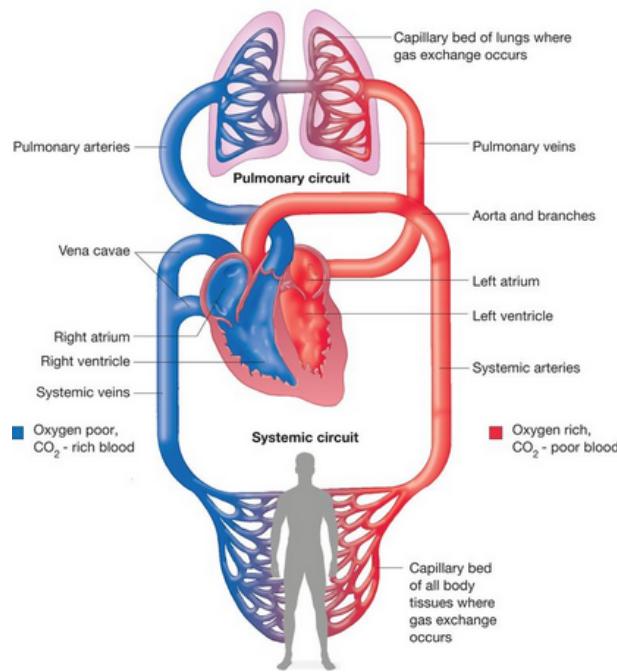


Cardiology

May 5, 2017

1 Physiology Overview

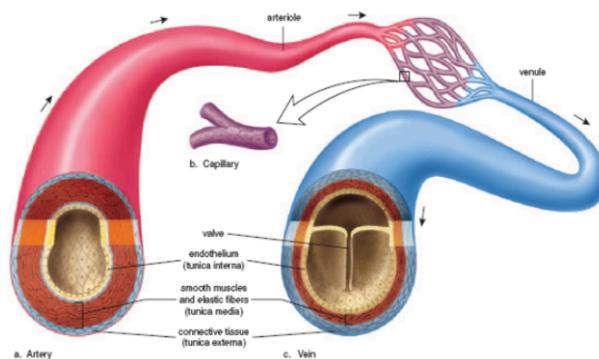
There are many systems we can divide the body into, and today we'll be looking at the Circulatory system: The heart and blood vessels.



The circulatory system can be divided into two parts: *the Pulmonary system* and *the Systemic system*.

The Pulmonary system: The system containing the lungs and the Pulmonary arteries and veins. The blood (oxygen poor and CO₂-rich) is pumped from the right ventricle (RV) to the Pulmonary arteries. There are two Pulmonary arteries, and they transport the blood to each of the two lungs. The blood runs through the lungs to receive oxygen and leave CO₂. When the blood is pumped out of the lungs, it's oxygen rich and CO₂ poor. It is now sent back to the heart through the left atrium (LA).

The Systemic system: The system where the blood runs through the rest of the body. The blood gives oxygen to the cells, as well as transporting CO₂ and waste from the cells to the lungs and kidneys respectively. The blood gets pumped out of the left ventricle (LV) to the aorta (the main artery). The aorta will divide into smaller and smaller blood vessels called arterioles (< 10 mm) and capillaries (~ 3 microns). The oxygen poor blood is now transported from the capillaries into thickened venules (< 10 mm). Finally the venules join into veins (~ 15 mm). The Systemic veins will transport the oxygen poor blood into the right atrium (RA), and then to the RV.

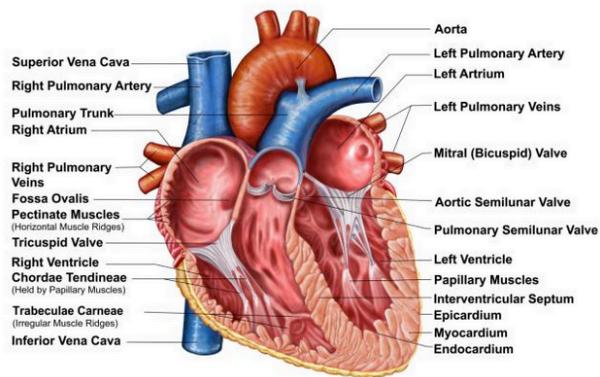


Artery: "Away from the heart" wrt. blood flow. Arteries are normally oxygen rich (see the Systemic system), but they can also be oxygen poor (see the Pulmonary system). The arteries are thicker than the veins.

Veins: "Back to the heart" wrt. blood flow. Veins are normally oxygen poor (see the Systemic system), but they can also be oxygen rich (see the Pulmonary system). The valves in the veins make sure that the blood is transported in

the right direction. When the heart beats, the valves open. The valves closes when the heart doesn't beat such that the blood can't fall back down through the veins.

Capillaries: The capillaries contains blood cells and plasma. The capillaries deliver oxygen rich blood and nutrients to the cells, and receives CO_2 and waste.



Superior vena cava: Carrying oxygen poor blood from the head to the heart.

Interior vena cava: Carrying oxygen poor blood from the body to the heart.

Endocardium: The "inside" of the heart.

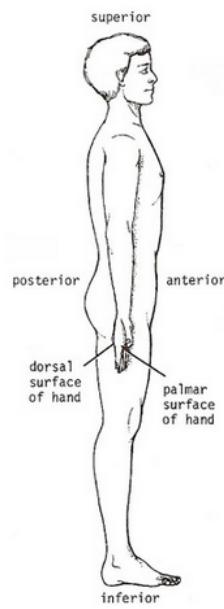
Epicardium: The "outside" of the heart.

Myocardium: The space between the endo- and epicardium.

Septum: The muscle in the middle of the heart that separates the RV and LV.

Lateral walls: There is a LV lateral wall and a RV lateral wall. They are the walls between the LV/RV and the outside of the heart.

Apex: The end of the heart.



Anterior: In front of the body. You will see The RV to the left and the LV to the right (see the image of the heart on page 3).

Posterior: In back of the body. You will see the RV to the right and the LV to the left.

Superior: At the top of the body.

Inferior: At the bottom of the body.

The different *muscles* in the body can be divided into three different muscle types: *smooth muscles*, *cardiac muscles* and *skeletal muscles*.

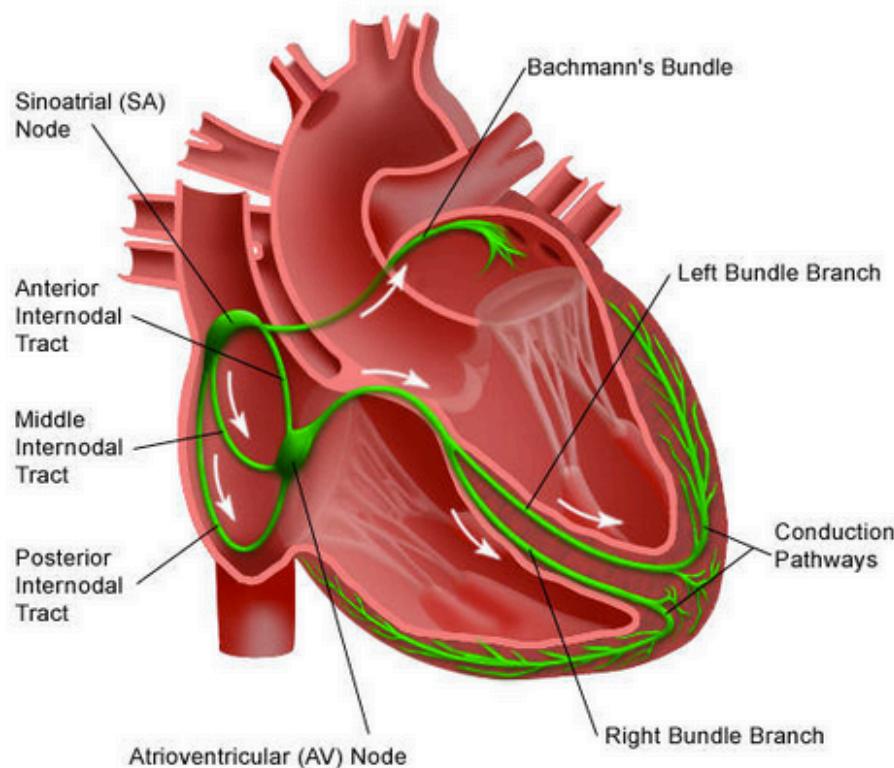
Smooth muscles: Automatic muscles in the body that forms organs such as the stomach.

Skeletal muscles: Moves bones and other structures (not automatic).

Cardiac muscles: The muscles that contracts the heart to pump blood.

The heart is also a muscle that needs oxygen to the muscle cells. This is called the *coronary circulation*. Finally we'll look at the *cardiac conduction system*, which is the system in the heart that makes the heart muscles contract.

Electrical System of the Heart



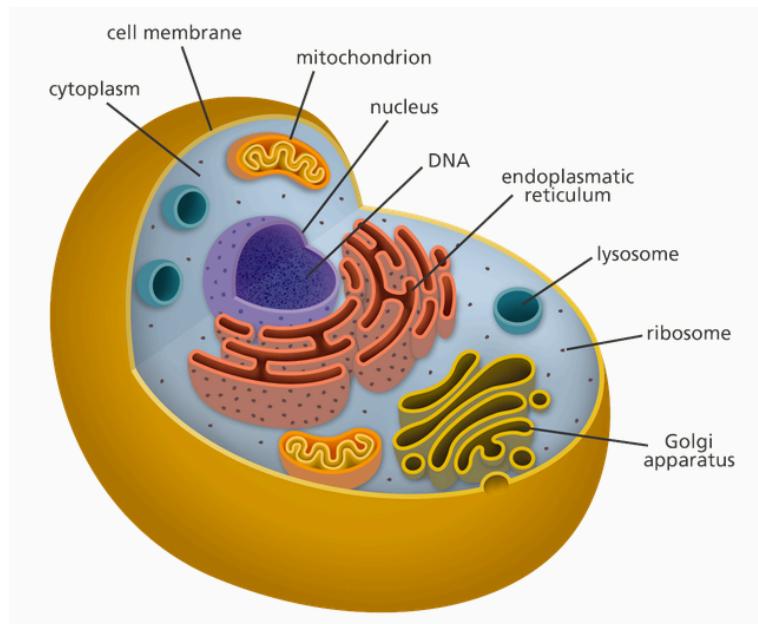
Sinoatrial node (SA): The main node that gives an automatic signal every time the heart muscles should contract. The SA is located in the right atrium (RA). The signal then travels from the SA to the *Atrioventricular node*.

Atrioventricular node (AV): Receives the signal from the SA, and passes it on to the *Bundle of Branches*. The AV is also located in the right atrium.

The signal from the SA will be a bit delayed on it's way to the heart muscles. Still, the LV and the RV will hopefully contract at the same time. If they don't, arrhythmia will occur.

2 The cell

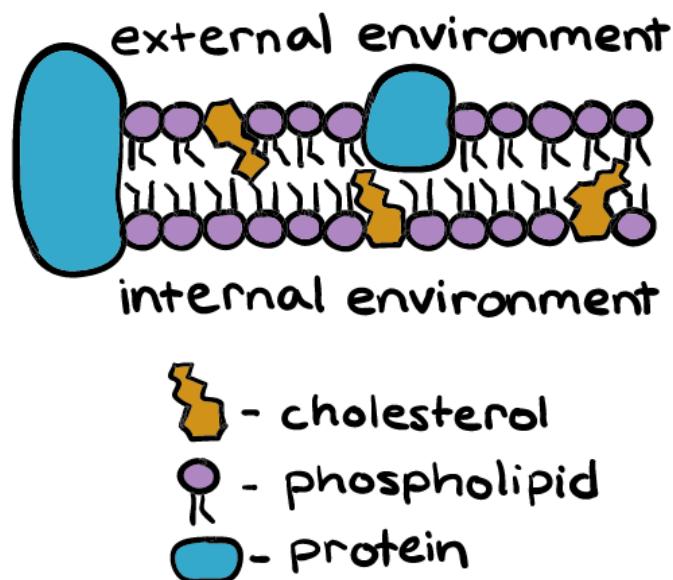
Today we will look into *cells*, and what all cells consist of. For each organ in an organism, the tissue within the organ will consist of cells. Even though cells are different wrt. what kind of organ they are located in, there are several common features of all cells.



Cells: All cells are made out of molecules, which are again built from atoms. The cell consist of the *cell membrane*, the *nucleus* and the *cytoplasma*.

Cell membrane: The cell membrane holds together the different cells, as well as allowing communication between them. It provides structural support, and separates the *ECF (extracellular fluid)* and the *ICF (intracellular fluid)*. The components of the cell membrane are called *phospho lipid*.

Phospholipid Bilayer



Phospholipid: Consist of two parts: The *Phosphate head* and the *Fatty tails*. The phosphate head is hydrophylic ("water friendly"), so they will always face towards the outside of the cell membrane (see image above). The fatty tails are hydrophobic ("not water friendly"), so they will always face towards other fatty tails inside the membrane.

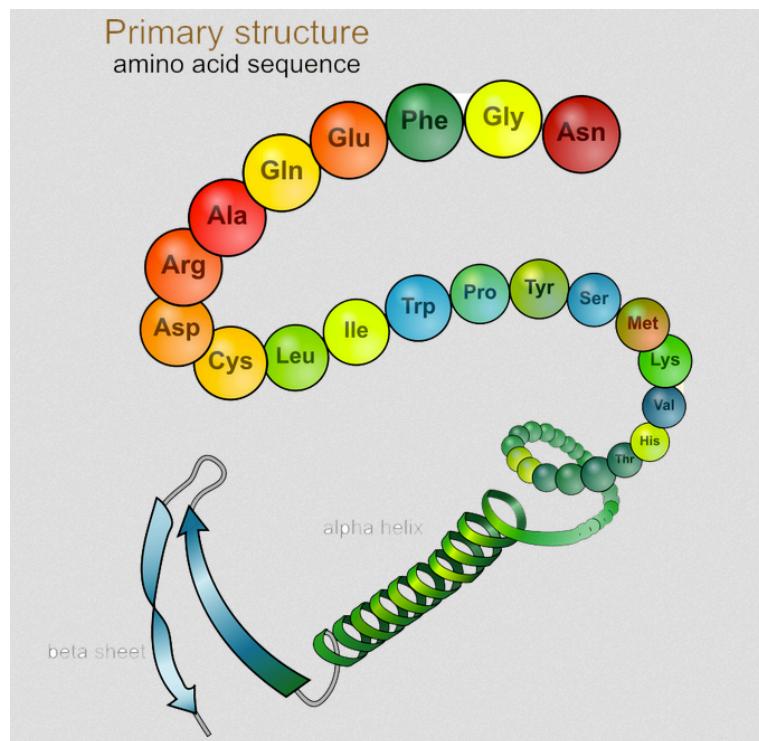
The building blocks of the cell membrane is called a *phospholipid bilayer*, since it consist of two lipids everywhere. Inside the bilayer, there are also cholesterol within the fatty tails, and membrane proteins. There are three types of membrane proteins. *Transmembrane proteins*, *Peripheral proteins* and *Lipid anchored proteins*.

Transmembrane proteins: These proteins goes through the membrane to the ICF and ECF. Many of these function as a gateway to permit transport of specific substances across the membrane.

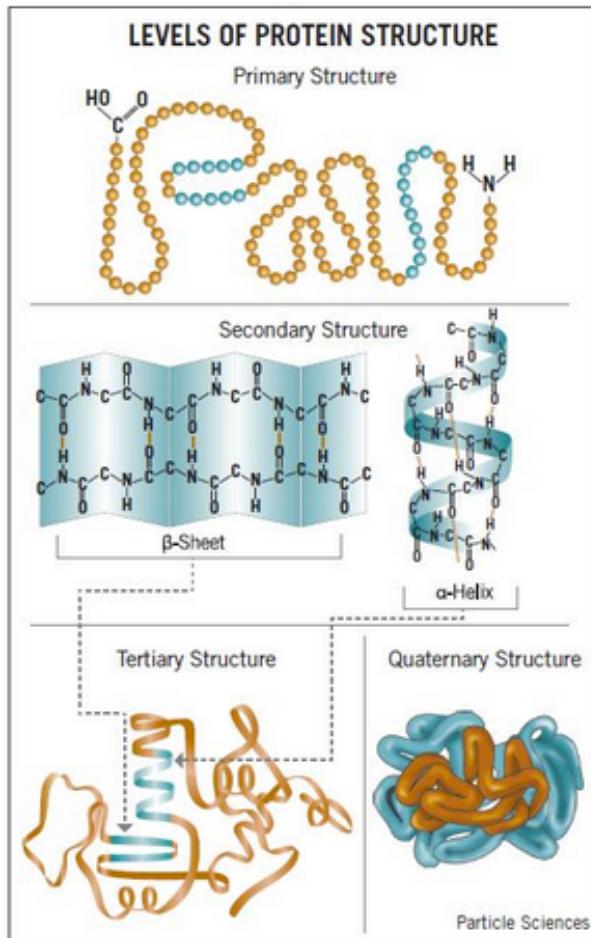
Peripheral proteins: These proteins adhere temporarily to the membrane. They attach to other proteins.

In general, proteins are large molecules consisting of *amino acids*. Every cell in the body has proteins. The larger the protein, the more amino acids are chained together.

Amino acids: There are 20 different amino acids, 11 nonessential and 9 essential. The essential acids are the ones we need to eat to have in our body, while the nonessential ones can be made out of the essential ones.



As you can see from the image above, a protein is a chain of amino acids. The shape of a protein is very important, as it decides the protein's function. If a protein changes its shape, it changes function.



Protein shape levels:

- 1) Primary structure. This can be any possible combination of the 20 amino acids.
- 2) Secondary structure. Two possible shapes, either the β -sheet or the α -helix.
- 3) Tertiary structure. This is a mix of the β -sheet and α -helix.
- 4) Quaternary structure. This shape determines the function of the protein.

There are several things that can be done to change the shape of a protein. Heat, acids, bases, salts and mechanical agitation are some of them. This is happening all the time within the cells.

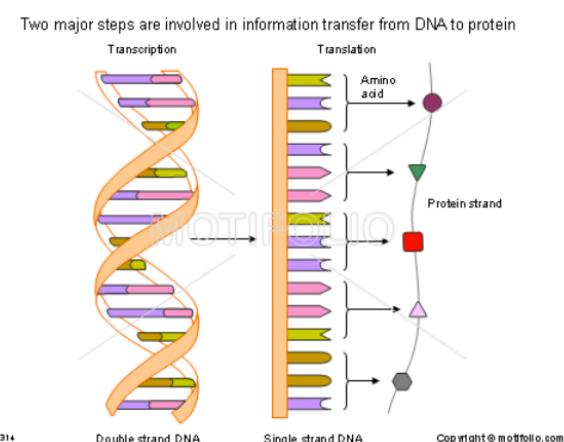
Nucleus: The nucleus contains the unique DNA and determines the function

of the cell. Like the cell has the cell membrane, the nucleus has the *nuclear membrane*.

Nuclear membrane: Protects the inside of the nucleus, as well as compartmentalize the nuclear materials. The outer nuclear membrane is in contact with the *endoplasmic reticulum (ER)*.

To see how proteins are built, we have to learn more about *DNA*.

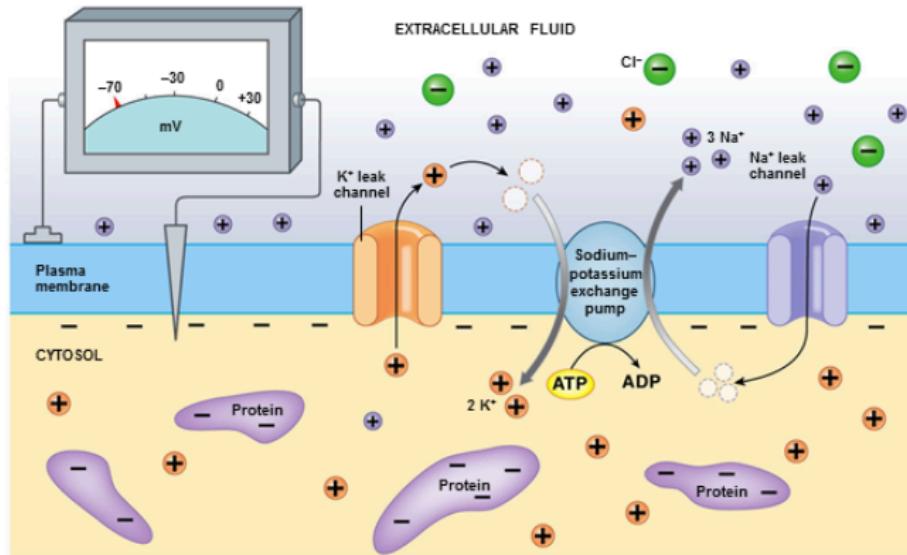
DNA - Deoxyribo nucleic acid: There are four DNA types: *Adenine (A)*, *Thymine (T)*, *Guanine (G)* and *Cytosine (C)*. The DNA is a double stranded chain of these types, where three types in a row is called a *codon*. Each codon represents a code for a specific amino acid. Since there are $4^3 = 64$ possible codons, but only 20 amino acids, the code for an amino acid is not unique. The chain of the different amino acids will together result in a protein.



3 Cellular electrophysiology

Ions: There are four ions that are the most important for this topic. Sodium (Na^+), Potassium (K^+), Chloride (Cl^-) and Calcium (Ca^{2+}).

The intracellular and extracellular environment is separated by the membrane. Within the membrane, there are "channels" that can make specific ions enter and exit the intracellular environment.



The voltage within the intracellular part of the cell is negative.

From earlier we have learned that the potential difference (voltage) is $V = IR$ where I is the current and R the resistance.

Nernst potential: Gives the potential for different ions at the resting membrane potential state. Most of the Na and Ca ions are located at the extracellular space in this state. Most of the K is located in the intracellular space.

Ion	Symbol	The Nernst equation
Potassium	K+	$E_K = 61.54 \times 10^{-3} \log \frac{[K+]_o}{[K+]_i}$
Sodium	Na+	$E_{Na} = 61.54 \times 10^{-3} \log \frac{[Na+]_o}{[Na+]_i}$
Choline	Cl-	$E_{Cl} = -61.54 \times 10^{-3} \log \frac{[Cl+]_o}{[Cl+]_i}$
Calcium	Ca ²⁺	$E_{Ca} = 30.77 \times 10^{-3} \log \frac{[Ca+]_o}{[Ca+]_i}$

The *Action potential of cardiac cells* can be divided into 4 phases:

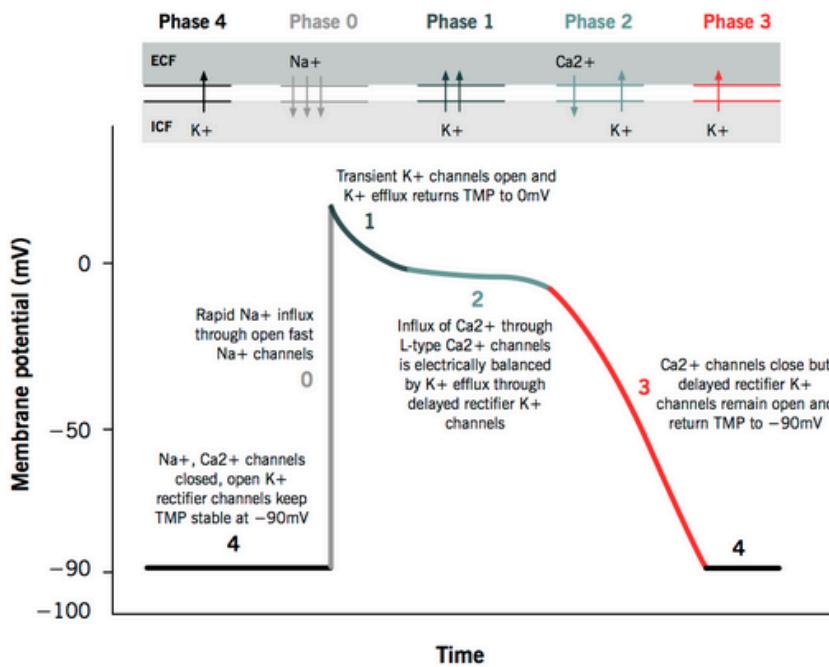
4) Resting membrane potential. The voltage is approximately -85 mV. Most of the Na and Ca is outside, and the K inside.

0) Upstroke: Stimulation makes the Sodium channels open. Since they have potential +67 mV, the influx of Na^+ increases the membrane potential.

1) Notch: Not all cardiac cells have this state. Early repolarization. Potassium channels opens, such that there is an efflux of K^+ . The Potassium potential is +129 mV. Therefore the membrane potential will decrease.

2) Plateau: The efflux of Potassium continues in addition to the Calcium channels open. The influx of Ca^{2+} will stabilize the membrane potential. There is also released a lot of Ca from the intracellular storage. Ca ions within this storage doesn't affect the action potential until they're released.

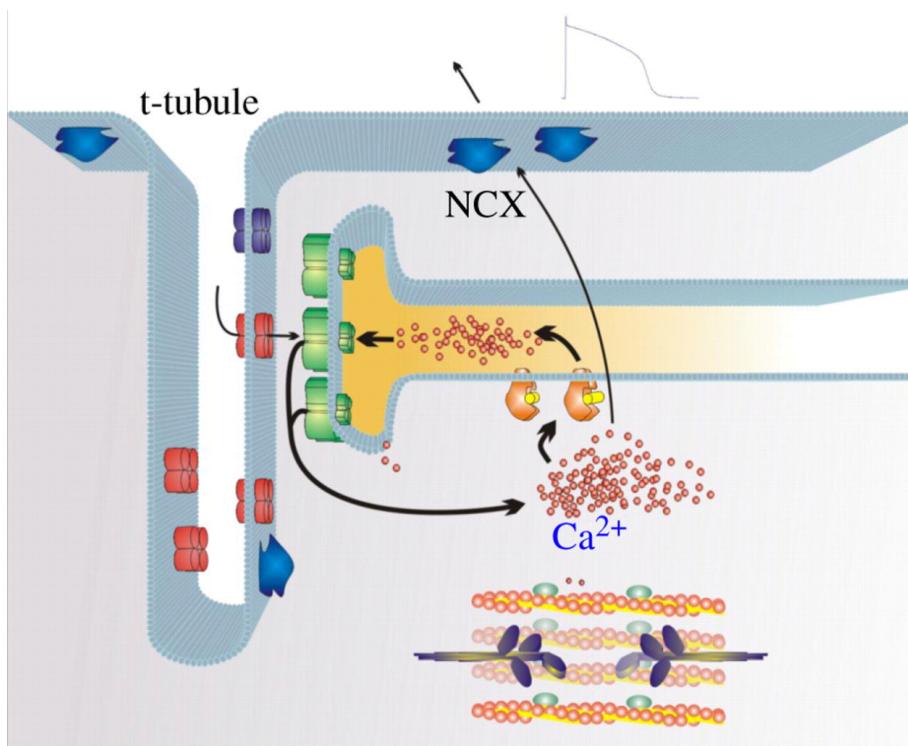
3) Repolarization: The Ca^{2+} channels close, but the K^+ remain open, decreasing the membrane potential back to the resting membrane potential state.



Absolute refractory period: No extra stimuli will affect the action potential. This will be from phase 0 up to the end of phase 2.

Relative refractory period: Stimuli will affect the action potential, but never as much as the original one. This period will be after the absolute refractory period, until the cell has "rested" at its resting membrane potential.

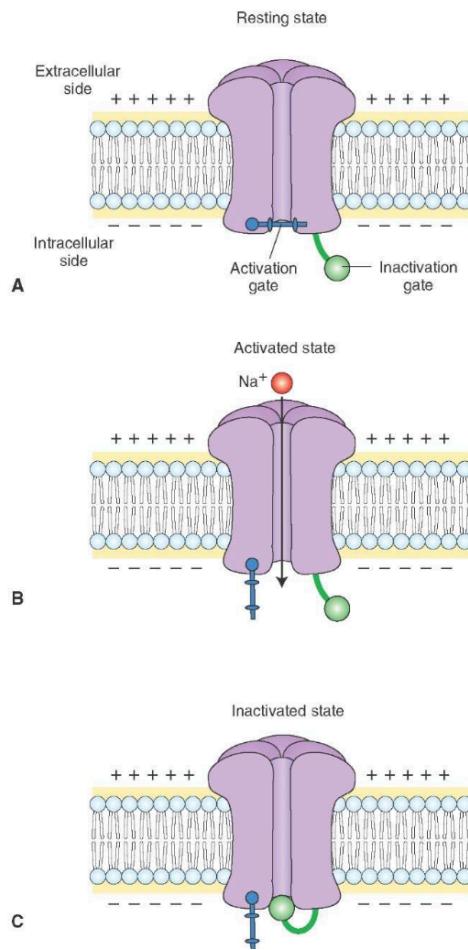
T-tubules: Part of the membrane cells (see image). The T-tubules enables signals to get deeper into the myocite.



K^+ (Potassium) has a negative Nernst potential since the concentration of ions are greater on the inside than the outside (intracellular K^+ > extracellular K^+). Hence $\frac{[x]_e}{[x]_i} < 1$ which causes the Nernst potential to be negative ($\ln a < 0$ when $a < 1$). Similar calculations give that Na^+ and Ca^{2+} have positive Nernst potential since the extracellular concentration is greater than the intracellular. Nernst potentials change during the four phases of the action potential. Still,

the only one noticeable is Calcium (Ca^{2+}) due to the large concentration of released ions from the intracellular storage.

Voltage sensitive ion channels: First looking at a Sodium channel. Voltage in the membrane can be calculated from $V = V_m - E_{Na} = I_{Na} \frac{1}{g}$ where g is conductance. It has been discovered (Hodgkin and Huxley) that the conductance can be calculated by $g_{Na} = g_{\bar{N}a} m^3 h$ where $g_{\bar{N}a} = \#$ of Na channels (Maximum conductance), $m = P(\text{gate activates})$ and $h = P(\text{gate is inactive})$. Hence m and h will be numbers between 0 and 1. Hodgkin and Huxley discovered that there are three "parts" each equal to m that needs to open to get an active Sodium gate. Also, there is one "part" equal to h that closes the Sodium gate. In the absolute refractory period, it is not possible to open the gate at all.



There are other equations to get the current through other ion gates. These equations (or models) can change from species to species. An ionic model is the combination of different specific ion currents: $I_{\text{ion}} = I_{\text{Na}} + I_{\text{Ca}} + I_{\text{K}_1} + I_{\text{K}_r} + \dots$. The action potential is determined by the different ion channels. For mutations in DNA, $g_{\bar{N}a}$ could be a lot lower than normal. This can be checked by Western Blot.

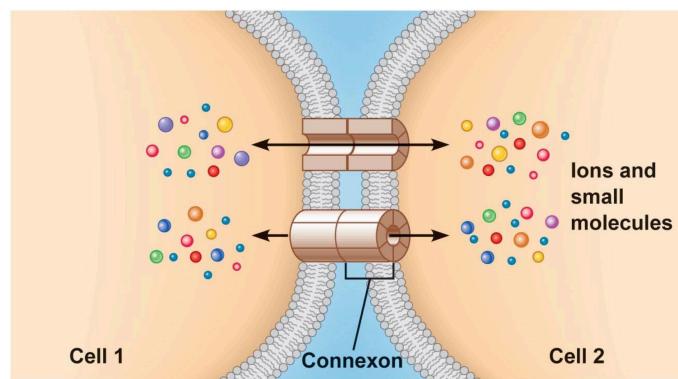
4 Modes of electrical conduction of the heart

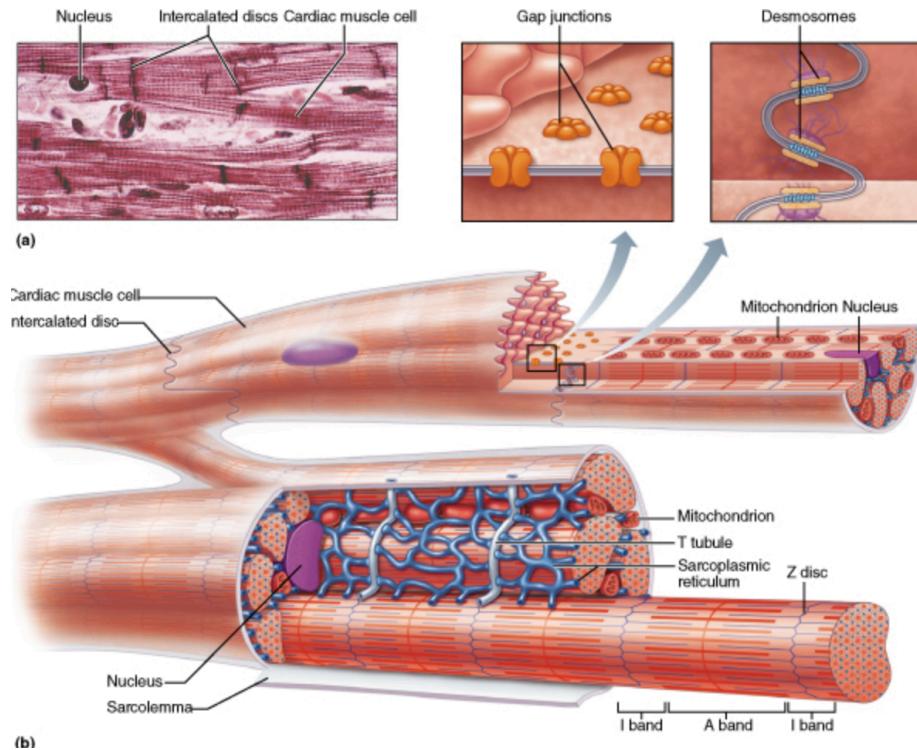
How the signal spreads:

SA Node (Sinoatrial Node) \Rightarrow Atria \Rightarrow AV Node (Atrioventricular Node) \Rightarrow Bundle Branches (Left and right) \Rightarrow Purkinje Fibers \Rightarrow Myocardium.

Arrhythmia: Irregular heartbeat. It can be too fast or too slow. The signals spreading within the heart will appear as spiral waves when arrhythmia occurs.

Cardiac architecture: The cardiac cells are organized into fiber networks, where there are *Gap junctions* between the cells to create an electrical connection. Some ions will pass through these channels. There are more connections in the *longitudinal* direction than the *transverse* direction (*Anisotropic*, not *Isotropic*).





So how do we model the heart? There are two specific ways that will be covered here.

Bidomain Formulation: Considering the extracellular, intracellular and the transmembrane currents. How many gap junctions there are will determine the resistance. All three spaces are reduced to one point. Each point will be modelled into a tissue network of points. This will result in a complex system of equations with boundary conditions.

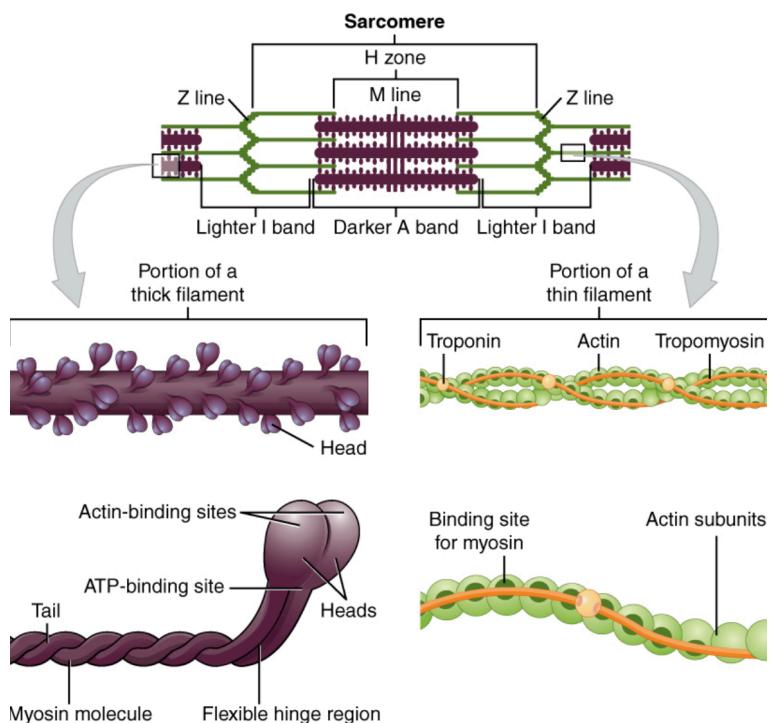
Monodomain Formulation: This formulation "ignores" the extracellular system, when the change in current is not significant. It is significant when simulating shock, otherwise not so much. This can speed up the process by a factor of 10.

5 Contraction

The action potential signals the cells to contract. During phase 2 of the action potential, Ca^{2+} influxes. The Calcium channels are right next to the *Sarcoplasmic Reticulum*, which holds a lot of Ca^{2+} in the intracellular space.

Ca^{2+} -Cycling: The signal that makes the myocyte contract.

In a cardiomyocyte muscle cell, there are light and dark bands. The dark bands contain more proteins than the light bands.

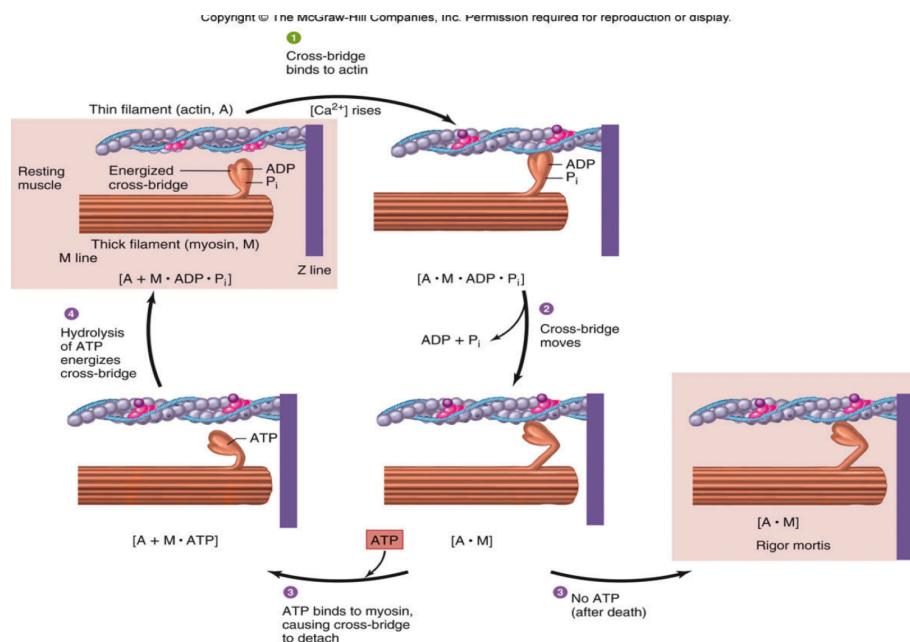


In the lecture I learned about the z-line, sarcomere, thin filaments and thick filaments. The thick filaments are made out of proteins called Myosin, while the thin ones are made out of the protein Actin.

When a muscle cell contracts, the sarcomeres are shortening, bringing the thick and thin filaments closer, such that they are overlapping.

Sliding filament theory: The theory of what's happening when the sarcomeres are shortening. The cells need ATP (Adenosine triphosphate) and Ca^{2+} to contract. ATP is a unit of energy within a cell. What happens is that ATP is transformed into ADP (Adenosine diphosphate), which releases energy.

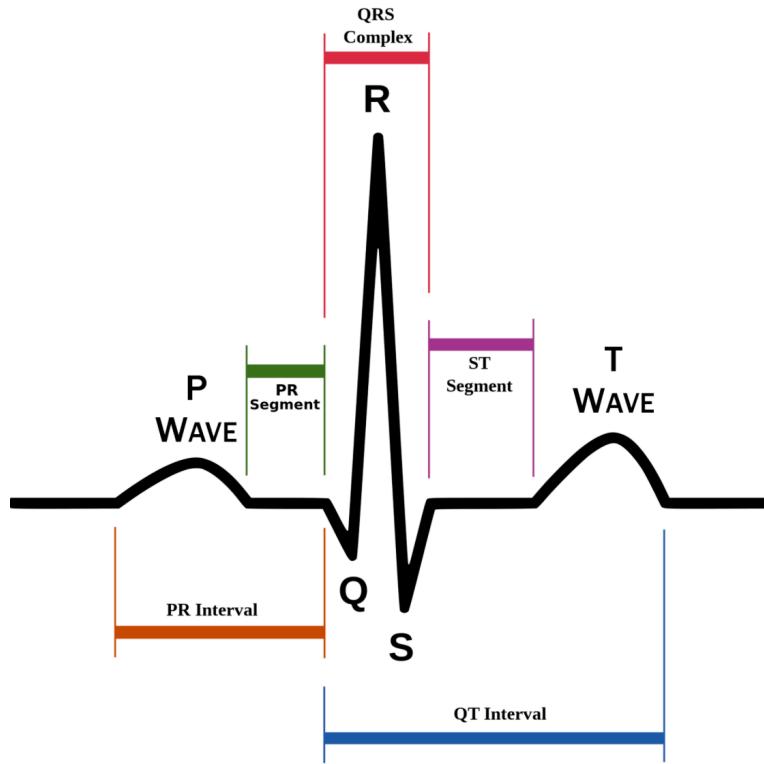
From the previous picture, you can see that the Thin filament consists of Troponin and Tropomyosin. The thick filament contains the myosin molecule, as well as the myosin heads. Ca^{2+} attaches to the troponin, which causes the thin filament to turn the active site of actin towards the thick filament. This causes the thin and thick filament to move closer and closer together, making the muscle cell contract. This is called the *Cross bridge attachment*. This happens during phase 2 of the action potential.



Rigor mortis: When the contraction is stuck in one position (what actually happens when you die).

6 ECG

There are 12 places on the body where it's normal to place electrodes during an ECG: on the hands, feet and chest. An ECG rhythm has been divided into different intervals with a letter for each interval.



The ECG amplitude is measured in mm, upwards is positive directions, and a flat wave is called isoelectric.

P-wave: The SA node activating. ≈ 2.5 mm amplitude, ≈ 0.12 sec in width.

QRS-wave: Ventricular depolarization. Signal reaches AV node. Abnormalities of a heart are often discovered here. If something is wrong with the pumping for instance.

RR-interval: Length between two R's.

QT-interval: Ventricular depolarization and repolarization. If this interval is too long, something is wrong with the patient's heart.

Atrial ECG = P-wave, while Ventricular ECG = QRST-wave.

Arrhythmia: Usually diagnosed from ECG. There are different types of arrhythmia that can occur. *Bradycardia*, *Tachycardia* and *Fibrillation*. The first induces a slow heart rate, while the second one induces a fast heart rate. Fibrillation is a chaotic heart rate, also called uncoordinated heart rhythm. This is normally the cause of death due to arrhythmia. Arrhythmia is often caused by a heart attack, or myocardial infarction.

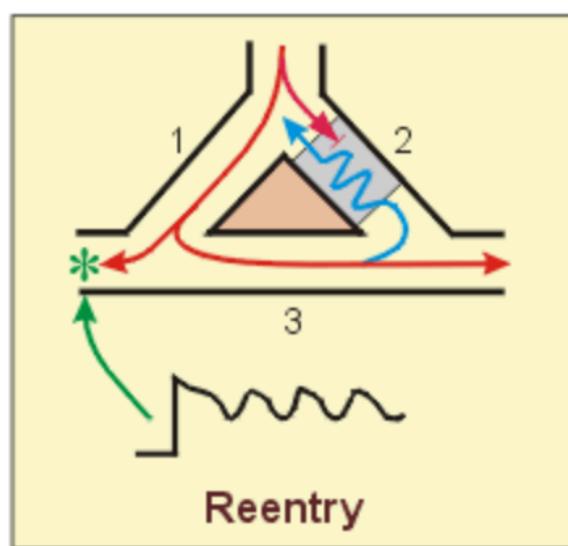
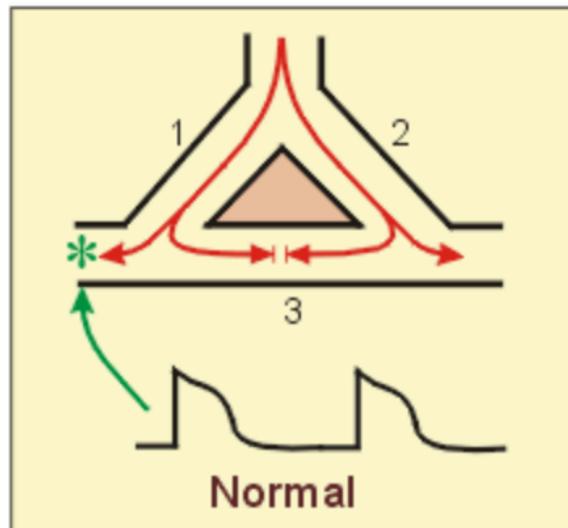
It is important to divide between atrial and ventricular arrhythmia. The last one is the most dangerous one.

Automaticity: Creating extra beats from other places in the heart than the SA node.

Parasystole: An extra beat on ECG. Uncommon.

Reentry can be Anatomical reentry. This is a big circle where the electrical signals reenter the same places. The pathway must be longer than the wavelength for reentry to occur. Wave length equals conduction velocity times ERP. Reentry requires a unidirectional block, propagation along alternate route around the block, as well as a sufficient pathway to support full wave length. Functional reentry is reentry without a block.

Spiral waves can be stable, meander or have a core that moves. It can break up, and create fibrillation. Unsustained reentry is when we almost have reentry, but then it dies out. Still, this can be dangerous for the patient, as it's not much of a trigger that is needed to induce a sustained reentry.



7 Research Paper

In this lecture we went through the details of a paper published in 2012. The hypothesis of the paper was that an increase of Connexin43 will heal (at least partly) an ischemic heart due to scar tissue. The results are convincing, there is a huge difference in the test pigs using connexin43 vs. the ones who doesn't.

This can in the future mean that it could be possible to inject Connexin43 into an ischemic heart to start the healing process. Hence, it can save lives, and increase the healing process compared to the natural healing process in ischemic hearts. The paper was well received, and published in a well respected journal.

8 Arrhythmias and Clinical Therapies

Atrial Fibrillation (AF) is common to get with age. The heart is "ok" at rest, but if exercising or increasing the heart beat, it can be dangerous. AF creates a blockage within the atria, which is released into the blood vessels. If these bits reaches the brain, it can cause a stroke. These pieces of old blood are called Thrombus. When blood is lying still for a long time, it changes state from liquid to solid.

There are two types of AF: The ones that last for less than 7 days, and the ones that last longer than 7 days. AF can be recognized from an ECG by the absence of the P wave, as well as an irregular RR interval. The heart is more fibrillating, which is one of the reasons why AF often occur among older patients, their hearts are more fibrillating than young hearts. This also causes reentry between the atria and the vein, which leads to the blood getting "stuck" near the reentry area.

There is a saying that AF begets AF. Also, there is possible to have a blockage many places, but the strokes due to a blockage in the brain is the most deadly one. β -blocks can lower the SA signal, leading to a fast heart rhythm.

There are three things that has to be present to induce reentry: A pathway to support full wavelength, an alternative route and a slow conduction rate (scar regions). Drugs can limit the first part, increasing part 2 of the action potential. Still, drugs also affects other parts of the body than the heart, which is not so good. Therefore drugs aren't much used on AF patients any more. A catheter ablation is now the most common procedure.

Ventricular Fibrillation (VF) is a common cause to sudden cardiac death (SCD). There are two types of VF. The first is the ischemic disease. A blocked coronary leads to scar tissue, which leads to a reentry circuit. This induces the VF. A normal cardiac output is about 60 % when the left ventricle is pumping out blood. If this percentage is a lot lower, it can be a sign of VF.

The second type is the non-ischemic disease. This type is caused by genetic disorders, due to mutations in cell channels. For instance, Brugada syndrome

is a non-ischemic disease leading to VF and then SCD. The QT interval is long for these patients, leading to a slow heart rythm. Thus, the time of death for Brugata patients will be when sleeping, the time when the heart rythm is at its lowest.

Mechanical force and/or electrical shock are two possible instant treatments of VF. Formation of the reentry circuit can break down. Possible therapies are drugs (non-effective), Cardioverter Defibrillator, Precordial thump and Cardiovert.

A pacemaker is for irregular heartbeats, it paces the heart with a signal to initiate beating. This is not a treatment for VF, but an ICD is. It detects the cardiac rythm, and delivers a shock if necessary. If the cardiac output is less than 35 %, a patient will get an ICD. Still, only about 5 % of these patients will ever be given a shock by the ICD due to arrhythmia. Thus, we need a better way to predict who will need an ICD.