber skeletal muscle there are around 100.000 sarcomere. In contraction shortening occurs in the sarcomere which leads to the shortening of the muscle. The sarcomere consists of thick filaments (myosin only) and thin filaments (Three contractile proteins: 1. Tropomyosin, 2. Actin, 3. Troponin). Those filaments are interdigitating, the myosin becomes in the middle and the other proteins in between. This is called the sliding filament theory.
In Slide #6 you can see the sarcomere, Z-line, thick filaments and part of the thin filaments (I-bands).
These filaments cause the striated appearance of the cardiac muscle filaments. They appear striated (contain Dark areas and light areas).
Dark area → thick filaments (myosin) → doesn't change during contraction because the sliding occurs for the THIN filaments on the thick filaments.
This also occurs in skeletal muscles.

(a) Cardiac muscle fibers

(b) Diagram based on an electron micrograph
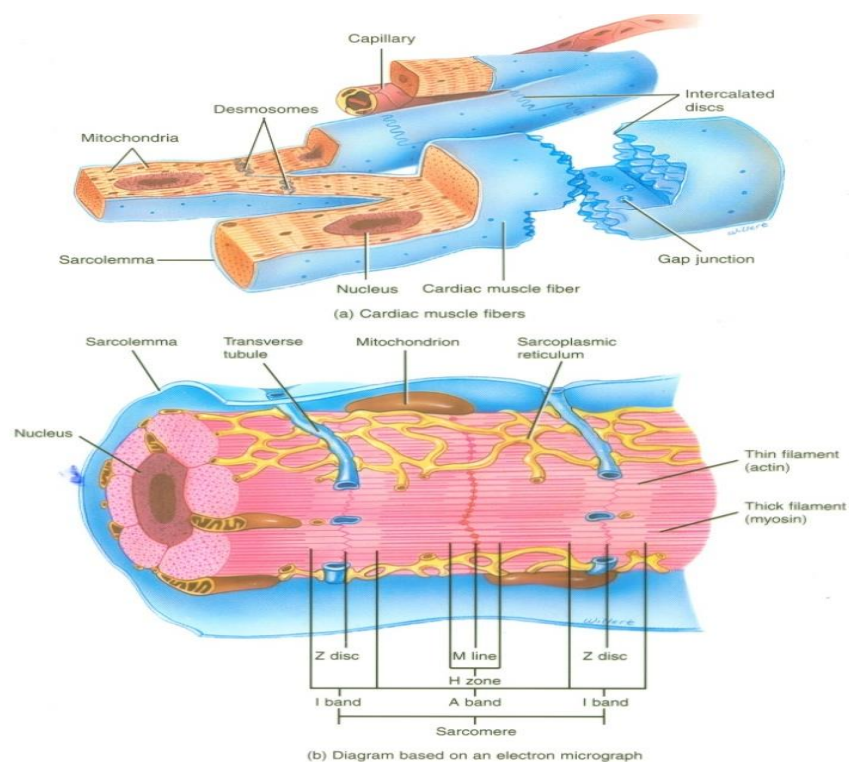
Gap junctions in cardiac muscle: hexagonal proteins that open and close according to the change in voltage, it looks like a voltage gated channel but it's of a low resistance: any change in the voltage will cause it to open. When it opens, the ionic change (membrane potential change) will spread to all cells at the same time.

Check the figure below (slide #7) to notice the difference in between the open and the closed states of the gap junction. Also note how the gap junctions are spread in between the membranes of the cells. Sometimes the gap junction is called the electrical synapse, since it's a synapse (connection) between cells but it's also electrical synapse not chemical synapse.
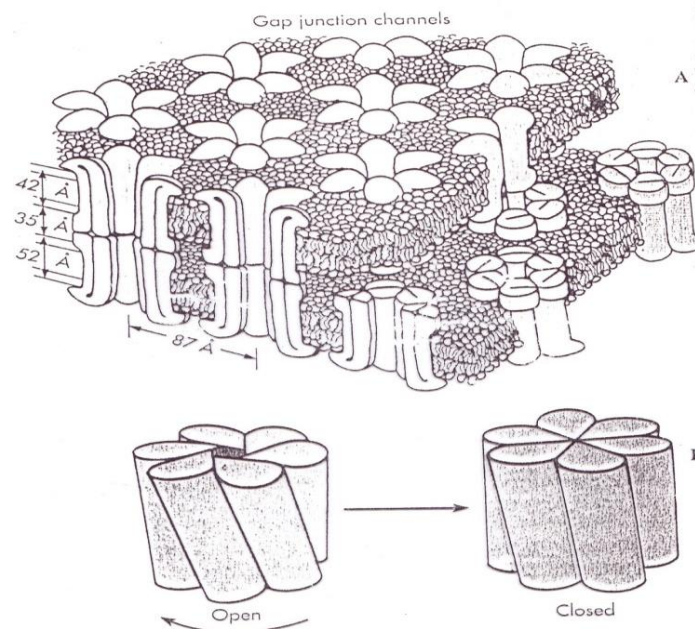

So as a summary (slide #8):

- Cardiac muscles show Syncytium structure because cells are connected to each other by gap junctions. They function as one unit.
- Gap junctions are electric couplers, which mean that they connect one cell to the other. And they're of low resistance.
- Poorly developed SR in contrast to the skeletal muscles that contain well developed SR.
- Transverse (T)Tubules are located on the Z-line (i.e.One T-tubule per sarcomere)
- Rich in mitochondria
- Low in nuclei

The action potential

Slide #9 shows the action potential of the skeletal muscles.
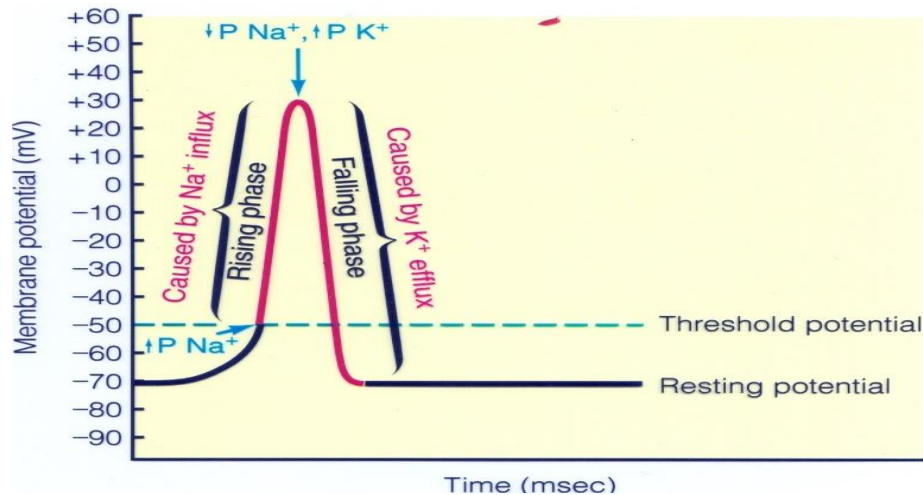
- The resting membrane potential is around -70 mV and it is due to the ionic permeability of K+, Na+... and the sodium-potassium pump.
  While in the cardiac muscle the resting membrane potential is around -90 mV.

- The first part of the skeletal muscle action potential is the fast depolarization phase (the rising phase), and it's due to the opening of the fast Na+ voltage gated channels. It opens whenever the membrane potential reaches threshold potential. Sodium will move according to its electrochemical gradient trying to reach its equilibrium potential. The equilibrium potential equals -61 which came from RT/ZF (Nernest equation)
  **R = gas constant. T = absolute Temperature (Kelvin). Z= valency. F= Faraday constant.

→ -61 log concentration of the ion inside/concentration of the ion ouside.

SO: **Nernest equation** (supposing the cell contains only one ion)**:**
Equilibrium potential = -RT/ZF ln (conc. Inside/conc. Outside) = -61 log (conc. Inside/conc. Outside)

Sodium conc. Inside = 14 millimolar or milliequivalents
Sodium conc. Outside = 140 millimolar
so the result shows that the equilibrium potential for sodium equals +61. This means that when the Na+ voltage gated channels open, the sodium will move according to this gradient passively to try to reach the equilibrium potential (+61) but of course it doesn't reach it because of the presence of other ions, it might reach +20 or +30 and we call this an over-shoot.

- The skeletal muscles have a falling phase, which is due to re-polarization due to the opening of voltage gated potassium channels. Potassium will also try to reach its equilibrium potential which equals around -90. So the membrane potential will become MORE negative.

> Note: MORE negative → for potassium.
> LESS negative → for sodium.

So here we have sodium influx for the depolarization, and potassium efflux for the re-polarization.

Now we come to the cardiac muscle action potential:

(a) Action potential, refractory period, and contraction

(b) Membrane permeability (P) changes
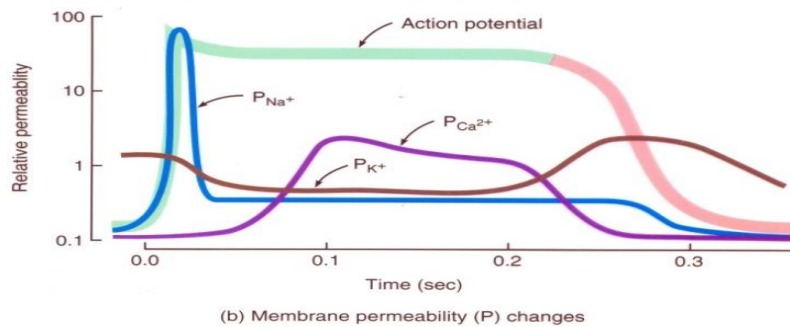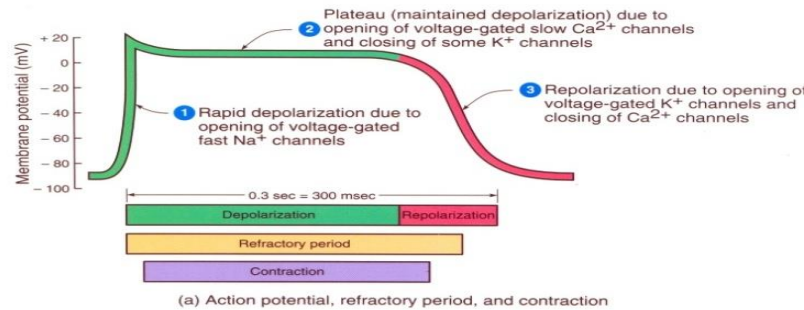
- The resting membrane potential is around -90.
- There's the Zero phase = fast depolarization phase which is due to the opening of voltage gated Sodium channels (same as skeletal).
- There's another phase that's called Phase 1 which is the partial re-polarization phase. This partial re-polarization is due to the transient increase in the permeability of this membrane to chloride and/or potassium.
- Phase 2 is the plateau phase which is the constant depolarization phase, and this is mainly due to the opening of the slow voltage gated Calcium channels and the decrease in the permeability of the membrane to Potassium.

The decrease in the permeability of this membrane to potassium is very important that it maintains this depolarization.

- Phase 3 is the re-polarization phase, and it's due to the opening of the voltage gated potassium channels.
- Phase 4 is back to the resting phase.

So we have 5 phases in the cardiac muscle action potential which are totally different than the action potential of the skeletal muscle: phase zero, phase 1, phase 2, phase 3 & phase 4.

Now, if we look at the changes in permeability during this action potential:

- Phase zero: we have very high conductance for Sodium and goes down during phase 1.
- At the end of phase 1 there's a decrease in potassium permeability, and this doesn't occur in skeletal muscle.
- At the same time there's an increase in the permeability of the cell to calcium.
  Note: if there wasn't a decrease in the cell permeability to potassium, there will be no maintenance for the depolarization because Ca^{+2} that comes in will be neutralized by the Potassium that gets out (Ca^{+2} outside= 10^{-3} while inside= 10^{-7}).
- Then during phase 3 the potassium permeability increases.

How is this important?
Always, in action potential, the electrical change is followed by mechanical change → which means that after the action potential we get the contraction and relaxation (mechanical change).
Note: after depolarization → contraction
       after re-polarization → relaxation.

Now, if we get back to the skeletal muscle, the action potential is very short, around 1 millisecond to 10 milliseconds maximum. The contraction phase and the relaxation phase take more than 50 milliseconds → so we can give/fire another action potential in the skeletal muscle before the muscle relaxes →so the first contraction was followed by a second contraction which leads to their summation to the extent that if the frequency of the action potential of the skeletal muscle is very high, the muscle will not relax → this is called Tetanus.

So the skeletal muscle might get tetanized, why?

1. Because it's action potential is very short.
2. You can get too many action potentials.
3. The refractory period is too short.

Now look at the cardiac muscle, its action potential is very long, at least 200 milliseconds… the refractory period (absolute refractory period) which is almost to half the way in the re-polarization phase. (Check figure (a) in slide #10 – the yellow bar shows the refractory period). So as soon as the refractory period ends, the muscle would be already relaxed, so when another action potential starts a new contraction occurs that isn't affected by the previous contraction because it was already relaxed. So no summation → no tetanization.

SO: The cardiac muscle never gets tetanized, why? Because of the long refractory period of its action potential.

Note: even if a person received an electrical shock, it wouldn't affect the heart (cardiac muscle), it would affect the skeletal muscles like the diaphragm or the respiratory muscles → this will lead to death.

Sodium channels

Conformations of a Voltage-Gated Na+ Channel
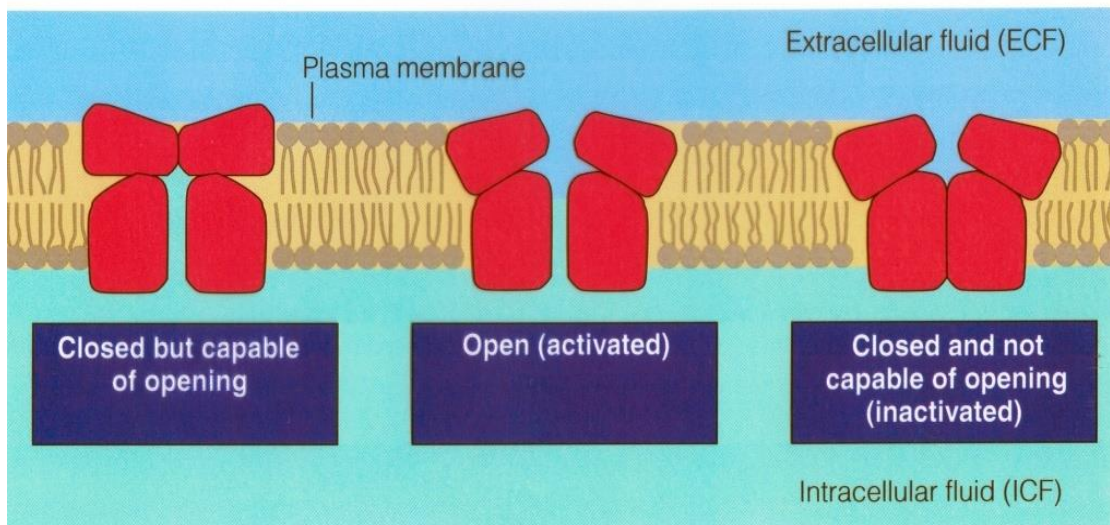
Sodium channels have two gates:

1. Activation gate (m gate), extracellularly.
2. Inactivation gate (h gate), intracellularly.

   -The activation gate during rest is closed and the inactivation gate is open.

-The activation gate opens when the membrane potential gets less negative. And the inactivation gate closes when the membrane potential gets less negative.

Note: since one gate opens and the other one closes, logically we didn't benefit anything, but actually we do because of the difference in timing. the activation gate is very fast while the inactivation gate is very slow. So when the membrane potential gets less negative, the activation gate opens → sodium will move according to its electrochemical gradient → after a while the inactivation gate closes (slow).

**So the difference is in the TIME CONSTANT while the VOLTAGE CONSTANT is the same.

Look to the figure above (slide #12):
first figure on the left is during rest (m is closed & h is open) → m opens very fast when threshold was reached → sodium gets in → h gate is closing but in a very slow manner → when the membrane potential reaches around +30, h gate closes → when h gate closes sodium stops getting in → but we reached the over-shoot already.

So here we go step by step: rest → threshold → m gate opens →h gate is still open (slow) → sodium keeps getting in → h gate closes → over-shoot is reached.

Done by: Hanin El-Banna