

Chapter 1: Basic Human Physiology

Table of Contents:

Basic Physiology:

A.1.1. What is physiology_____	2
A.1.2. Physiological Concepts_____	6

The Cell:

A.2.1. Structure of the Cell_____	11
A.2.2. The Plasma Membrane_____	22
A.2.3. Passive Transport Systems_____	20
A.2.4. Active Transport Systems_____	28
A.2.5. Mitosis and Meiosis_____	32

The Nerve Cell:

A.3.1. The Nerve Cell_____	36
A.3.2. The Resting Potential_____	39
A.3.3. The Action Potential_____	45
A.3.4. Action Potential Propagation_____	53
A.3.5. Saltatory Propagation_____	58
A.3.6. The Electrical Synapse_____	63
A.3.7. The Chemical Synapse_____	66

The Muscle Cell:

A.4.1. The Muscle Cell_____	71
A.4.2. The Motor End Plate_____	75
A.4.3. The Sarcomere_____	83
A.4.4. Twitch and Tetanus_____	92
A.4.5. Contraction Types_____	95
A.4.6. Motor Units_____	99
A.4.7. The Cardiac Muscle_____	106
A.4.8. The Smooth Muscle_____	111

Basic Physiology Info:	113
-------------------------------	------------

A1. What is Physiology?

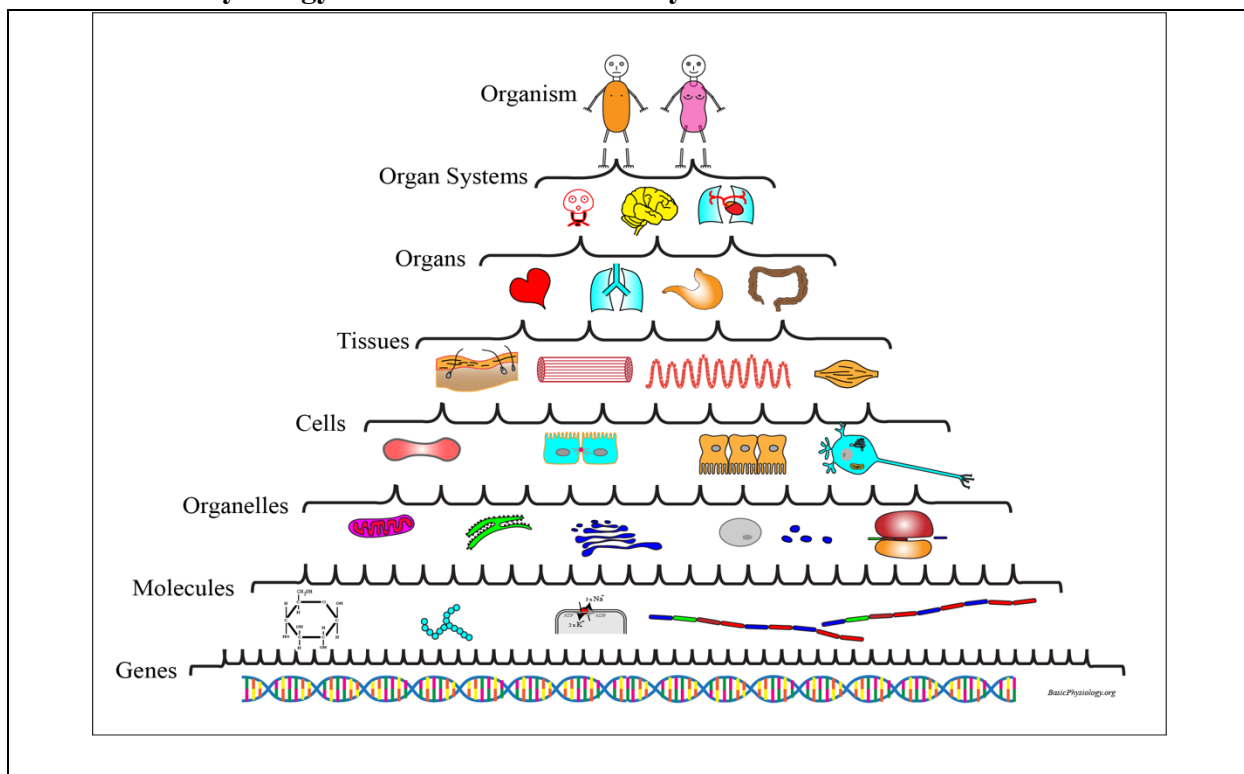
A. What is physiology?

1. Physiology is the science that studies the function of an organism; i.e. a body.	2. It studies for example how the heart beats, or how the stomach digests or how the lungs breathe.
3. It can also study how other bodies (= animals) or plants or bacteria function.	4. In this site, we will stick to the human body, which is complicated enough!



BasicPhysiology.org

B. How does Physiology describe the human body?



1. As a physiologist, we look at the human body at different levels. From very small to very large (figure).	2. At the smallest level, we look at the genes , molecules, enzymes, hormones that occur in and around cells.
3. An important component at this level is the cell membrane , which divides the fluid that is inside the cell (the cytosol) from the fluid that is outside the cell (= the extracellular fluid).	4. The next level is the cell . This is THE basic unit of the body. It contains different types of organelles (=small organs), such as mitochondria, nucleus, etc. And all this is packaged (surrounded) by the cell membrane.
5. At a higher level, we look at how cells work together, for example in tissues , such as in muscles, in the heart or in the brain. Tissues can also be fluids, such as blood or lymph.	6. At the next higher level we look at groups of cells and tissues that make up an organ , such as the heart, the lungs, the stomach or the brain.
7. At the following higher level, physiologist look at organ systems , such as the circulation system that combines the heart, the arteries, veins, lymph vessels etc. into one 'system'.	8. Other organ systems are the nervous system (brain, nerves etc.), the respiratory system, the reproductive system, etc.
9. Finally, at the top of this whole pyramid, we reach the level of the organism, the whole body, the organism , which is the total of all the organ systems put together.	10. And this whole body is surrounded (packaged), again, by another organ: the skin!

C. Where does Physiology fit?

1. Physiology is part of the medical sciences.	2. Some of these science subjects are basic (basic knowledge) while others are more clinical (applied).
---	--

3. Other basic medical sciences are Anatomy (which describes the structure of the body) and Biochemistry (which describes the chemical processes in the body).	4. Clinical sciences are easily visible in the hospital such as Cardiology (science of the heart), Surgery (cutting!), Neurology (science of the brain and nerves), etc.
--	--

D. Who study physiology?

1. Students that study physiology are, most often, students that follow a study in healthcare; such as nursing, midwife, dentistry, doctor, etc.	2. As a basic science, Physiology, together with Anatomy and Biochemistry, are the subjects that these students will study first.
3. Later, other subjects will be taught such as Pharmacology (study of drugs), Pathology (study of diseases), Microbiology (study of viruses and bacteria), etc.	4. Then, finally, students will learn specific topics in nursing, physiotherapy, medical practitioner, general physician, cardiologist, neurosurgeon etc, etc.
5. Physiology is also taught to biologist ; to study the function of other than human organism, such as dogs, cattle, bacteria etc.	6. And, even in agriculture , there is a fair amount of physiology such as in plants, the function of roots, the breathing of forests etc.

E. Who practices physiology?

1. Physiologists are usually found in universities or other institutions of higher learning where people study to become nurses, doctors etc.	2. In some countries, one can study to become a physiologist, usually in a graduate program terminated with a PhD (=Doctor in Philosophy)
3. So, your physiology teacher could have a PhD in a physiological subject.	4. But, often, those teaching physiology have a background in Biology or in some other Health Care specialization.

5. In my case, I first studied medicine, from basic to general practitioner. But then, when I was finished, I realized I liked to teach and to do research much more than treating patients. So, that's how I became a physiologist!	6. Yes, physiologists often have the possibility of performing research, to understand better how a tissue, an organ or an organ system works, in a normal or in a pathological situation.
--	---

Reference: Many textbooks have described the levels in physiology, but I liked best the one described by Dennis Noble in his wonderful book (The Music of Life, Oxford University Press, 2006)

A.1.2. Physiological Concepts

A. What are Physiological Concepts?

1. There are in physiology, a few concepts or ideas that are important to start with before going into further (physiological) details.	2. On this page, we will discuss three of these concepts: a. Homeostasis b. Set point c. Feed-back (positive or negative)
---	--

B. Homeostasis

1. Homeostasis is the ability of the body to keep its internal environment stable (that is; equilibrated or constant).	2. Homeostasis = “homeo-” which means home or body and “-stasis” which means static or stable.
3. What do we mean with “internal environment”?	4. These are all the conditions inside the body such as temperature, pH (=acidity), pressure, volume etc.
5. So, homeostasis is the capacity of the body to keep its inside organs and tissues stable as to temperature, pH, blood pressure, blood sugar, and many other variables.	6. One of the most familiar homeostatic systems is that of the body temperature control. A normal body temperature is set at 37 °C (= 98 °F)
7. The temperature outside the human body however can vary from very cold to very hot! In all these different external temperatures, the temperature inside the body must stay constant at 37 °C.	8. How does the body do that?

C. Homeostasis Temperature Control

1.	2. But, if the outside temperature is lower than 37°C then the body will lose heat, through the
----	--

The point of this regulatory system is to keep the temperature inside the body constant at 37 °C, irrespective of the outside temperature.	skin, and through the respiration (breathing out the warm air). This would then lower the temperature inside the body.
3. To push the temperature inside the body back to 37 °C, the body must generate heat.	4. The most common way to generate heat is with its metabolism (=biochemical reactions inside the cells of the body).
5. All biochemical reactions always generate some heat. This will increase the body temperature.	6. If the outside temperature is very low, then other mechanisms to generate heat are also put in action. A good example is shivering . This generates a lot of heat!
7. But what happens if the inside temperature gets too high , above 37°C?	8. Then the opposite happens, the body must lose heat to get back to 37°C. Again, there are several mechanisms to do that, such as sweating, evaporation, etc.
9. In summary, the homeostatic temperature control system works by either generating heat or by losing heat, as required.	10. But, how does the body know that it has to lose or has to generate heat? That is the function of a set point together with a feedback loop!

D. Set point and feed-back loop

1. A set point is the value at which the body wants to keep something constant and stable, in this case the temperature.	2. Such a set point is often located in the brain , although nobody has yet been able to identify the exact location of this set point.
3. The homeostatic system, also called a 'control system', always uses this set point as a constant reference for its action.	4. So, if the body temperature threatens to be too low , then the body will generate more heat. The opposite will happen if the body gets too hot .

5. But how does the body know its internal body temperature is too low or too high? For this, the body needs temperature sensors .	6. These body sensors measure the temperature in different parts of the body, inside the chest, the abdomen, the brain and in the skin.
7. These sensors constantly tell the brain set point whether the body temperature is ok, or too low, or too high.	8. If the temperature is too far off from the set point, then the brain decides to either increase metabolism, or to start sweating or shivering, or whatever is necessary to get the body temperature back to normal.
<pre> graph LR SP["37 °C (set point)"] T1["als lichaams temp. 40 °C"] T2["als lichaams temp. 34 °C"] A1["dan zwenen"] A2["dan rillen"] SP --> T1 SP --> T2 T1 --> A1 T2 --> A2 A1 --> SP2["37 °C (terug naar set point)"] A2 --> SP2 style SP fill:none,stroke:none style SP2 fill:none,stroke:none </pre>	
9. In other words, there is a loop from the sensors, through the set point to the action (shivering, metabolism etc.).	10. This loop is called ‘feed back’!!

E. Negative and Positive Feedback Loops

1. This is an important concept in physiology: a feedback loop.	2. A sensor measures, constantly, the body temperature, pressure, pH or whatever. These values are transmitted to specialized centers, often in the brain.
<pre> graph TD S["sensor (temperatuur)"] E["effector (zwenen)"] M["40 °C (gemeten waarde)"] SP["37 °C (set point)"] S --> M M --> E E --> SP style S fill:none,stroke:none style E fill:none,stroke:none style M fill:none,stroke:none style SP fill:none,stroke:none </pre>	

3. In that center, the measured value is compared to the set point of that variable such as the temperature.	4. If the value is too high, then effectors are stimulated that will lower the value (temperature). If the value is too low, other effectors will be stimulated to raise the value.
5. Please note that the system works in such a way as to reduce the fluctuations, in this case in temperature. In other words, the control systems works to restore the situation to the set point, i.e. the normal value.	6. This is called a negative feedback. ‘Negative’ because it minimizes the fluctuations of the variables such as temperature in the body.
7. The opposite is also possible. This is the case in a positive feedback loop.	8. For example, hypothetically, if the temperature had increased, and if the system had stimulated the wrong effector, such as metabolism or shivering, then the temperature would further increase!
9. That obviously is not compatible with life. In fact, in biology, there are very few examples of positive feedbacks.	10. Most control loops in the body are negative feedbacks.

F. Other examples of negative and positive feedback loops

1. The most famous example of negative feedback system is the heating in your house. The value of the thermostat in the living room is the set point . If the temperature in the room gets too cold, then the heater (= the effector) will be turned on and will heat the room until the set point is reached again.	2. Another example, outside of biology, is the cruise control of your car . When it is set at a chosen speed (= the set point), the car will automatically accelerate or decelerate if the speed gets too low or too high.
3. An example of a positive feedback is seen in blood clotting. When a blood vessel is damaged, platelets will stick to the injured vessel and release a chemical attracting even	4. Other examples of positive feedback can be found elsewhere; such as your money in a bank account with a nice interest . As the

more platelets to the same site. This will attract more and more platelets and increase the clotting process (until the bleeding has stopped).	interest value raises the total amount, over time, more and more interest is accrued!
5. Some scientist think that the current global warming is an example of increasing CO ₂ emissions that, in turn, further raises the earth temperature; a positive feedback loop !	6. By the way, there are situations in the body when the set point can be changed ! This is for example the case when one runs a fever . Then the set point is raised, because the body needs extra metabolism to battle an infection, and this increase in set point will then ‘automatically’ increase the body temperature.

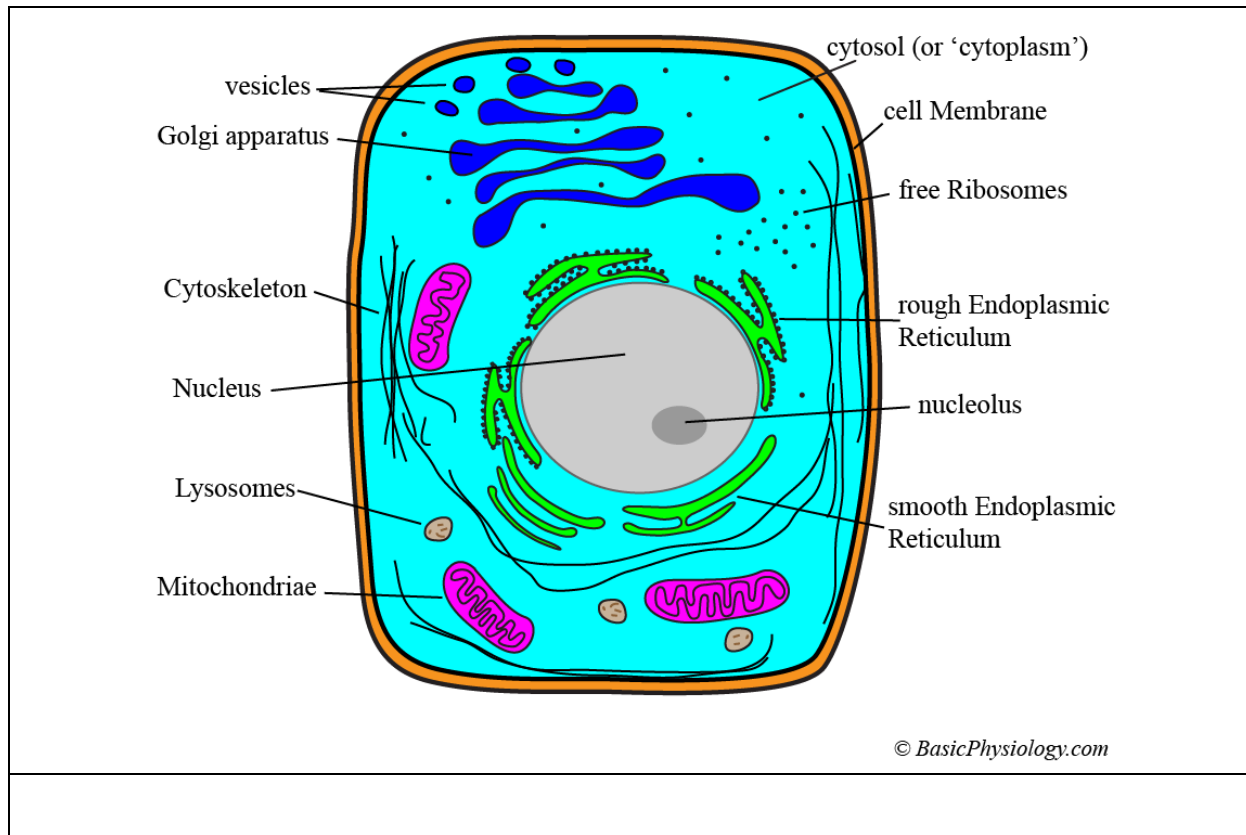
G. Interesting to know!

1. Oh yes; not all animals have a stable body temperature.	2. Those animals that have a stable temperature in their internal environment are called homeotherm or endotherm (=warm blooded).
3. This is the opposite of animals that cannot regulate their body temperature: poikilotherm (= cold-blooded), such as frogs.	4. These poikilotherm bodies cannot regulate their body temperature at all!
5. As usual, this is a first introduction into the concept of ‘homeostasis’ and its components. As always in Physiology, there is much more known about this concept. If you are interested, I would encourage you to read a recent review written by Billman about this concept.	

A.2.1. Structure of the Cell (very brief!)

A. What is a cell?

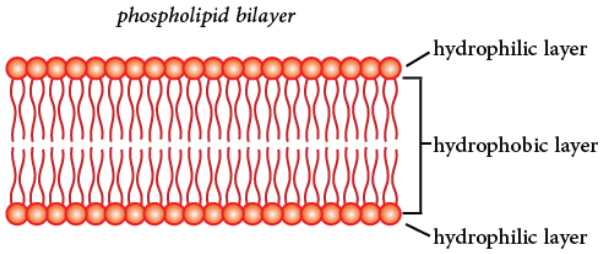
1. A cell is the basic component of a body. The body contains about 13 billion cells!	2. There are many types of cells; skin cells, red and white blood cells, nerve cells, muscle cells, just to name a few types.
3. All cells contain several types of organelles (= a small organ inside the cell).	4. Some cells will have specific organelles such as contracting fibers in muscle cells or vesicles in gland cells etc.
5. But most cells have similar organelles, which we will now discuss.	6. The major organelles in a cell are: 1. Nucleus 2. Cell Membrane 3. Endoplasmic Reticulum 4. Golgi apparatus 5. Lysosomes 6. Mitochondria 7. Cytoskeleton 8. Ribosomes
7. By the way, the interior of the cell is filled with a fluid that is called cytoplasm (cyto=cell and plasm=plasma or fluid).	8. So, what is the name of the fluid inside the nucleus ? Right: nucleoplasm!



B. The Nucleus:

1. The nucleus contains the genetic material of the cell (and therefore of the whole body) in the form of DNA (=deoxyribonucleic acid).	2. This, together with supporting proteins, is formed in strands called chromatin. Together, they chromosomes (in humans 46, that is 23 pairs).
3. The nucleus contains a dense body called the nucleolus ; this contains a lot of ribosomes and RNA (=ribonucleic acid).	4. The nucleus has many functions, but its main function is making messenger RNA from its DNA data bank.
5. Some cells don't have a nucleus. A well-known example is the red blood cell (=erythrocyte). Because they don't have a nucleus, they cannot repair themselves and are therefore doomed to die (in about 120 days).	6. Some cells have several nuclei (plural of nucleus). The best-known examples are the muscle cells .

C. The Cell Membrane:

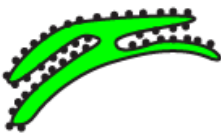
1. The cell membrane consists of two layers of phospholipid molecules. These molecules are pretty 'fluid', like a gel. That is why this membrane is called 'plasma'.	2. Inside this double layer, there are several other structures 'floating' around, such as protein channels, receptors, etc.
3. The cell membrane is so important in physiology that we have created a special page dedicated to the structure and the function of the plasma membrane: link .	

D. The Cytoplasm:

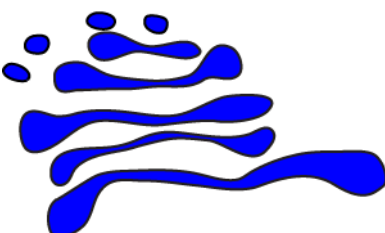
1. The cytoplasm (=intracellular fluid; also called <i>cytosol</i>) consists of the fluid (=water) and all the soluble elements inside the cell, such as ions, proteins and metabolites.	2. In the cytoplasm, the organelles are also located, sometimes 'floating' around, sometimes fixed to the nucleus, cytoskeleton or to the plasma membrane.
3. The composition of the cytoplasm is very different from that outside the cell: the extracellular fluid (extra = 'outside' the cell).	4. For example, there are many more K⁺ ions inside than outside the cell (140 mM vs. 5 mM) whereas the opposite is true for Na⁺ ions; much more outside than inside (10 vs. 145 mM).

E. The Endoplasmic Reticulum (=ER):

1. This 'reticulum' is a network of channels and sacs. They play a major role in collecting and transporting products through the cell.	2. There are two types of endoplasmic reticulum: the ' rough ' and the ' smooth '.
3. The rough ER is studded with small ribosomes, all located on the cytosolic surface	4. The rough ER is linked and connected to the nuclear membranes. Its ribosomes are involved in the synthesis of proteins.

of the reticular membrane whereas the smooth ER does not have ribosomes.	
smooth ER  rough ER 	
5. The smooth ER is involved in the synthesis of lipids, hormones and carbohydrates.	6. In muscle cells, the smooth ER are involved in the regulation of Ca^{2+} ions, which is important for generating muscle contractions. There, they are called ‘Sarcoplasmic Reticulum’. <i>More about this in ‘Muscle Cell’.</i>

F. The Golgi apparatus:

1. This is also a kind of a reticulum, a collection of sacks and tubules. It was first discovered by the Italian Camillo Golgi; hence its name.	2. The Golgi apparatus (also called Golgi complex) gathers simple molecules, mainly from the ER, and combines them into larger and more complex molecules.
Golgi apparatus 	3. Finally, it also packages these new molecules into vesicles (small sacks).
4. These vesicles are then sent to their destination, usually the plasma membrane where the content of the vesicles are dumped to the outside world: the extracellular fluid.	5. This process is called exocytosis (exo = 'exit' out of the cell). exocytosis 

G. The Lysosomes:

1. These are small sacks or vesicles (produced by the rough ER and released inside the cell by the Golgi complex). They contain enzymes that break down complex molecules such as proteins, carbohydrates and lipids.	2. Essentially, they destroy cellular organelles and large cellular molecules! They are literally the garbage collectors of the cell, which gets rid of cellular waste. It breaks down molecules into smaller and simpler molecules that can be used again; recycling!
3. Sometimes, they can also destroy their own cells. The lysosomes then behave as ‘suicide sacs’!	lysosomes 

H. The Mitochondrion:

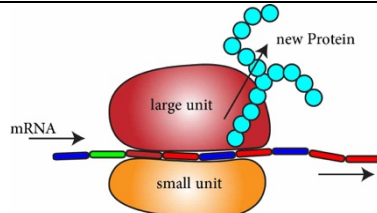
1. This is the energy center of the cell. It produces ATP required for activating all biochemical processes in the cell.	2. It consists of a double plasma membrane: an outer and an inner membrane. The inner membrane is folded several times thereby forming ‘cristae’.
	
3. The mitochondria (plural of ‘mitochondrion’) also have other functions, such as calcium homeostasis in certain cells. Other functions are regulation of the cell cycle, cell growth, and sometimes even cell death!	4. Interestingly, these mitochondria also contain DNA molecules. This DNA comes from one parent, the mother (and not, as in the nucleus, from both parents). It forms therefore another genome than the DNA located in the nucleus.

I. The Cytoskeleton:

1. These are fibers that form, together, the ‘skeleton’ of the cell.	2. In other words, the cell is not just a simple sack filled with fluid, but has a shape and a stiffness , caused by its own skeleton: the cytoskeleton.
---	---

3. These fibers can vary from relatively simple microfilaments to more complex microtubules.	4. The microfilaments are involved in cellular motility, muscle contraction, transport of organelles etc.
5. The microtubules are cylinders ('tubes'), often connected to a central centrosome.	6. They play a central role, during the division of a cell (= mitosis), and in the distribution of the chromosomes.

J. The Ribosomes:

1. The ribosomes are large complex molecular machines that are involved in the synthesis of proteins .	2. The ribosomes link amino acids together in the order specified by the messenger RNA (which comes from the nucleus). That's why there are so many ribosomes located on the rough ER.
3. The ribosome consists of two units, a small one that 'reads' the RNA and a large one that connects individual amino acids into a protein molecule.	 The diagram illustrates a ribosome with a large red subunit and a small orange subunit. A blue mRNA strand is threaded through the small subunit. A new protein chain, represented by a string of blue spheres, is being synthesized from the large subunit. Arrows indicate the direction of mRNA movement and protein synthesis.

K. Important Note:

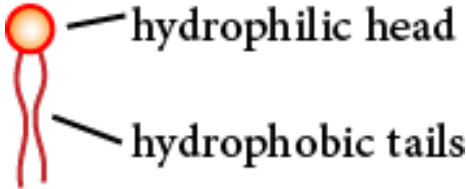
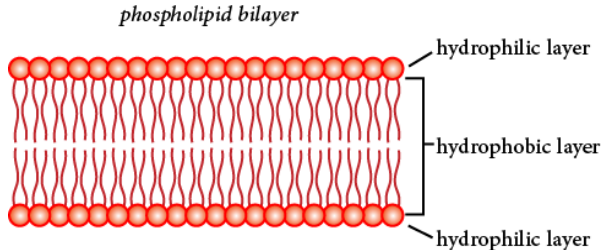
1. This is a very small and condensed review of the structure and the function of a cell.	2. There is an enormous variation in types and content of cells, some of which we will see in the next pages.
3. For more information, there are many books and websites that go much deeper into this field of cellular biology.	4. For starters, Wikipedia is not bad at all!

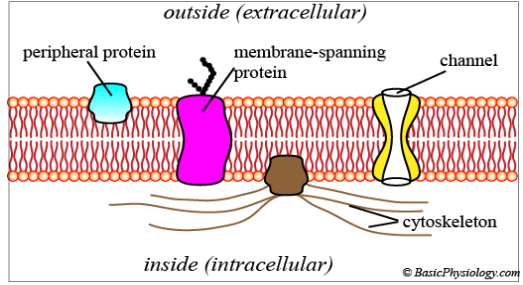
5.

Btw, the word “cell” originates from the latin word “*cella*” which means “*small room*” (see Jason Roberts “[Every Living Thing](#)”). Isn’t that nice to know?

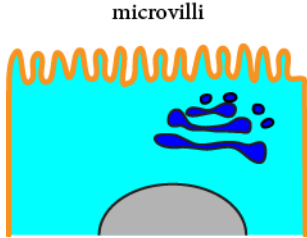
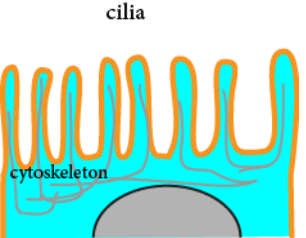
A2.2. The Plasma Membrane.

A. The Plasma Membrane

1. The plasma membrane envelops all the cells in the body and separates the intracellular environment (=cytoplasm) from the extracellular environment.	2. It consists of two layers of phospholipids. Each phospholipid consists of a head, which is hydrophilic (=likes water’) and two hydrophobic (=repels water’) tails.
	3. If you place a lot of these phospholipid molecules together in water, they will tend to cluster in such a way that their heads are in contact with water and their tails are oriented inwards and away from the water.
4. Since both the intracellular and the extracellular fluid contain a lot of water, all the heads will point towards the intra- or the extracellular water while the tails will point away from the water and towards each other!	
5. In this way, a bi-layer (=two layers) are formed with the hydrophobic layers located inside this layer and two hydrophilic layers located outside and in contact with water.	6. However, in order for the cell to be able to communicate with the outside world, other molecules, in most cases proteins , are located in the plasma membrane. Since the phospholipids are not fixed, these protein molecules literally ‘float’ around in this plasma membrane.
7.	

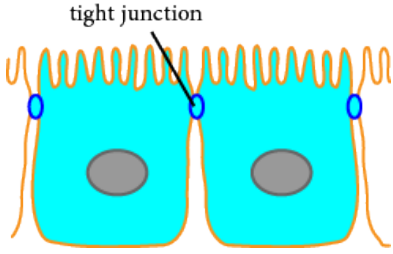
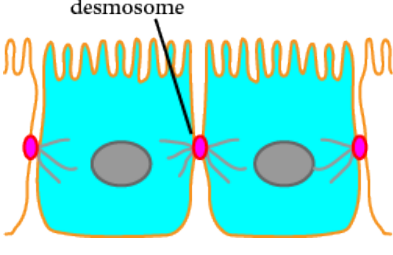
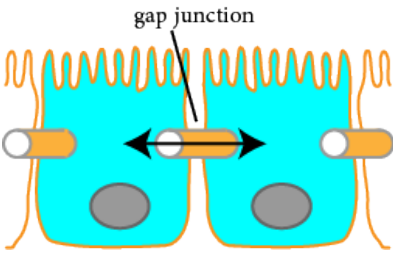
There are many types of membrane-bound proteins such as channels, transporters, receptors, anchors for the cytoskeleton etc. The function of several of these transporters will be discussed in these two pages: <i>A.2.3. Passive Transport Systems</i> and <i>A.2.4. Active Transport Systems</i>.	
---	--

B. Specialized Plasma Membranes

1. In some cells, the shape of the plasma membrane is modified, by the cytoskeleton, into different shapes.	2. For example, in cells lining the intestines, the plasma membrane shows several folds (microvilli) extending into the intestinal lumen (space).
	
3. These microvilli are useful because they increase the surface area of the plasma membrane for the absorption of nutrients from our ingested food.	4. In other cells, much longer finger-like projections occur from the plasma membrane. These are called cilia and are supported by the cytoskeleton. They occur for example in the respiratory tract (= the lungs).

C. Plasma Junctions between cells

1. In some tissues, there are also special connections between neighboring cells.	2. We will discuss here three types: 1. tight junctions 2. desmosomes 3. gap junctions
3.	

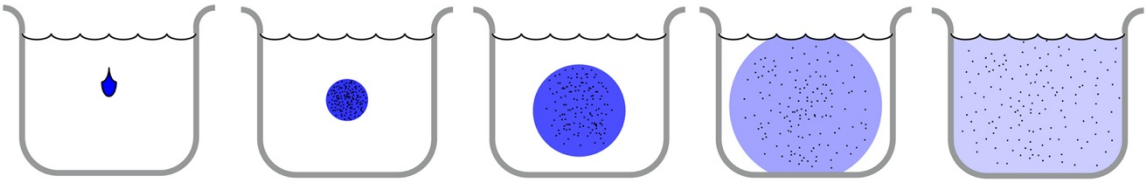
In tight junctions, adjacent plasma membranes are fused together, to avoid ‘leakage’ or transportation of molecules from one side of the extracellular space to the other. This is for example the case in epithelial cells, lining the lumen of a tube such as in the intestine.	
4. Desmosomes are even stronger connections between adjacent cells, when stronger forces are involved (in the stomach and the intestinal system for example).	
5. Gap junctions are very specialized structures that bridge the gap between cells. They consist of several channels (called ‘connexons’) through which ions and small molecules can flow from one cell to another. See: A.3.6. <i>The Electrical Synapse</i>.	

A.2.3. Passive Transport Systems across the Cell Membrane.

A. Introduction Transport Systems:

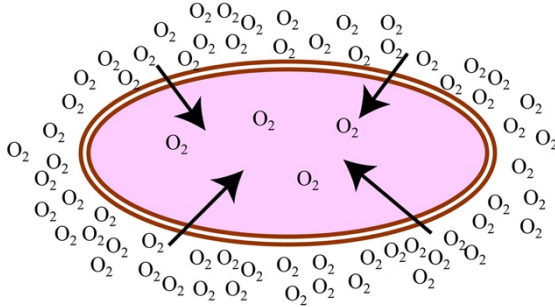
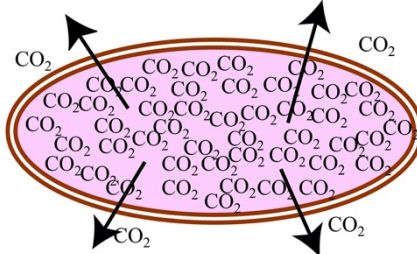
1. For a cell to be able to live, there must be communication (=transport) between the intracellular fluid (=the cytoplasm) and the extracellular fluid (= interstitial fluid).	2. Some of these transports are passive and do not require energy . Other transport systems are more complicated and require energy (= ATP).
3. These are the four major passive transport systems: 1 diffusion 2 facilitated diffusion 3 osmosis 4 filtration	4. These are the three major active transport systems: 1 pumps (co-transporters, etc.) 2 exocytosis / endocytosis 3 phagocytosis

B. What is diffusion?

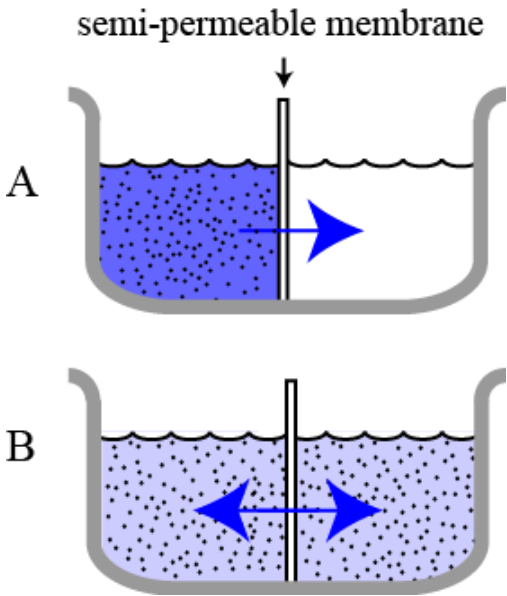
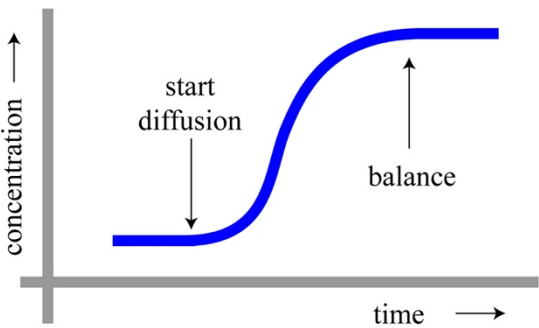
	
1. Diffusion is the process whereby something soluble that is placed in water is 'automatically' distributed, dissolved, in that water.	2. The classic example is a drop of ink that is dropped in a glass of water. If you wait long enough, the ink will be dispersed throughout the water.

3. The same is true for sugar, aspirin, oxygen etc. as long as this material can be dissolved in water. If it can not be dissolved then of course diffusion will not take place.	4. Diffusion takes place because of the Brownian movements of the particles. (Brownian movements are caused by the kinetic energy stored in every particle. (<i>What is kinetic?</i>)
---	--

C. Diffusion across the cell membrane:

1. In the body, diffusion occurs all the time across the cell membranes. This will occur if the concentration of something (=the solute) is higher at one side of the membrane than at the other side, AND if the membrane is permeable for that solute.	2. For example, oxygen , dissolved in water, can easily cross the membrane. Usually, the oxygen concentration outside the cell is higher outside than inside the cell (because it is used by the cell).
3. So, if there is a concentration difference for oxygen, then oxygen will diffuse through the membrane and transport itself, automatically, into the cell. This does not require energy.	
4. The same thing happens in the opposite direction with the combustion of oxygen; carbon dioxide . This molecule is formed inside the cell (by converting oxygen) and will diffuse out of the cell into the extracellular space.	

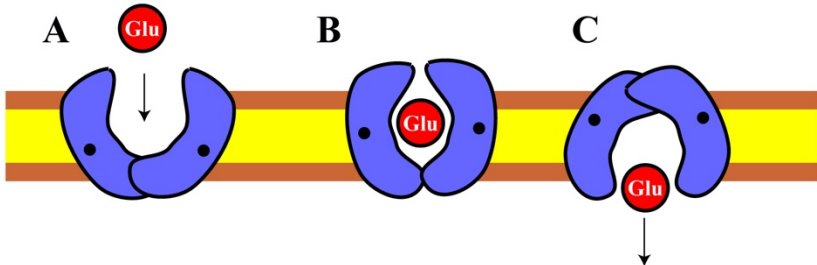
D. Factors that determine the rate of diffusion:

1. In this diagram, a beaker is divided by a membrane. On the left, a solute (blue) has been added to the fluid.	
2. As the molecules can pass through the membrane, with time, more and more molecules will pass the membrane to the other side.	
3. Eventually, the concentration will be the same in both compartments, left and right of the membrane (light blue in both halves).	
4. The factors that determine the speed of diffusion are: 1 temperature 2 the difference in concentration 3 the diffusion distance 4 the size of the area of diffusion	
5. Increasing the temperature will increase the movements of the particles and this will speed up the diffusion.	
6. The higher the difference in concentration, the quicker the diffusion takes place.	
7. The longer the distance between the two compartments (thicker membrane), the longer the diffusion will take place.	8. The graph shows what happens when the diffusion is started. After some time, the concentration has become equal on both sides and net diffusion will be stopped (<i>why 'net'?</i>)

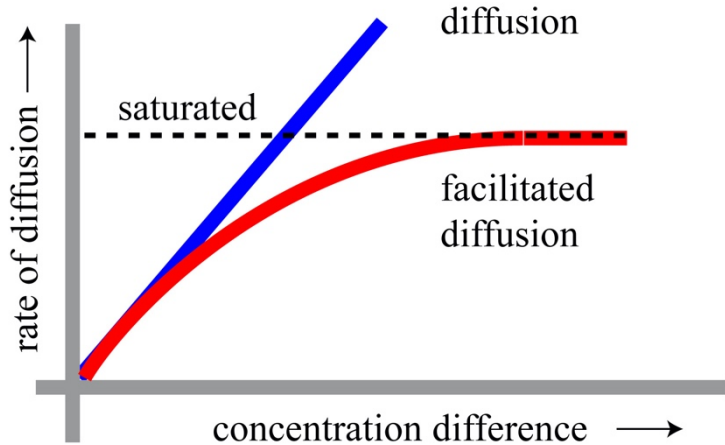
E. Facilitated Diffusion:

1. This type of diffusion is performed by special carrier proteins located in the membrane of the cell.	2. So, the membrane, in principle, is not permeable for these molecules but still, they are carried through the membrane by these special carriers.
3. A famous example of facilitated diffusion is the transport of glucose (=sugar) into the cell.	4. Glucose is a molecule that is too big to diffuse through the membrane.
5. But there is a special carrier in the membrane that can transport glucose, free of energy.	6. This carrier is specific for glucose; it cannot transport anything else.
7. The carrier can transport in both directions; in or out of the cell, depending on the concentration gradient for glucose.	8. But usually, glucose is used (=metabolized) in the cell so the concentration inside is lower, so the transport is usually from outside into the cell.

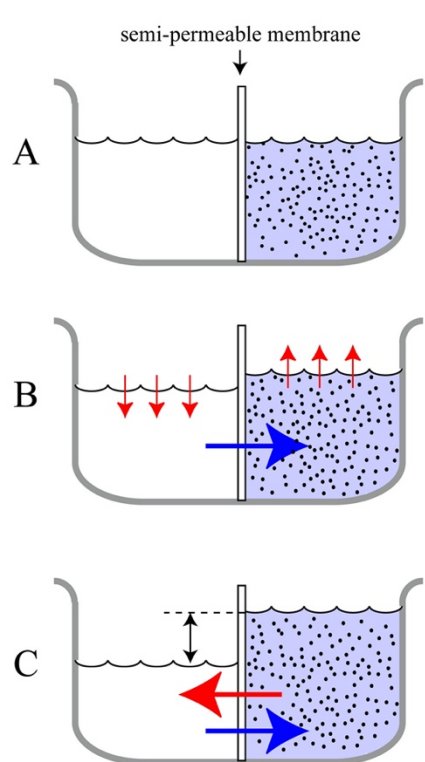
F. Mode of action:

1. When a glucose molecule comes in contact with this carrier, the glucose will couple (=attach) to the carrier.	2. This coupling will change the shape (= the configuration) of the carrier.
	
3. This configuration change makes it possible for the glucose to 'diffuse' to the other side of the membrane.	4. Once the glucose has reached the other side of the carrier, it is released, into the cell and the carrier is free to transport another glucose molecule.

G. Similarities and differences between diffusion and facilitated diffusion:

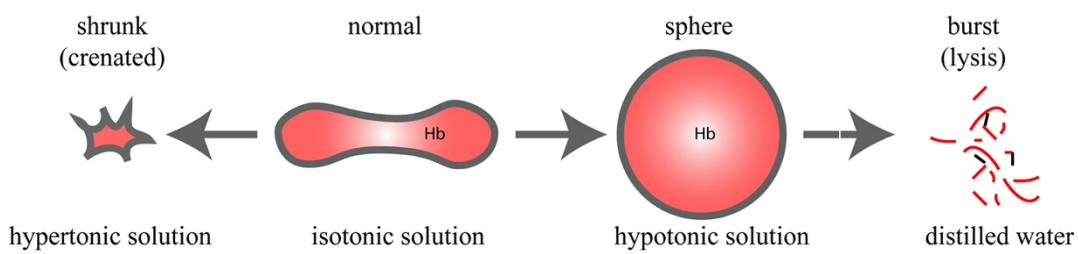
1. Similarities: 1 no energy required 2 concentration dependent 3 bi-directional	2. Differences: 1 saturation 2 specificity
3. The similarities are obvious if you have studied diffusion (bi-directional means the molecule can go either way; in or out of the cell)	4. Saturation means that there is a maximum to the amount that can be transported. This is reached when all the available carrier molecules are occupied.
	
5. In normal diffusion, there is no saturation, and the process can go on as long as possible, as long as there is a concentration gradient.	6. Specificity means that a particular carrier can only transport a particular molecule, such as glucose, and not something else.
7. Example of facilitated diffusion is transport of glucose , as discussed, in all body cells essentially, but especially in the brain. Also, amino acids can be transported in this way through the cellular membrane.	8. Another example of facilitated diffusion occurs in the kidney when sodium is reabsorbed. This is also done by facilitated diffusion.

H. Osmosis:

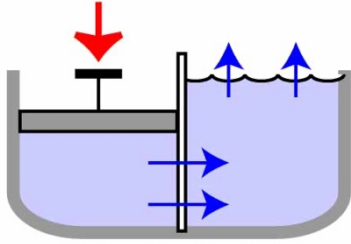
1. A special type of diffusion, which also does not require energy, is diffusion of water, a process that is called osmosis.	2. Osmosis takes place across a membrane. This membrane is permeable for water (as usual) but NOT permeable for a solute (a substance that is dissolved in water). We call this a semi-permeable membrane (not permeable for the solute but permeable for water).
3. If, in that situation, there is a concentration difference of the solute, then there is also a concentration difference for water.	4. In the diagram (A), there is more solute (blue) to the right then to the left of the membrane. But this solute can not pass the membrane whereas water can.
5. Since there is (a little) more water at the left side of the membrane, then there is a concentration difference for water and the water molecule will cross to the right side (blue arrow).	
6. This will increase the amount of water at the right side! As indicated in B, the water level will raise on the right side (and decrease on the left).	
7. As with any diffusion, this process will in principle continue until the concentration difference across the membrane has become the same. But this is not always possible.	
8. As indicated in the diagram, the increase in water will also increase the column of water (and thereby also increase the pressure) to the right of the membrane.	

9. This pressure increase will cause the water molecules to move to the left (red arrow).	10. In other words, a concentration gradient to the right is causing an opposite pressure gradient towards the left. As soon as the pressure gradient is equal (but opposite) to the concentration gradient, this system (osmosis) has become stable (indicated by the blue and red arrows).
--	---

I. An example of Osmosis; the red blood cell:

1. A well-known demonstration of the effects of osmosis is the behavior of red blood cells in a water solution.	2. Like all other cells, the red blood cells (=erythrocytes) have a plasma membrane that is permeable for water but not permeable for many molecules (such as salt, hemoglobin etc.).
3. If the red blood cell is placed in a solution that contains less non-permeable particles than in the cell, then water will go into the cell; the cell will expand.	4. The solution that contains less non-permeable solute is called: ' hypotonic '. If the solution contains the same amount of solute, then the solution is called ' isotonic ' (iso=equal; tonic=tone).
 The diagram illustrates the osmotic behavior of a red blood cell in four different environments, connected by arrows from left to right. Hypertonic solution: The cell is 'shrunk (crenated)', shown as a small, irregular, spiky shape. Isotonic solution: The cell is 'normal', shown as a smooth, oval shape containing 'Hb' (hemoglobin). Hypotonic solution: The cell is a 'sphere', shown as a large, smooth, circular shape containing 'Hb'. Distilled water: The cell has 'burst (lysis)', shown as a fragmented, irregular shape. Arrows indicate the progression from the hypertonic solution to the isotonic solution, then to the hypotonic solution, and finally to distilled water.	
5. If the difference is too big, for example if there is no solute at all in the environment, then the cell may blow itself up, break and burst (=lysis).	6. The opposite can also happen. If the red blood cell is placed in a solution that has too much salt (=hypertonic), then water will move out of the cell; the red blood cell will then shrink!

J. Filtration:

1. In filtration, there is a pressure difference between one side of the membrane and the other side.	2. Because of this pressure difference, water will flow from the region of high pressure to that of low pressure, assuming that the barrier is permeable to water.
3. Filtration occurs in many parts of the body, but especially in the transport of plasma through capillaries, in the kidneys (formation of urine) and in the lungs.	

Sub-notes:

B.4. What is kinetic?

Kinetic energy (from the Greek word 'Kinein' = to move) is present in all dissolved particles and molecules. This energy will 'shake' these particles all the time. The shaking intensity increases with higher temperatures and slows down at lower temperatures. The shaking stops completely at the absolute zero (zero Kelvin = -273°C = -459°F).

D.8. Why 'net'?

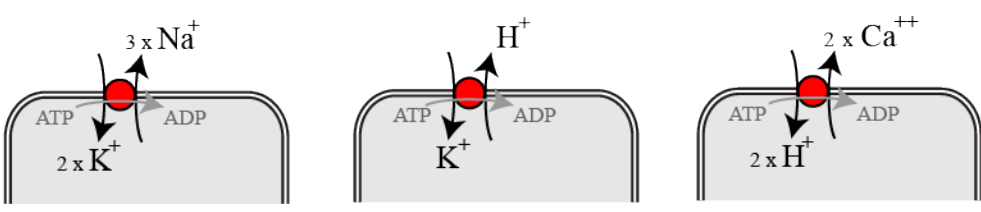
In reality, because the molecules are still moving according to their kinetic energy, some molecules will accidentally cross the membrane and move to the other side. But other molecules that are moving accidentally in the opposite direction will offset this. In other words, the molecules are still moving left and right but the net effect is zero.

A.2.4. Active Transport Systems across the Cell Membrane.

A. Introduction Transport Systems (repeat of previous page):

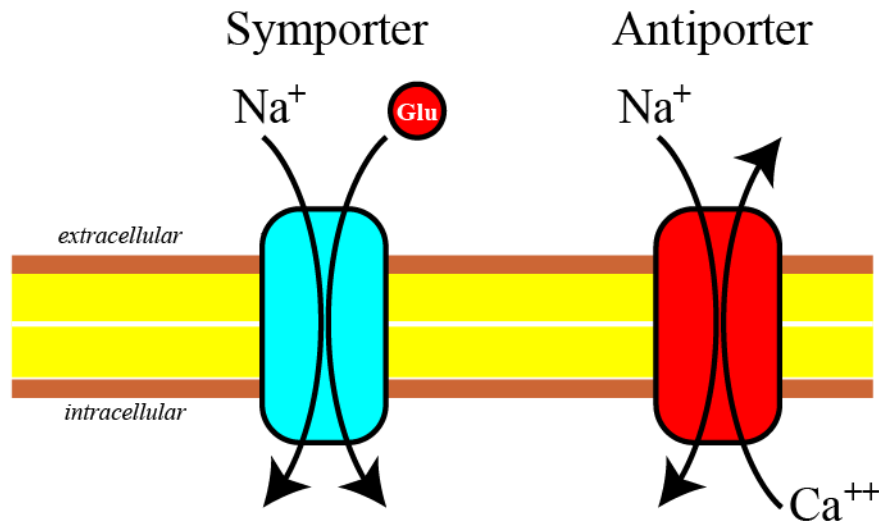
1. For a cell to be able to live, there must be communication (=transport) between the intracellular fluid (the cytoplasm) and the extracellular fluid (= interstitial fluid).	2. Some of these transports are passive and do not require energy . Other transport systems are more complicated and require energy (= ATP).
3. These are the four major passive transport systems: 5 Diffusion 6 facilitated diffusion 7 osmosis 8 filtration	4. These are the three major active transport systems: 4 pumps (co-transporters, etc.) 5 vesicular (exocytosis/endocytosis) 6 phagocytosis

B. Pumps

1 These are proteins located in the cell membrane that 'actively' pump ions and molecules in or out of the cell.	2. 'Actively' means that this pumping requires energy, usually in the form of ATP .
3. The most famous pump is the Sodium-Potassium pump ($=\text{Na}^+-\text{K}^+$). This Na^+-K^+ pumps sodium ions out of the cell and, at the same time, potassium ions into the cell.	4. Other pumps are the $\text{H}^+-\text{Ca}^{2+}$ pump (used in muscles) and the H^+-K^+ pump (in the stomach).
 The diagram shows three active transport pumps embedded in a cell membrane. Each pump is represented by a red oval. Arrows indicate the direction of ion movement, and labels show the ions and their quantities. ATP is shown being converted to ADP for each pump. sodium-potassium pump: 3 x Na^+ out, 2 x K^+ in. hydrogen-potassium pump: H^+ out, K^+ in. calcium pump: 2 x Ca^{++} out, 2 x H^+ in.	

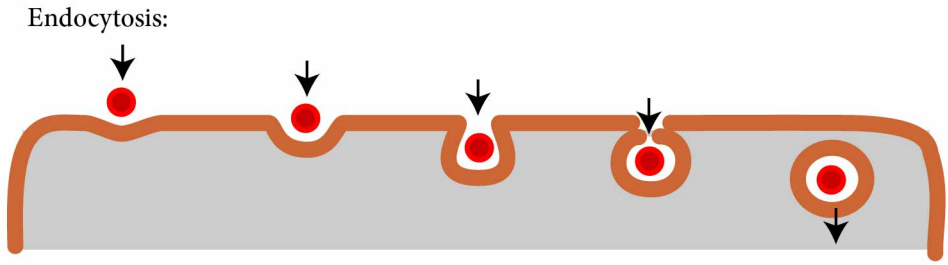
B1. 'Pumps ' more in Depth:

1. The Sodium-Potassium pump is extremely important in the body. It is located in every cell membrane. And its main task is to produce a significant difference in the sodium and potassium concentrations inside and outside a cell.	2. Because of this pump, there are many more potassium ions inside the cell compared to outside (140 vs. 4 mEq/L outside) while, at the same time, there are many more sodium ions outside than inside (142 vs. 10 mEq/L inside)
3. As we will see later (in the <i>Nerves</i>), this concentration differences for sodium and for potassium is crucial for a proper functioning of the nerves and the muscle cells.	4. More recently, active transport has been subdivided into two parts: primary active transport and secondary active transport.
5. Primary Active Transport is transport that is made possible with energy from the breakdown of ATP (or other high-energy phosphate compound).	6. Secondary Active Transport is made possible by the 'energy' that is created by the differences in sodium concentration across the membrane; a difference which was made possible by the primary active transport in the first place!



7. Examples of Primary active transport systems are the sodium-potassium pump, the hydrogen-potassium pump and the calcium pump (as discussed in panel B).	8. In Secondary active transport systems, specialized proteins in the membrane use the concentration difference of, for example, the sodium ions across the membrane to “co”-transport another molecule.
9. For example, in the case of a symporter, every time a sodium ion goes back into the cell (based on its concentration gradient), it takes another molecule with it, such as glucose, amino acids etc. into the cell.	10. In the case of an antiporter, the situation is the opposite; every time a sodium ion flows into the cell, another molecule, often a calcium or a hydrogen ion, is pumped out of the cell. (<i>Q: what happens to the sodium ion that just went into the cell?</i>).

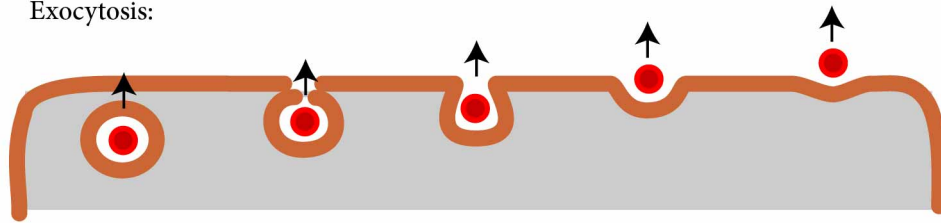
C. Vesicular Transports

1. In this transport system, vesicles are formed that either transport particles or molecules into the cells or moves them out of the cell.	2. In endocytosis ('endo' = into the cell), a particle binds to the receptor lining the plasma membrane, which reacts by forming a 'pit'.
Endocytosis: 	
3. This pit then gradually invaginates and finally forms a vesicle that separates itself from the plasma membrane to disappear into the machinery of the cell.	4. In exocytosis ('exo' = out of the cell), the opposite occurs. Vesicles that contain certain molecules, for example produced by the Golgi apparatus, migrate towards the plasma membrane of the cell and are then expelled out of the cell.

5.

At the plasma membrane, the vesicle then fuses with the membrane and releases its contents into the extracellular space.

Exocytosis:



D. Phagocytosis:

1.

Phagocytosis ('engulfing') is like endocytosis in the sense that something is picked up and transported into the cell.

2.

Finger-like extensions of the plasma membrane (pseudopodia) extend and surround an extracellular particle.

3.

These pseudopodia fuse to each other thereby creating a vesicle, also called a **phagosome**, that contains the particle, and is moved into the cell.

4.

Phagocytosis is performed by special cells such as macrophages, to 'eat' extracellular material such as bacteria, pathogens or cellular debris (as when cleaning up a wound).

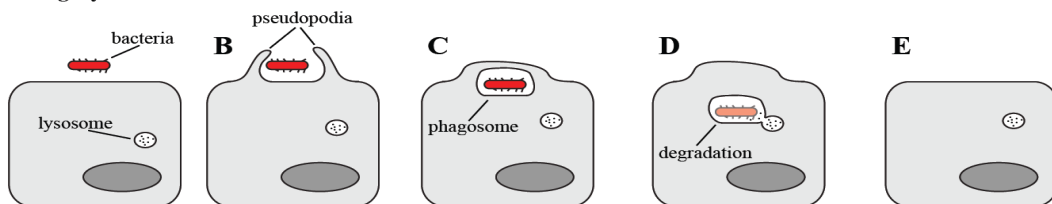
5.

Often, after the phagosome has been created, it fuses with neighboring lysosomes that contain destructive enzymes.

6.

These enzymes then destroy the cellular debris or the bacteria (= degradation).

Phagocytosis

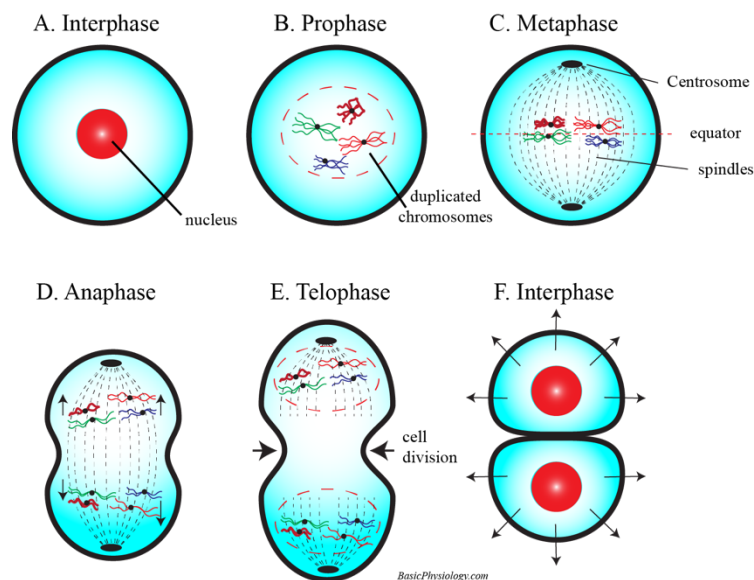


A: the sodium ion is simply pumped back to the extracellular space by the sodium-potassium pump.

A.2.5. Mitosis and Meiosis

A. Mitosis:

1. The vast majority of all the cells in our body will die at some moment. Before they do that, they often divide into daughter cells to preserve their function and their DNA!	2. The process of a cellular division is called mitosis . This occurs million of times in every single minute that you are alive; blood cells, skin cells, liver cells etc, etc.
3. This process of mitosis is quite complicated and consists of several steps: a. Interphase b. Prophase c. Metaphase d. Anaphase e. Telophase	4. The Interphase is the time between mitosis, between the cell divisions, when the cell is actually doing what it should do. This is the longest period for a cell (days to years depending on the type of cell). At the end of the interphase, when the cell has decided to divide, the chromosomes are duplicated (from 2x24 to 4x24). Actually, the most important step in mitosis.



5. The Prophase is the stage when: a) The membrane of the nucleus gradually disappears b) The chromosomes become visible. Every chromosome pair is coupled to each other at a centromere. c) Cellular structures called centrioles (also called centrosomes) appear and stretch towards the two poles in the cell.	6. The Metaphase is the phase when the chromosomes move towards a row located in the centre, the equator, of the cell. In addition, spindle fibres connect every chromosome to the centrioles.
7. In the Anaphase, the centromeres are split and the spindles pull each chromosome towards the centrioles at one side of the cell: 2 x 24 chromosomes to one side, another 2 x 24 to the other side of the cell.	8. In the Telophase, the spindle fibres disappear, a nucleus membrane is formed around each chromosome cluster and the cell membrane squeezes inside the cell to develop two separate cells.
9. When the cellular membranes have formed and divided the two cells from each other, both daughter cells now enter their own interphase.	10. This is the 'growth' phase when water flows into the cell, making it bigger and when all the organelles have to multiply their numbers (mitochondria, vesicles, Golgi apparatus etc.) to be able continue their function in the new cells.

B. The names of the mitosis phases:

1. The names of the different phases during mitosis may sound difficult and confusing. Let's try to explain them!	2. Interphase: this is not so difficult; the phase between the subsequent events (= the mitosis!).
--	---

3. Prophase: from the Greek word “Pro”, which means “before”. The cell starts to get ready for the mitosis; the nucleus membrane disappears, the centrioles appear etc.	4. Metaphase: from the Greek word “Meta” which means “adjacent”. So, in this phase, all the chromosomes are aligned together (‘adjacent’) to each other along the equatorial plane.
5. Anaphase: from the Greek word “Ana”, which means “Up”. This is the phase when the replicated chromosomes are split and the ‘daughter’ chromosomes are pulled, by the spindle fibres, towards the opposite poles of the cell.	6. Telophase: from the Greek word “Telo” which means the “end”, as this is the final stage of the mitosis, when the nuclear envelope is re-assembled, the centrioles and spindle fibres are disassembled.

C. Meiosis:

1. There is however one type of mitosis which is ‘slightly’ different from mitosis but crucial for our survival! This is the cellular division of our ‘sex’ cells; our gametes. These are the sperm cells (in males) and the oocytes (in females).	2. As you may know/remember, life starts when a sperm cell and an oocyte ‘merge’ together to form an embryo. If their chromosomes were simply put together into the cell of the new embryo, his (or her!) cells would contain 2 x 2 x 24 chromosomes! That is impossible. (<i>Why not?</i>)
3. Therefore, the number of chromosomes has to be reduced (halved) before fertilization occurs. This is (one of) the purposes of meiosis.	4. Meiosis actually consists of two parts, or two steps, called “meiosis I” and “meiosis II”. Each meiosis contains the same phases as during mitosis: prophase, metaphase, anaphase and telophase.

Meiosis I	
A. Prophase I	B. Metaphase I
C. Anaphase I	D. Telophase I
Meiosis II	
E. Prophase II	F. Metaphase II
G. Anaphase II	H. Telophase II
5. Meiosis I is very similar to a normal mitosis whereby the number of chromosomes is duplicated. Then, when the cells divide into two daughter cells, the number of chromosomes is still 2 x 24 in each cell.	6. The purpose of meiosis I is to exchange the genes (=DNA) across their chromosomes during the actual duplication. This is called “crossing-over” or “recombination”. In this way, the daughter cells are actually genetically different from each other!
7. After Meiosis I, Meiosis II will start. Now, in contrast to all other divisions, the chromosomes are NOT duplicated.	8. So, when the daughter cells are created, each cell, in its nucleus, contains only one set of chromosomes: 1 x 24!!
9. This is SO important that we have names for cells that have one or two sets of chromosomes; “diploid” and “haploid”.	10. Diploid means two sets of chromosomes while Haploid means one set. Therefore, sperm cells and oocytes are haploid, while all other cells in the body are diploid.

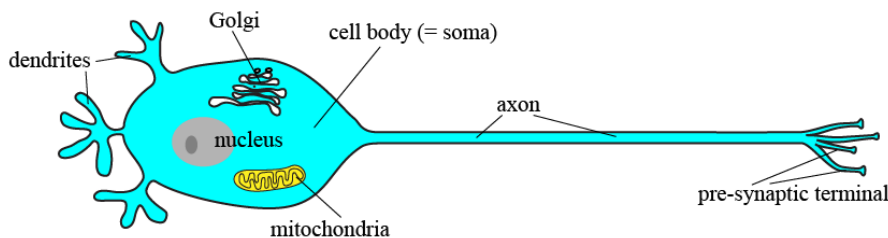
Link: *Why not?* Suppose that the numbers of chromosomes is not halved during meiosis II. Then the daughter cells will each get 2x2x24 chromosomes (total of 96). In the next child, this will become 2x2x2x24 (=192), and in the next ‘generation’ 2x2x2x2x24 (=284), etc etc. Simply impossible!

A.3.1. The Nerve Cell

Introduction: In this and the next Basic Physiology chapter, we discuss in more details **two** types of cells in the body that demonstrate several basic physiological principles that are very useful to know and to understand before studying specific organ systems. These are a) the **nerve cells** and b) the **muscle cells**. In this and the next pages, we will concentrate on the physiology of the nerve cells.

A. What is a nerve cell?

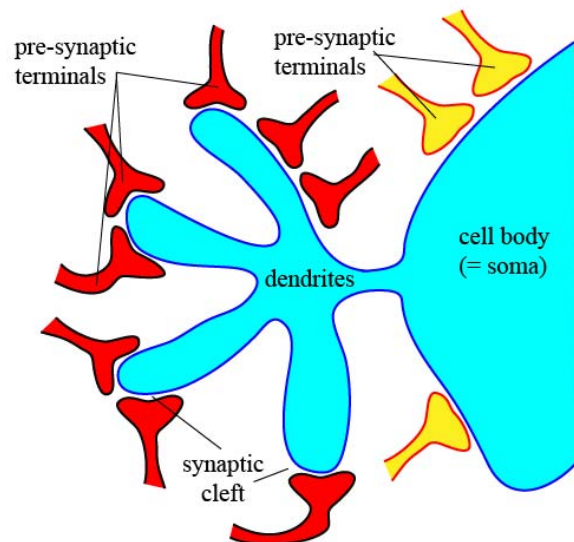
1. A nerve cell, also called a neuron , is a cell that is specialized in passing on messages, which are called ‘action potentials’	2. These action potentials are electrical potentials that are picked up at one end of the neuron and are then propagated to the other end. It is like an electrical wire.
3. Our body contains billions of nerve cells, most of them located in the brain but there are also many nerve cells outside the brain, located throughout the body.	4. A nerve cell, like any other living cells, has a body (called ‘soma’), which contains the usual cellular components such as a nucleus, mitochondria, endoplasmic reticulum, Golgi apparatus, and a plasma membrane (<i>see A.2.1. Structure of the cell</i>).
5. But, typical for a nerve cell, are the following three components: a. dendrites b. axon c. pre-synaptic terminals	6. The dendrites are folds of the cell body that extend into the extracellular space, relatively short in length. Their function is to pick up a signal from another nerve cell.



7. The axon is a long extension of the cell body and its function is to transmit the electrical signal from the dendrites and the soma (=cell body), sometimes over a very long distance, to the next nerve cell.	8. The pre-synaptic terminal is part of the system that connects this nerve cell to the next nerve cell. This connection system is called a 'synapse' (see A.3.7. <i>The Chemical Synapse</i>).
---	--

B. Typical nerve cells

1. Typical of a nerve cell is that it has many dendrites (10-100) and many terminals (100-1000) but only one (or a few) axon.	2. In this diagram, you can see several pre-synaptic terminals (from other neurons) close to the membrane of a few dendrites. It is also possible for these pre-synaptic terminals to get close to the membrane of the soma of the nerve cell. These terminals are indicated in yellow.
---	--

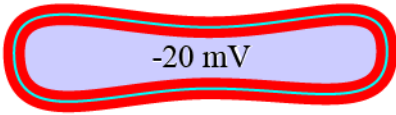
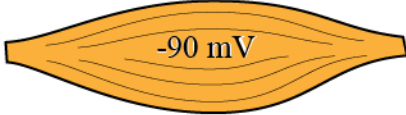


3. Note that there is always a cleft (a small space) between the pre-synaptic terminal and the plasma membrane of the dendrite or the soma.	4. This cleft is called the synaptic cleft (much more on this in A.3.7. <i>The Chemical Synapse</i>).
---	--

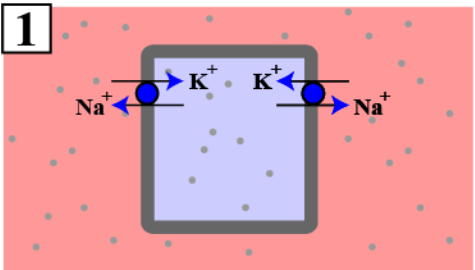
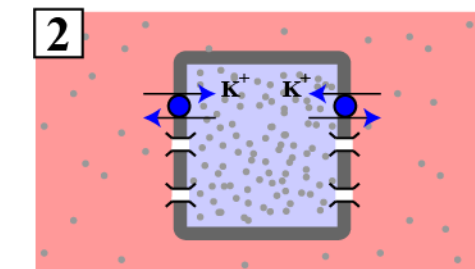
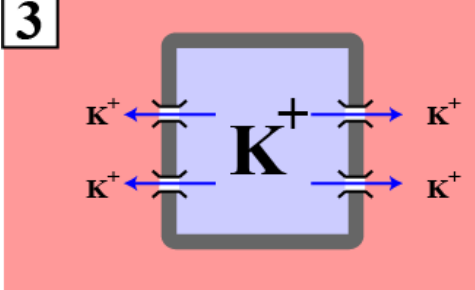
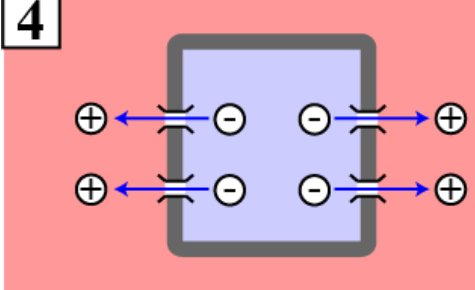
5. In general, there are three different types of nerve cells in the body: a. sensory neurons b. motor neurons c. inter neurons	6. Sensory neurons are sensitive to stimuli such as touch, temperature, sound or light and send their signals to the brain.
7. Motor neurons receive signals from the brain and stimulate muscles to contract.	8. Inter neurons are nerve cells that connect to other nerve cells, as in the brain or in the spinal cord.

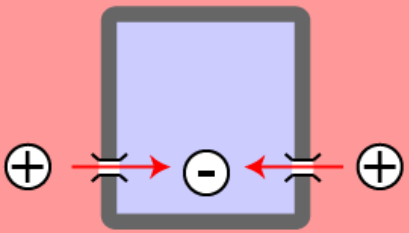
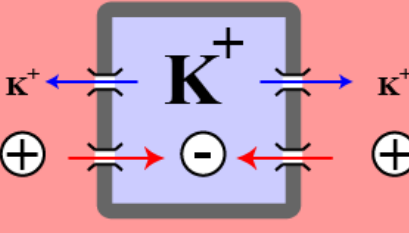
A.3.2. The Resting Potential

A. Introduction to Cellular Potentials

1. All cells in the body show some degree of electrical behavior. They show this by having an electrical potential difference between the inside of a cell and outside.	2. This difference in potential is called the ' resting potential '. This potential difference is not very big, ranging from -20mV to -90 mV but, as we shall later see, very important! (mV = millivolt; one thousand of 1 Volt).
erythrocyte: 	muscle cell: 
3. For example, the red blood cell (= erythrocyte) has a relatively 'small' resting potential; -20 mV while the muscle cell has a much higher resting potential: -90 mV!	4. By the way, we say '-20mV' or '-90 mV' because the inside is negative compared to the outside, extracellular, space.
5. Some cells however, are more excitable than others; these are cells such as the nerve cells and the muscle cells. These cells are capable, when stimulated, of producing an ' action potential '.	6. In this and the next page, we will discuss how the resting potential and the action potential are created.

B. Creation of the Resting Potential:

1. To create a resting potential, the following four components are required: - a cell membrane - sodium-potassium pumps located in the cell membrane - potassium channels - potassium ions	1 
2. The sodium-potassium pumps, continuously, potassium ions into the cell and sodium ions out of the cell. Therefore, the concentration of potassium will become higher inside the cell than outside the cell. This is called the 'concentration gradient' for potassium ions.	2 
3. Then, because the potassium channels, in the resting membrane, are open, the potassium ions will flow (=diffuse) out of the cell (from high concentration inside to low concentration outside).	3 
4. Every time potassium ions flow out of the cell, small positive charges are also taken out of the cell, leaving behind negative potentials.	4 

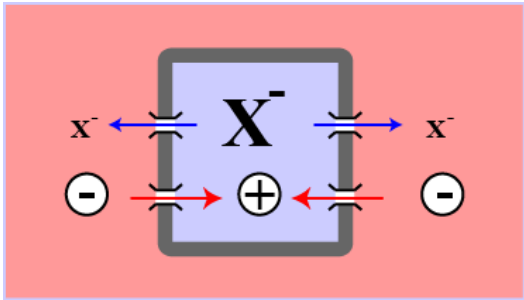
5. This makes the inside of the cell gradually negative (and outside positive). In other words, a potential gradient is being created (= this is the resting potential!).	5 
6. This potential gradient is opposite to the concentration gradient (since there are many more positive potassium ions inside than outside the cell).	6 
7. Once the potential gradient is equal (but opposite!) to the concentration gradient, then equilibrium will have been reached and both gradients remain stable.	8. The potential reached at this stage is called the 'equilibrium potential'. Because this relates in this case to potassium, this is called the E_{K^+}. (=Equilibrium potential for potassium)

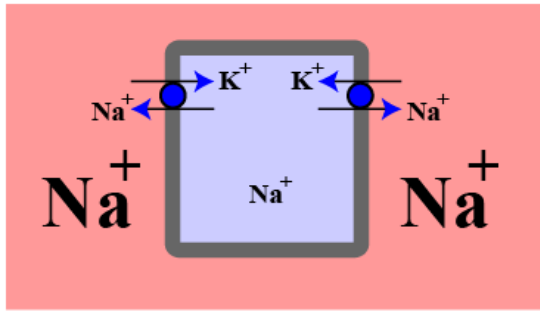
C. Some important Notes:

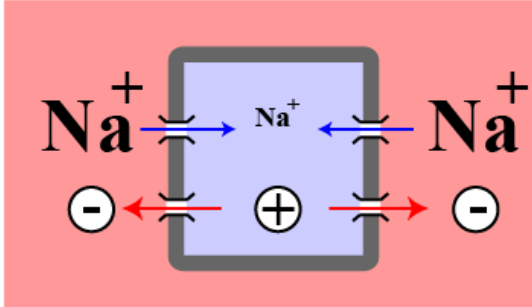
1. Students often come up with the following problem; does the concentration gradient not decrease when the potassium ions diffuse outside? The answer is; yes but very little. Charge and concentration are not the same. In fact, very little potassium diffusion is necessary to induce a large potential difference.	2. There is sometimes confusion about cause and effect! The sequence must be very clear: - The pump generates the concentration gradient. - The concentration gradient generates the electrical gradient!
3. So, this is the correct sequence: Na-K pumps -> concentration gradient for K^+ -> electrical gradient (resting potential).	

4. If something would decrease or stop the pump, then of course the concentration gradient, and therefore, the electrical gradient, would decrease and disappear.	5. As the Na-K pump needs energy (=ATP), anything that affects the energy supply, will affect the resting potential.
--	--

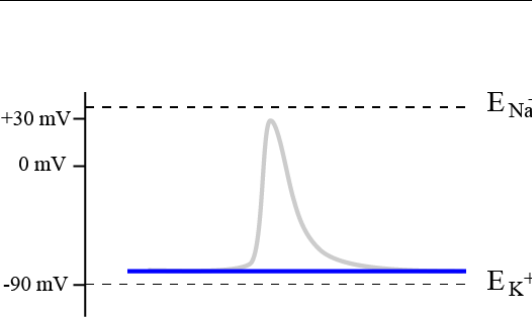
D. Some Mind Games to test if you understand the physiology of the resting potential!

1. As a mind experiment, you could figure out, in this example, what would the potential gradient become if the (potassium) ion was not a positive but a negative ion?	 The diagram shows a central blue square representing the cell interior, containing a large X^- ion. This square is surrounded by a red area representing the extracellular space. On the left and right sides of the blue square, there are pairs of arrows: a blue arrow pointing outwards and a red arrow pointing inwards. Below each pair of arrows is a circle containing a minus sign ($-$), indicating negative charges outside the cell.
<i>(Answer: resting potential becomes positive inside the cell)</i>	

2. Another (simple) mind experiment: The Na-K pump also pumps sodium ions out of the cell. What then is the concentration gradient for sodium?	 The diagram shows a central blue square representing the cell interior, containing a Na^+ ion. This square is surrounded by a red area representing the extracellular space, which contains large Na^+ ions. On the top left and top right of the blue square, there are blue circular pumps. Each pump has a red arrow pointing outwards (towards the extracellular space) and a blue arrow pointing inwards (towards the cell interior). Above each pump, Na^+ and K^+ ions are labeled, indicating the movement of these ions across the membrane.
<i>(Answer: High sodium concentration outside and low inside the cell).</i>	

3. Following on that experiment; if the channels for potassium were closed and the channels for sodium ions were open, what would the sodium ions do and what would happen to the potential gradient?	 The diagram shows a central blue square representing a cell. Outside the cell (top and bottom) are three large Na^+ ions. Inside the cell (top and bottom) are three smaller Na^+ ions. Below the cell, there are three circles representing charges: a negative charge (-) on the left, a positive charge (+) in the middle, and a negative charge (-) on the right. Blue arrows point from the outside Na^+ ions into the cell, and red arrows point from the inside Na^+ ions out of the cell.
<i>(Answer: Sodium ions will flow into the cell, as they are attracted by the negative potential, taking positive charges with them; this will make the inside positive). (Hint: this is actually how the action potential starts!)</i>	

E. More in depth: Equilibrium Potentials.

1. When a cell achieves equilibrium between the concentration gradient and the (opposite) electrical gradient for a particular ion, the cell is then at its 'equilibrium' (= 'E').	2. In the case of potassium ion, of which there many more inside the cell than outside, the equilibrium potential will be negative inside the cell, as discussed above.
3. For sodium ions, of which many more ions are located outside the cell than inside, the equilibrium potential will be positive! (see Mind Game #D3).	 The graph shows membrane potential in mV on the y-axis. A horizontal blue line is at -90 mV, labeled E_{K^+}. A dashed horizontal line is at +30 mV, labeled E_{Na^+}. A grey curve starts at -90 mV, rises sharply to a peak at +30 mV, and then falls back to -90 mV.
4. These two equilibrium potentials are very important in order to understand the generation of the action potential (next page).	
5. In this diagram, I have plotted the values of E_{Na^+} (= +35mV) and E_{K^+} (= -90mV).	
6. And, between these two, a shadow of an action potential (see <i>next page!</i>).	

7. Please note that the resting potential is not the same as the Equilibrium potential for potassium. In fact, the resting potential is slightly less negative than the E_K .	8. This is because the cell membrane is not perfect; there are always some sodium channels open and therefore some sodium ions will leak into the cell making the inside less negative than the Equilibrium potential for potassium.
--	---

F. More in depth: The Nernst Equation.

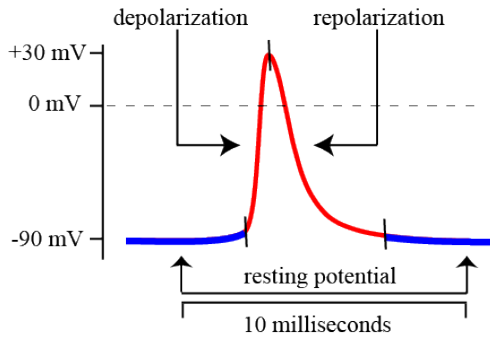
1. In fact, if you know the intra- and extracellular concentrations of a particular ion, you can calculate its Equilibrium potential!	Nernst potential: $E = \frac{RT}{F} \ln \frac{(\text{ions outside the cell})}{(\text{ions inside the cell})}$
2. This was first developed by Walter Nernst, a German chemist who got a Nobel prize in 1920 for his work!	3. The R, T and F are physical constants that don't change in normal physiology (<i>see below</i>).
4. So, in the case of potassium ions , and given the usual concentration difference in a muscle cell, the Nernst formula would look like this:	Nernst potential for K^+ : $\frac{RT}{F} \ln \frac{(5 \text{ mM})}{(140 \text{ mM})} = -84 \text{ mV}$
5. And, in the case of sodium ions , the Nernst potential would look like this:	Nernst potential for Na^+ : $\frac{RT}{F} \ln \frac{(140 \text{ mM})}{(12 \text{ mM})} = +66 \text{ mV}$

R = ideal gas constant; T = temperature in Kelvin; F = Faraday's constant

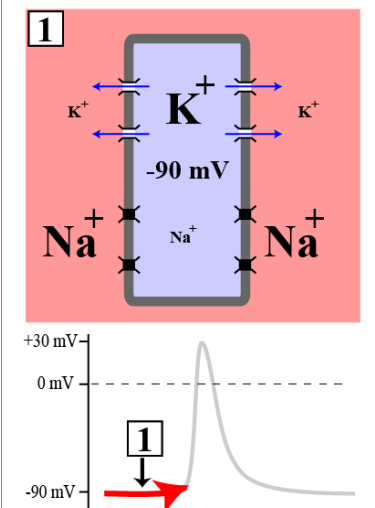
A.3.3. The Action Potential

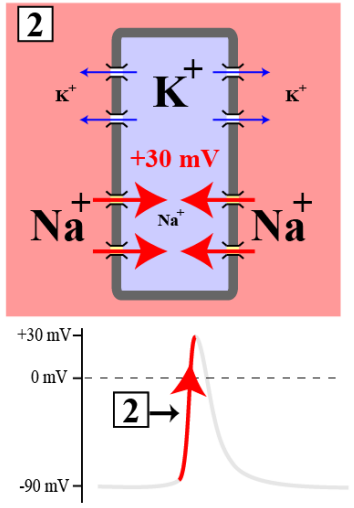
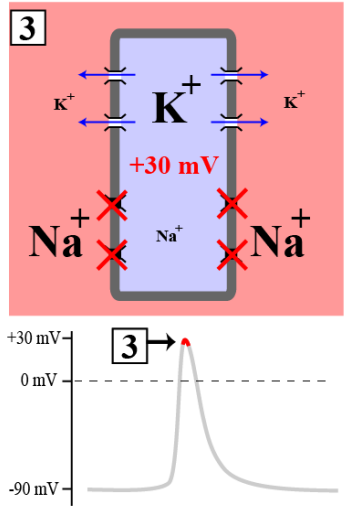
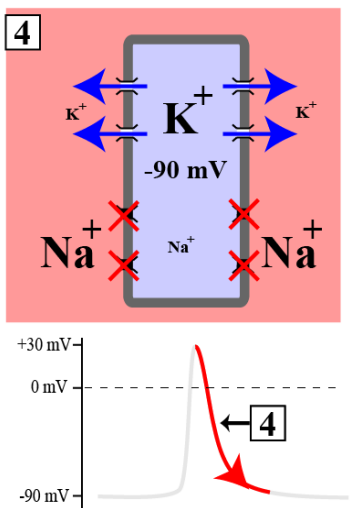
Introduction: an action potential is an electrical impulse that is used in the body to transmit information (in the nerves and the brain) or to initiate an action (such as contraction of a muscle or secretion from a gland).

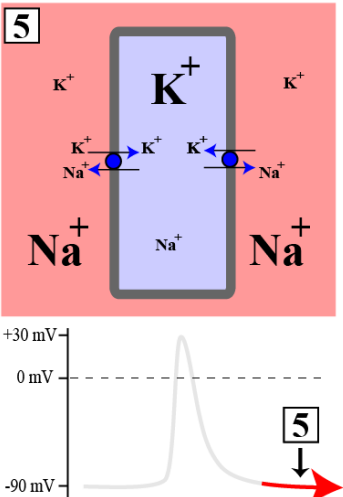
A. What is an Action Potential?

1. An action potential is a sudden change in the membrane potential. In the diagram, in red, the potential suddenly changes from the resting potential (approx. -90 mV; blue) to +30 mV (red). After a few milliseconds, the membrane potential returns to the resting potential.	
2. The initial phase is called the depolarization (because the potential goes from very negative to zero; 'de' = less potential difference).	3. The potential actually crosses the zero level and reaches values up to +30 mV (inside positive!). The restoration of the potential back to the resting potential is called the repolarization.

B. How is an Action Potential created?

1. Remember, in the resting state, that the inside of the cell is negative (-90 mV) because of the potassium concentration gradient. The potassium channels are open and therefore, there is an efflux of potassium ions and their charges, making inside negative and outside positive.		2. There is also a sodium concentration gradient, induced by the same sodium-potassium pump. But this sodium concentration gradient is opposite to the potassium gradient; there is much more sodium outside then inside the cell. However, at rest, the sodium channels are closed.
---	---	--

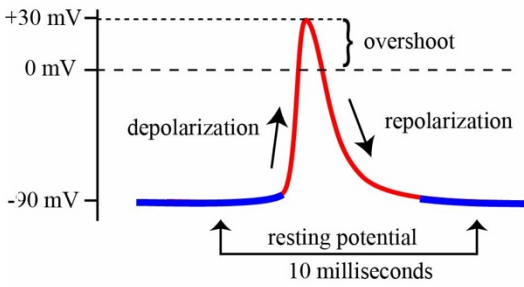
3. If the cell becomes excited (by an external stimulus), then the sodium channels will open. This will cause a massive and rapid influx of sodium ions into the cell!		4. Why is there a rapid sudden influx of sodium ions? Two reasons: a. Concentration gradient (there is less sodium ions inside then outside). b. Potential gradient (inside is negative at rest and this will attract the positive sodium ions).
5. Because of this sudden and rapid influx of sodium ions into the cell, a lot of positive charges (=potential) also flow into the cell, thereby reducing the resting negative potential. This is the depolarization and the inside of the cell now becomes positive (+ 30 mV).		6. After a little time (millisecond), the sodium channels closes (automatically; they always do; it is a property of these channels). This will stop the influx of sodium ions and stop the depolarization.
7. But the potassium channels are still open! And now the potential gradient has disappeared! Therefore, the potassium ions, once again, will flow out of the cell (efflux).		8. The potassium ions will flow out of the cell, according to their concentration gradient, and they will take positive charges with them, thereby inducing negative potential inside the cell; this process is called the repolarization. This process continues until the potential is back to the resting potential.

9. So, at the end of the action potential, the potential inside the cell is back to -90 mV (= resting potential).		10. In summary: the action potential was actually performed by the influx of sodium ions followed by the efflux of potassium ions.
--	---	--

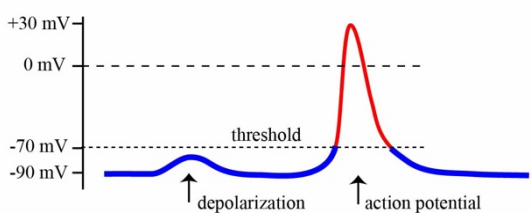
C. Some additional notes:

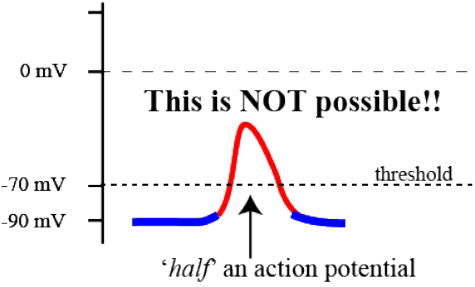
1. It is important to realize that only a small amount of sodium and potassium ions have to flow in and out of the cell to depolarize and repolarize the cell. But it does mean that the concentration gradient for Na^+ and K^+ has decreased a little.	2. Still, a cell could generate thousands of action potentials before the concentration gradients have fallen to such low levels that action potential generation has become impossible.
3. Fortunately, it is of course the sodium-potassium pump that will restore this concentration gradient. As this pump works continuously, as it were in the background, the concentration gradients will be kept at their required levels.	4. Of course, the pump will only work if it gets ATP (=energy). This is typical of a living cell. If the cell dies, ATP formation stops, the pump stops and the concentration and electrical gradients will gradually disappear.

D. Overshoot of an Action Potential:

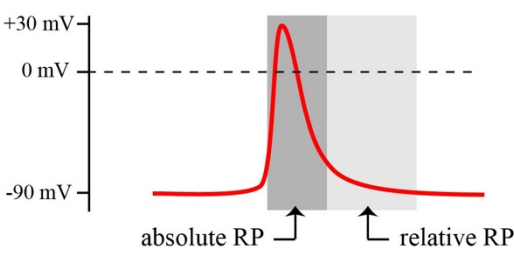
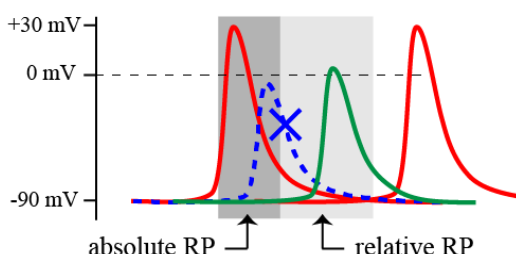
1. As we said above, the initial phase of the action potential is called 'depolarization' and the second phase is called the 'repolarization'.	 The graph shows the membrane potential in mV on the y-axis (ranging from -90 to +30) against time on the x-axis. A blue line represents the resting potential at -90 mV. A red line shows the action potential: it rises sharply (depolarization) to a peak at +30 mV (overshoot) and then falls back to -90 mV (repolarization). A bracket labeled 'resting potential' spans the blue line, and a bracket labeled '10 milliseconds' indicates the time scale.
2. The word 'depolarization' means 'decrease in polarization'. This is because, in the old days, physiologists believed the potential, during the action potential, decreased to zero.	3. Later, it was discovered that the depolarization did not stop at zero but continued into a positive potential, usually about +30 mV. We now call this positive potential, an overshoot!
4. However, we still call the change of potential from -90 to +30 mV '<i>depolarization</i>', although this is technically not fully correct.	5. The same reasoning applies of course to the 'repolarization'.

B. Threshold of an Action Potential:

1. Another important concept in the context of creating an action potential is the concept of the 'threshold'.	 The graph shows the membrane potential in mV on the y-axis (ranging from -90 to +30). A blue line shows a small depolarization from -90 mV to -70 mV, labeled 'depolarization'. A dashed line at -70 mV is labeled 'threshold'. A red line shows the action potential starting once the threshold is reached, peaking at +30 mV and then falling back to -90 mV, labeled 'action potential'.
---	--

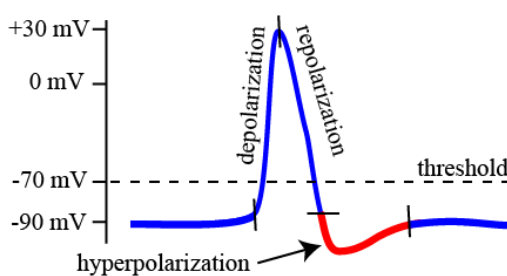
2. In this diagram, you can see at first that there is a small fluctuation, a small depolarization, which does not reach the value of the threshold (in this case about -70 mV).	3. These small depolarizations are caused by local potentials, hormones, or chemical transmitters flowing from neighboring cells or areas.
4. If such a fluctuation is strong enough, then this will cause enough sodium channels to open, which will cause a massive influx of sodium ions into the cell and induce a fully-fledged depolarization.	5. In other words, if a depolarization is strong enough to reach threshold, this will generate an action potential. If the depolarization is not strong enough, there will not be an action potential.
6. In other words, it is not possible to have a small action potential or half an action potential or something like that; it is either a full action potential or not at all. This is called the 'all-or-none' law.	

F. The Refractory Period of an Action Potential:

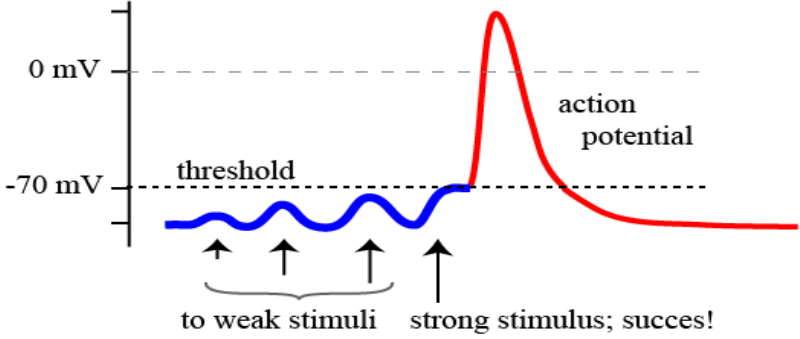
1. One more important concept: the refractory period! This is the period, during and after the action potential, during which, another action potential cannot be generated.	2. This is caused by the fact that the sodium channels, after they have opened and (automatically) closed, are for a short period, not able to open again. During that period, these channels are inexcitable.
	

3. In classic physiology, there are two types of refractory periods; a) the absolute refractory period b) the relative refractory period.	4. During the absolute refractory period, which starts immediately at the depolarization of the action potential, it is absolutely not possible to induce a new action potential (illustrated as the blue dashed action potential in the figure).
5. During the relative refractory period, it is possible to induce a new action potential but it takes more strength (more energy or electricity), as shown by the green action potential in the figure. The action potential is then often somewhat smaller (as not all channels are fully excitable again).	6. After the relative refractory period, all sodium channels are excitable again and a full action potential can again be generated (second red action potential).

G. Advanced 1: Hyperpolarization

1. In some (nerve) cells, after the repolarization, the membrane potential ‘undershoots’ below the resting potential. This is called ‘hyperpolarization’ (= more negative than the resting potential) or ‘after potential’.	
2. This happens when the potassium channels become even more open than before. After some time, the potassium channels go back to their normal state and the membrane potential stabilizes at the normal resting level.	3. Important is that during this brief period; the potential is further ‘away’ from the threshold making it more difficult to initiate an action potential during this period.

H. Advanced 2: Threshold; positive feedback loop!

1. There is something interesting about the threshold, the potential at which a membrane potential has to reach before generating a full-blown action potential.	2. Remember that an action potential is generated by an (electrical) impulse that depolarizes the membrane at a location.
3. This local depolarization is due to the opening of some of the sodium-channels in that location, which therefore allows some sodium-ions to flow into the cell.	4. However, it is important to know that the sodium channels are sensitive to the potential level across the cell membrane potential. As the resting potential decreases (=closer to zero), more sodium channels will open.
	
5. If only a few sodium-channels open, the resulting depolarization will not reach threshold and no action potential will be initiated.	6. But if the initiating impulse is strong enough, and threshold is reached, then the opening of the sodium channels, and the resulting sodium-influx, will induce more sodium-channels to open!
7. Such a cycle is called a positive feedback loop (remember the negative and positive feed back loops?). In other words, more and more sodium channels will now open until they are ALL open!	8. This is what actually happens during the depolarization phase of the action potential. It is really an explosion of sodium channels that all open in a very brief period of time.

9. Of course, the end of this ‘explosion’ occurs when all the sodium channels are open, and after a few milliseconds, automatically start to close!	10. This marks the end of the depolarization (and high time to start the repolarization!)
--	--

A.3.4. Action Potential Propagation

Introduction: An action potential is propagated along the cell **membrane** of a nerve or a muscle cell.

Structural and physiological components required:

1. A cell membrane.
2. Na^+ and K^+ ion channels in this membrane.
3. The cell has a resting potential (approx. -80 to -90 mV).

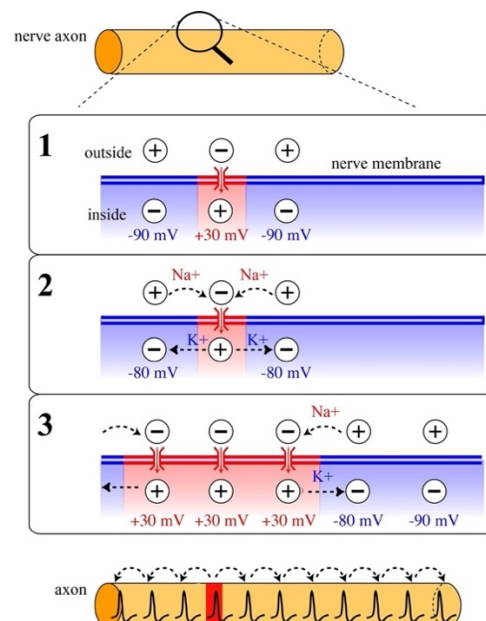
A. Propagation of an Action Potential:

1.
An action potential has been initiated (by whatever mechanism) at **one location** in the cellular membrane (indicated in panel 1 in red).

2.
This means that at that location, the inside of the cell is then briefly **positive** and the outside is **negative** (because the Na^+ channels are open and the positive Na^+ ions have flown into the cell). This occurs at the height of the action potential, during the 'overshoot'.

3.
But in the neighborhood of that activated membrane, left and right, the membrane is still **resting** and displays a resting potential: i.e. inside negative and outside positive. This membrane is still passive (blue), and its trans-membrane potential is approximately at -90 mV.

4.
Because both the activated and the resting membranes are **adjacent** to each other and bathed in extra- and intracellular fluids that contain ions, several of those ions will start to flow from one area to the neighboring area according to their charges, as shown in panel 2 with the arrows.



5. For example, inside the cell, positive ions (such as K^+) will flow from the activated region to the resting region, as they are attracted by the negative polarity in those regions. Similarly, outside the cell, positive ions (such as Na^+) will flow from the resting area to the central activated area.	
6. These current fluxes or current circuits (as these are called) will affect the resting potential in the neighboring resting membranes. The flux of positive K^+ ions inside the membrane will decrease locally the negative resting potential.	7. At the same time, the removal of positive Na^+ ions outside the membrane adjacent to the activated area will decrease the local positive potential; hence the difference between the inside and outside becomes less.
8. In this example, the potential difference across the neighboring membranes is decreased from -90 mV to -80 mV. This is a local depolarization, and the potential comes closer to the threshold.	9. When the depolarization in the neighboring resting membrane reaches threshold, a new action potential is generated at that new location. This is indicated in panel 3; that part of the membrane now shows a full action potential with a value of $+30$ mV. In other words, the action potential has now ‘moved’ or propagated (or ‘jumped’ or ‘conducted’; they all mean the same thing) to this new location.
10. Because in this example the action potential started in the middle of the membrane, the action potential will depolarize the membrane both to its left and to its right; both will reach threshold and both will show a new propagation. In other words, the action potential is propagating in both directions, left and right.	11. These new action potentials will then influence the next piece of resting membrane, initiate a new action potential and the whole story starts all over again.

12.

So, **step-by-step**, the action potential generates every time a new action potential in 'front' of itself. This is called 'propagation'!

B. Some important Notes

1.

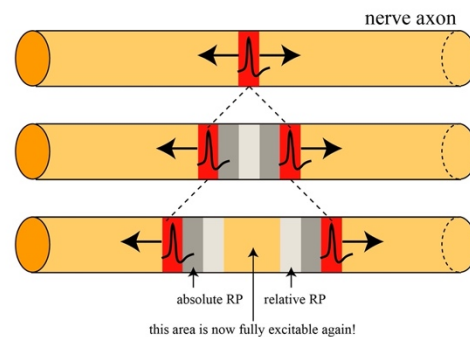
This propagation is quite fast as it depends on the speed of opening of the Na^+ channels and the flux of ions in- and outside the membrane.

2.

Propagation can occur in any direction, forward or backward, left or right, because the structure of the membrane, with its potassium and sodium ion channels, is the same in all directions.

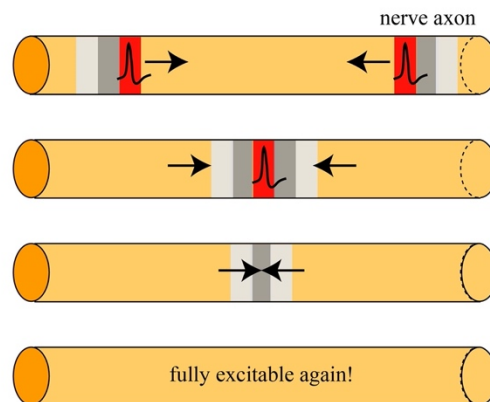
3.

Once an action potential is propagating in one direction, it **cannot turn back**. That is because the part of the membrane that has been activated with an action potential is now **refractory**. This means that the membrane cannot be re-activated again for a (short) time period. This period is called the **refractory period**.



4.

If two separate action potentials propagate towards each other in the same membrane they will eventually **collide**. Because each action potential cannot activate the channels that were already activated by the other action potential (= because they are refractory/inactivated) both action potentials will **stop** propagating. They therefore cannot 'cross' each other such as waves in the sea can.



5. Propagation of the action potential, once initiated, continues ‘automatically’ as described here. But where does it stop? In general, the action potential stops propagating when it reaches the end of the membrane, at the end of the cell.	6. In small cells, this is quickly achieved but some cells can be quite long such as for example the axons of nerve cells; these can reach many centimeters up to a meter in length (the axons in the leg for example; these run from the lower part of the spinal cord all the way to the big toe!).
--	---

C. But, we have a problem here!

1. In the previous paragraphs, we have described the propagation of an action potential along the membrane of a cell. This propagation is not very fast; about 0.25 cm/sec.	2. In most cases, this is absolutely fine. In small cells, the speed of this propagation is good enough to pass on a message.
3. However, some nerve cells are very long. This is the case for example in the arms and the legs when the cell body is located in the spinal cord and the synapses are located in the hand or the feet, several feet (or meters) away.	4. At a speed of 0.25 cm/sec, it will take 4-6 seconds to pass the message to the muscles in your feet and your big toe! This takes too much time!
5. How can we speed up the propagation of the action potential? Fortunately, nature, during the evolution of the body, has provided for a solution!	6. The solution is to speed up the propagation speed of the action potential by a system that is called “saltatory propagation”. This is discussed in the next page!

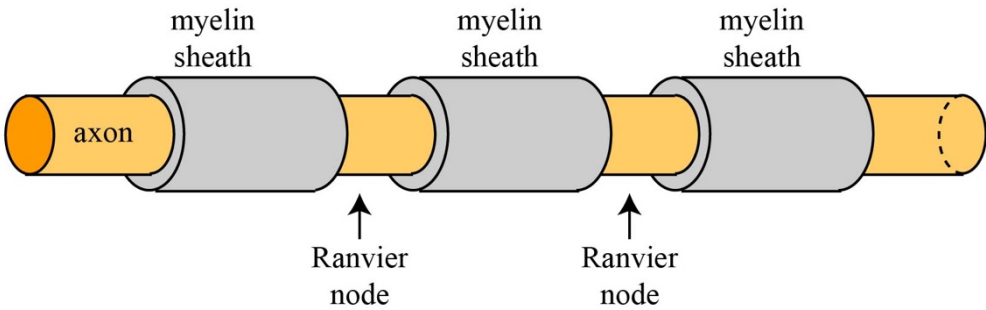
D. We also have a second problem:

1. On this page, we have described the propagation of an action potential, along the cell membrane, in one cell.	2. In many cases, the action potential has to propagate into a next, adjacent, cell. How is this done?
3. Propagation from one cell to another is a very different issue and is dealt with in two different ways:	4. a) in the electrical synapse b) in the chemical synapse .

A.3.5. Saltatory Propagation

Introduction: ‘Saltatory’ propagation is a special type of propagation for the action potential. It only occurs along the ‘very’ long axons of nerve cells. The purpose of this type of propagation is to increase the **speed** of propagation.

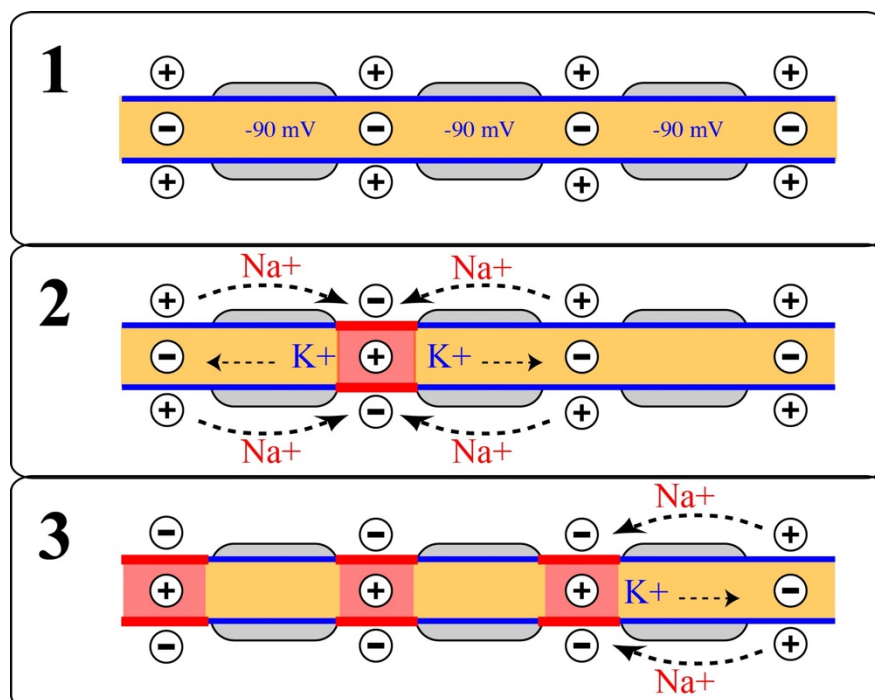
A. Structural and physiological components required:

1. A cell membrane, along an axon, with Na^+ and K^+ ion channels located in this membrane.	2. A myelin sheath wrapped around the axon. This sheath is interrupted by nodes of Ranvier . The myelin sheath is like an insulator that isolates the axon membrane from the extracellular fluid.
 The diagram illustrates a segment of a myelinated axon. It consists of a central orange cylinder labeled 'axon'. This axon is covered by a grey, segmented layer labeled 'myelin sheath'. The gaps between these segments are labeled 'Ranvier node' with arrows pointing to them. The axon ends on the right with a dashed line, indicating it continues.	
3. The nodes of Ranvier are the locations where the cellular membrane of the axon is in contact with the extracellular fluid.	4. The Na^+ and K^+ ion channels are only located at those Nodes of Ranvier (spoken as ‘ranveer’)

B. Saltatory Propagation; how does it work?

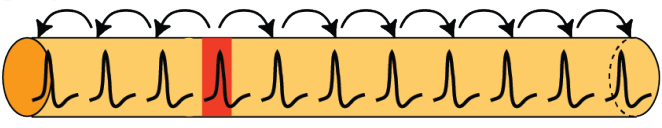
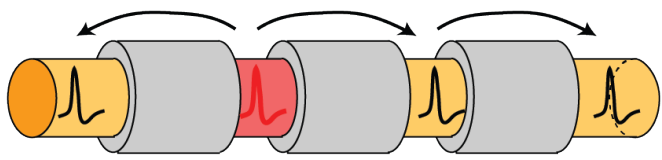
1. The potential distribution in a myelinated axon is the same as in a ‘naked’ axon. Inside is negative and outside is positive (see panel below).	2. In panel 2, an action potential has been initiated (by whatever mechanism) in one node of Ranvier panel (red color)
---	---

3. This means that at that location, the inside of the cell is then positive and the outside is negative. This occurs at the height of the action potential, during the overshoot.	4. Similar to normal electrical propagation, the neighborhood, left and right of this activated membrane, are still at rest and displays a resting potential: i.e. inside negative and outside positive.
5. In contrast to normal electrical propagation however, the next available channels are located further away, at the next node. The myelin sheath between these two nodes works as an insulator to the extracellular current flow.	6. In spite of the larger distance (0.5 – 2 mm max), there is still sufficient flow of ions (K^+ inside and Na^+ outside) between the active site and the two (left and right) resting sites (panel 2).



7. These current fluxes or current circuits (as these are also called) will influence the resting potential of the resting membrane in the left and the right node.	8. So, the flux of positive K^+ ions inside the membrane will decrease the negative resting potential while the removal of positive Na^+ ions outside the membrane will decrease the positive potential.
9. Hence the difference between the inside and outside becomes less, inducing a local depolarization, just like during a normal propagation.	10. When the depolarization of the resting membrane in the neighboring nodes reaches threshold, a new action potential is generated at these nodes.
11. This is essentially the same process as with normal propagation; the only difference is that saltatory propagation 'skips' a piece of the membrane.	12. Then, this new action potential will influence the next patch of resting membrane in the next node of Ranvier and the whole story starts all over again (panel 3).

C. In summary: small steps vs. LARGE steps!

1. A local action potential, by influencing the flow of ions in its neighborhood, will effectively induce a new action potential in the next node of Ranvier. The action potential propagates therefore in larger steps from one node of membrane to the next and so on.	2. Because it makes bigger steps, the propagation will go faster (think of running with big steps in contrast to running with many small steps).
niet-gemyeliniseerde axon:  gemyeliniseerde axon:  © BasicPhysiology.nl	

D. Some important Notes:

1. The big difference between normal propagation and saltatory propagation is speed . In normal propagation, the action potential is making small steps and that takes time. In saltatory propagation, these small steps are avoided by the myelin isolation that forces the action potential to make bigger steps.	2. Normal propagation along a non-myelinated axon is typically in the range of 0.5-1 m/sec. In myelinated axon, this ranges from 15 to 150 m/sec (i.e. 30-150x faster!)
3. Saltatory propagation is much faster than normal propagation because most of the distance is covered by current flow of ions, which is very fast. In normal propagation, this flow is each time interrupted by having to induce a new action potential, which has to reach threshold, and then to depolarize and reach the overshoot, before the next current flow starts etc.	4. The term 'saltatory' means 'jumping' (salto = a leap), as in ' <i>Salto Mortale</i> ' (= a deadly or daring jump!)
	5. As with normal propagation, saltatory propagation can occur in any direction. Normally however, the propagation occurs from the soma to the pre-synaptic terminals.

E. Nice to know:

1. In primitive animals, such as the squid, there are also nerve cells and axons but these axons are not myelinated.	2. You only see myelinated axons in more advanced animals such as vertebrates (although some invertebrates, like the shrimp, do have myelin-like structures).
3. The theory is that during evolution, the nervous system became more complicated and needed faster propagation to control the body.	4. Therefore, myeline structures were developed to force the action potential to propagate faster.

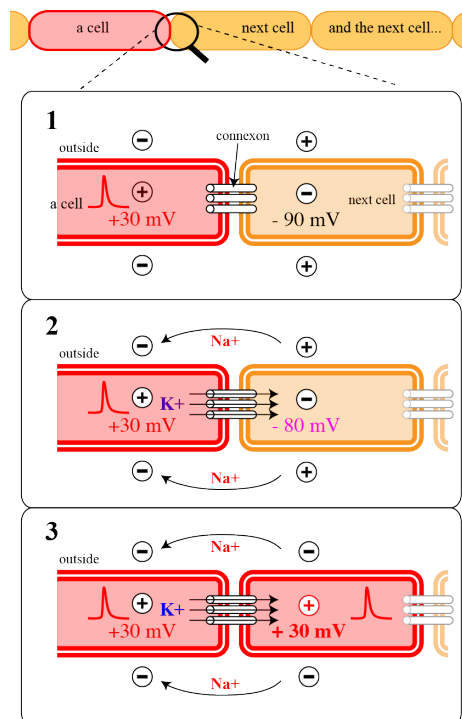
5. There are several diseases, such as multiple sclerosis, in which the myelin cells are destroyed.	6. Although a lot of research is going on in this area of demyelination, a treatment is not yet available.
--	---

A.3.6. The Electrical Synapse

Introduction: In previous pages, we discussed how the action potential propagates along the membrane in one single cell. But action potentials can also propagate from one cell to the next cell. On this page, we will discuss one type of propagation from one cell to the next; the electrical ‘synapse’.

A. Function of an electrical synapse:

1. In the ‘electrical’ synapse, there is a special structure joining (or ‘bridging’) neighboring cells; the connexons .	2. These connexons are molecules shaped like long little tubes that run from one cell to the next; small ions, such as K^+ , can flow through them.
3. In this diagram, the two cells are connected with several connexons.	4. An action potential has been initiated in the left cell (red cell). The inside of the cell is therefore positive (+30 mV) and the outside is negative.



5. The next cell (right) is still in the resting phase and the membrane potential inside is therefore negative (brown), usually -90 mV.	6. Outside the cell, in the extracellular fluid, the situation is very similar to that during electrical propagation along a membrane.
7. Therefore, sodium ions, which are positive, will be attracted by the depolarized membrane and flow away from the resting cell towards the excited cell.	8. Inside the excited cell, the potassium ions are attracted to the negative resting potential in the resting cell (right). These ions can flow into that cell through the tubular connexons.
9. Because of this external and this internal ion flow, the membrane potential in the resting cell will decrease (in this case from -90 to -80 mV; panel 2).	10. This depolarization will reach threshold and an action potential is initiated in the next cell (panel 3).
In Summary: An action potential in one cell, by inducing a flow of potassium ions from this cell to the next through the connexons, will induce a new action potential in the next cell. The action potential propagates therefore in steps from one cell to the next.	

B. Important notes:

1. This process is nearly as fast as the propagation along a membrane and much faster than transmission in a chemical synapse _(see next page).	2. That is because in an electrical synapse, the speed depends on the flow of ions through the connexons.
3. As with propagation in a single cell, the direction of propagation is bi-directional . If cell 2 had been activated first, then the action potential would as	4. Also important: the ratio of propagation is 1:1. This means that propagation is always successful (in a normal tissue). If the first cell is activated, then, after a

easily have propagated from the second to the first cell (from right to left in the panel).	small delay, the second cell will also be activated.
5. It is important to realize that this electrical propagation from one cell to another is only possible if the connexons are open.	6. If the connexons are not open, then there will be no intracellular current flow from one cell to the next, and therefore the threshold will not be reached and propagation is then stopped. This is not normal but can occur in pathological situations.
7. In the brain, chemical synapses are more common than electrical synapses but in other tissues, especially in the heart and in smooth muscles, electrical synapses are very common.	

A.3.7. The Chemical Synapse

Purpose: A chemical synapse transmits electrical signals (= action potentials) from one nerve cell to the next.

Structural and physiological components required:

4. A pre-synaptic membrane in the first nerve cell
5. This pre-synaptic membrane contains Na^+ , K^+ and Ca^{2+} ion channels.
6. Vesicles in the pre-synaptic cell that contains the (neuro-) transmitter
7. A post-synaptic membrane in the second nerve cell
8. The post-synaptic membrane contains receptor operated channels (=ROC)

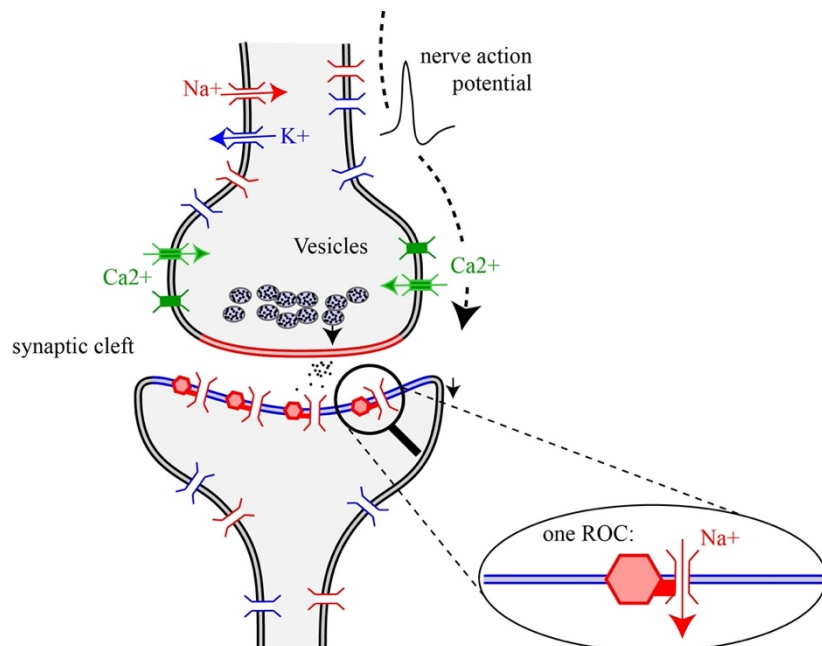
A. Function of a chemical synapse:

1.

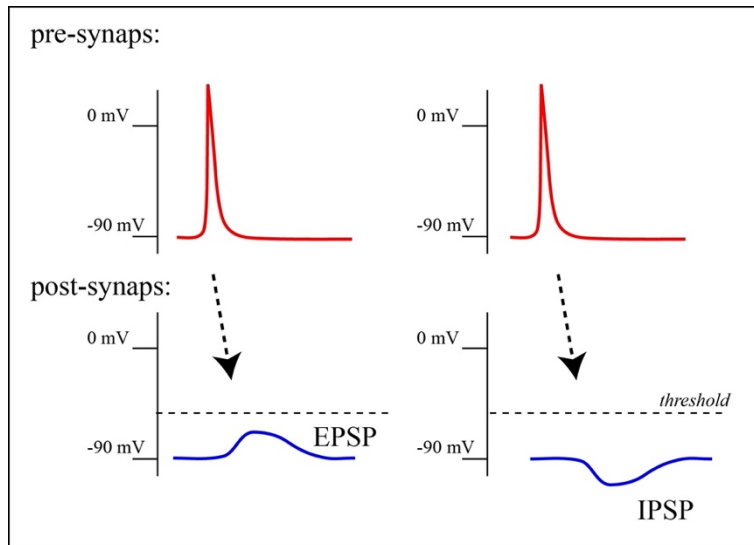
A nerve action potential propagates down the axon of the first nerve cell towards the pre-synaptic membrane (thereby opening and closing the relevant Na^+ and K^+ channels)

2.

When the action potential arrives in the pre-synaptic membrane, it also opens the Ca^{2+} channels.



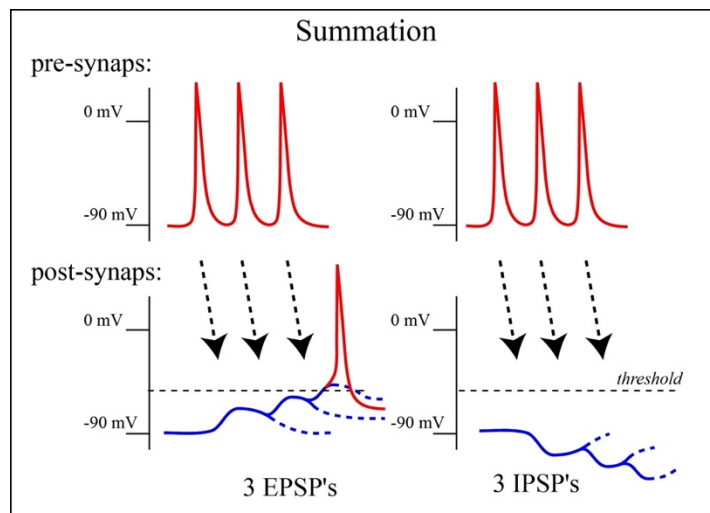
3. Because of the concentration gradient for calcium, calcium ions will then flow into the cell	4. This intracellular calcium will induce one of the vesicles to move towards the pre-synaptic membrane	5. Once at the pre-synaptic membrane, this vesicle will fuse with the membrane and release its content (the neurotransmitter) into the synaptic cleft. This process is called exocytosis (<i>link; A.2.4. Active Transport Systems</i>).
6. The transmitter diffuses into the synaptic cleft and some of it will reach the post-synaptic membrane	7. The transmitter can then couple to the receptors located in the post-synaptic membrane	8. These receptors are linked to ion channels (= receptor operated channels = ROC).
9. The linkage of the transmitter to the receptor will open that channel.	10. As more and more transmitters attach to the receptors, more and more channels will open.	11. Opening the channels will cause a flow of ions in or out of the post-synaptic cell (influx or efflux)
12. These ions will cause either a depolarization or a hyperpolarization around that membrane	13. If the membrane depolarizes , then this potential is called an EPSP (= Excitatory Post Synaptic Potential).	14. If the membrane hyperpolarizes , then this potential is called an IPSP (=Inhibitory Post Synaptic Potential).



B. IPSP's or EPSP's?

1. Usually, a single pre-synaptic action potential will only cause a small change in potential in the postsynaptic membrane, either a depolarization or a hyperpolarisation.	2. Whether or not the potential is an EPSP or an IPSP depends on the transmitter, the receptor and the attached ion channel. Some synapses are excitatory (EPSP) while others are inhibitory (IPSP) in nature.	3. In the case of an IPSP synapse, the membrane potential moves further away from the threshold potential. This is inhibition as it makes it more difficult for the next action potentials to reach threshold (= inhibition).
4. In the case of an EPSP synapse, the membrane potential moves closer to the threshold potential but usually does not reach the threshold. Therefore, an action potential is not (yet) generated.	5. It must be realized that EPSP's and IPSP's are local and temporary potential changes . They do not propagate to the rest of the nerve cell.	6. Therefore, an EPSP or an IPSP, by itself, has no effect at all. They will only have an effect if something else happens, and that is summation .
7. Meanwhile, the transmitters in the synaptic cleft and those	8. They cannot stay there because this would keep the channels open and the	9. Fortunately, there are enzymes in the synaptic cleft that break down the

coupled to the receptors must be removed and inactivated .	membrane in a permanent de- or hyper-polarized state and the whole transmission would be stopped.	neurotransmitters. Often, these broken components are recycled into the pre-synapse to make new transmitter molecules in new vesicles.
---	---	---



C. Summation of EPSP and/or IPSP's

1. In contrast to action potentials, EPSP's and IPSP's can summate on 'top' of each other (figure).	2. Because the duration of the EPSP's is much longer than the action potential, the second EPSP can be initiated while the depolarization of the first EPSP is still present.	3. Therefore, the second EPSP starts at a more depolarized level and achieves a more depolarized value, which is closer to the threshold.
4. A third EPSP will again start at a higher level and, as shown in the figure, reaches threshold , thereby (finally!) inducing an action potential. That action potential will then propagate to the rest of this nerve cell.	5. Please notice in this example, that three pre-synaptic potentials were required to generate a single action potential in the post-synaptic membrane.	6. In general, this ratio is about 10: 1 (10 pres-synaptic potentials are required to make 1 post-synaptic action potential).

D. Important comparisons with the electrical synapse (previous page):

1. This process of action potential transmission is much slower than the propagation along a nerve membrane and also much slower than transmission in an electrical synapse .	2. That is because in an electrical synapse, the speed depends on the flow of ions through the connexons. In a chemical synapse, the speed is mostly determined by the diffusion of the transmitter through the synaptic cleft. This is very much slower .
3. Also, in contrast to the electrical synapse, the direction of propagation in a chemical synapse is one-directional . If the nerve of the post-synaptic membrane had been first activated, then there are no vesicles in that part of the structure to diffuse back to the pre-synaptic membrane, nor are there ROC's in the presynaptic membrane for the transmitter to couple to.	4. In other words, the whole structure of pre- and post-synaptic membranes, of the vesicles and the ROC's, dictates the direction of propagation.
5. Also, in contrast to the electrical synapse, the ratio of propagation is not 1:1. In general, there are many (usually about ten) action potentials necessary to depolarize the post-synaptic membrane, to reach threshold and to generate one action potential in the next cell.	6. This is not the case in an electrical synapse . In an electrical synapse, the ratio is always 1:1.
7. In the brain , chemical synapses are more common than electrical synapses but in other tissues, especially in the heart and in smooth muscles , electrical synapses are very common.	8. So, the important differences between the electrical and the chemical synapse are: 1. fast vs. slow propagation 2. bi- vs. one-directional 3. 1:1 vs. 10:1 ratio

A.4.1. The Muscle Cell

Introduction: *(repeat of previous page)*

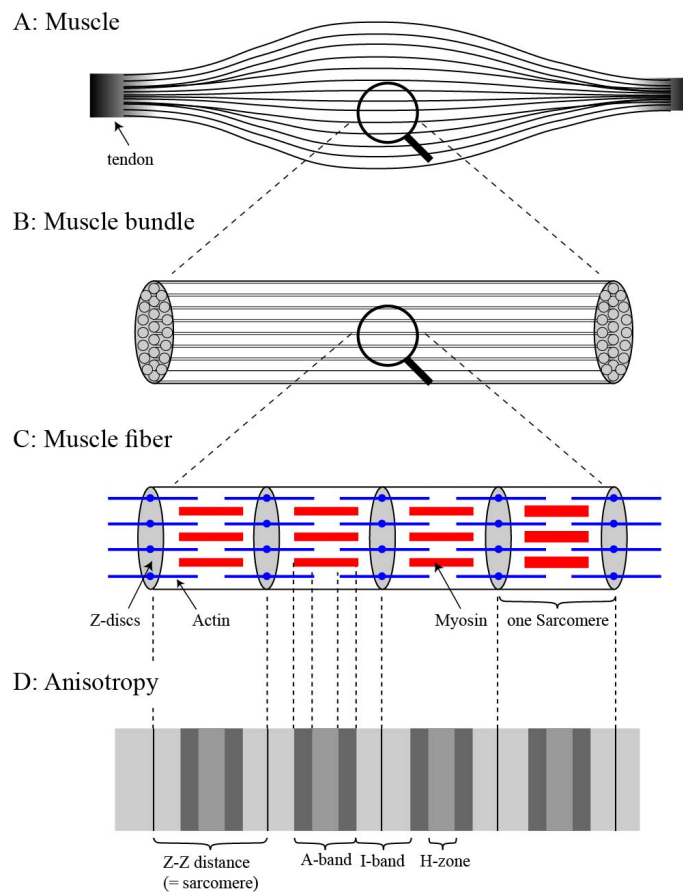
In this Basic Physiology chapter, we discuss **two** types of cells in the body that demonstrate several basic physiological principles that are very useful to know and understand before starting the study of specific organ systems. These are a) the **nerve** cells and b) the **muscle** cells. In this and the next pages, we will concentrate on the physiology of the muscle cells.

A. What is a muscle cell?

1. A muscle cell is a cell that, when stimulated, contracts .	2. The muscle cell is part of a whole muscle which, when stimulated, contracts. This makes all kind of things happen in the body.
3. There are three types of muscles in the body: a. the skeletal muscle b. the cardiac muscle c. the smooth muscle	4. The skeletal muscles are muscles that are attached to the skeleton (hence its name). Contraction of these skeletal muscles makes the skeleton move (arms, legs, walking, etc.).
5. The cardiac muscle is the heart that contracts (=pumps) to push the blood around our body.	6. The smooth muscles are muscles that are located in many organs in our body like the stomach, the intestines, the blood vessels etc.

B. The skeletal muscle cell

1. A skeletal muscle is typically long and attached to two or more tendons. The tendons, in turn, are attached to the bones of the skeleton.	2. The muscle consists of elongated cells grouped together by layers of connective tissues (called endomysium, perimysium and epimysium depending on the level of the connection from small to large)
3. The tendons and the connective tissues are all connected to each other and surround the working muscle cells.	4. One single muscle fibre (= cell) can be very long (centimetres) and very thin (10-100 microns).



5. One muscle cell contains: - several nuclei (plural of nucleus) - one motor-end plate (for connecting the motor nerve to the muscle cell) - several mitochondria for producing ATP (= energy for the contraction) > 1000 sarcomeres arranged along the cell.	6. The sarcomere is essentially the working unit of the muscle: - A sarcomere runs from one Z-disk to the next Z-disk - Sarcomeres contain two type of molecules (=myofilaments): actin and myosin - The actin molecules are attached to the Z-disks - The myosin molecules are arranged in a regular pattern between the actin molecules
---	---

C. Striation (= Anisotropy)

1. When viewed under the microscope, the skeletal muscle shows a typical striated pattern of light- and dark bands. This striation is caused by the structure of the sarcomere.	2. There are two bands; the dark A-band and the light I-band.
3. The dark A-band corresponds to the length of the myosin molecules (these are thick molecules and therefore less light is transmitted though them; hence the darkness as seen under the microscope).	4. The lighter I-band corresponds to the length of the actin molecules, which are thinner and therefore allow more light to pass through.
5. The Z-disk is hardly visible in the microscope (often called Z-line).	6. Because the Z-line is hardly visible, the I-band stretches from one A-band to the A-band in the next sarcomere.
7. Some people have also noticed and described a somewhat lighter zone in the middle of the A-band; called the H-zone. This is the zone in which the myosin	8. All this is not terribly important except for the fact that some teachers like to ask what would happen with these bands

molecules do not overlap with the actin molecules (and hence a little bit more light is transmitted through this small region).	when contraction of the sarcomere occurs (see A.4.3. The Sarcomere).
--	---

D. The cardiac and the smooth muscle cells

1. The cardiac and smooth muscle cells differ in several important ways from the skeletal muscle cells.	2. The cardiac muscle is also striated whereas the smooth muscle is not. Hence its name; smooth!
3. More pages on the cardiac and smooth muscle cells are available at link: A.4.7. Cardiac Muscle and link: A.4.8. Smooth Muscle.	

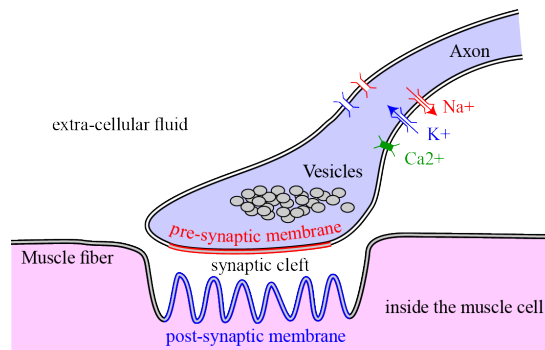
A.4.2. The Motor End Plate

Introduction:

The motor end-plate is the connection between the motor **nerve** and the skeletal **muscle** cell. Its function is to transmit the electrical signal (= action potential) from the nerve cell to the muscle cell. This is the stimulus that will make the skeletal cell contract. Another name for the motor end plate is 'neuromuscular junction' ('*neuro*' = *nerve* and '*muscular*' = *muscle*).

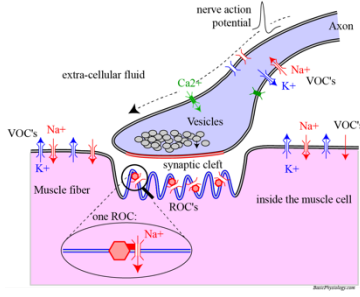
A. Structural components of the motor end plate:

1. A presynaptic membrane in the distal part of the axon
2. This presynaptic membrane also contains Na^+ , K^+ and Ca^{2+} ion channels.
3. Vesicles in the presynaptic cell that contains the (neuro) transmitter.
4. Neuro-transmitter. In the motor endplate, the neuro-transmitter is always acetylcholine (ACh)
5. A postsynaptic membrane of the muscle cell. These are typically folded (*guess why? See panel H*)
6. Receptor operated channels (=ROC) located in the postsynaptic membrane.



B. Functional Steps:

- | | |
|--|--|
| 1.
A nerve action potential propagates down the axon towards the pre-synaptic membrane. | 2.
The action potential, in the last part of the axon, opens the Ca^{2+} channels. |
|--|--|

3. Because of the concentration gradient (more calcium outside and less calcium inside), calcium ions will flow into the cell.	4. This intracellular calcium will induce one of the vesicles to move towards the pre-synaptic membrane.
5. Once at the pre-synaptic membrane, the vesicles will fuse with the membrane and release its content (acetylcholine) into the synaptic cleft. This process is called exocytosis.	
6. The transmitter molecules (Acetylcholine = ACh) will diffuse through the synaptic cleft and some will reach the post-synaptic membrane.	
7. These acetylcholine molecules will then couple to the specific receptors (ACh-receptors) located in the post-synaptic membrane.	8. The ACh-receptors are linked to ion channels (Receptor Operated Channels = ROC).
9. The coupling of acetylcholine to the ACh-receptor will open that particular channel.	10. As more and more transmitters attach to the receptors, more and more channels will open.
11. Opening of the channels will cause a flow of Na^+ ions into the post-synaptic cell (=influx).	12. These positive ions will cause a depolarization around that part of the membrane.

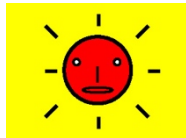
13. This potential is called a generator potential .	14. When the generator potential reaches threshold, an action potential is generated.
15. The action potential, once initiated, will propagate, along the muscle membrane, all around the cell, and into the transversal tubuli.	16. This will start the process of contraction in the sarcomeres (<i>see next page</i>).

C. Acetylcholinesterase (=AChE):

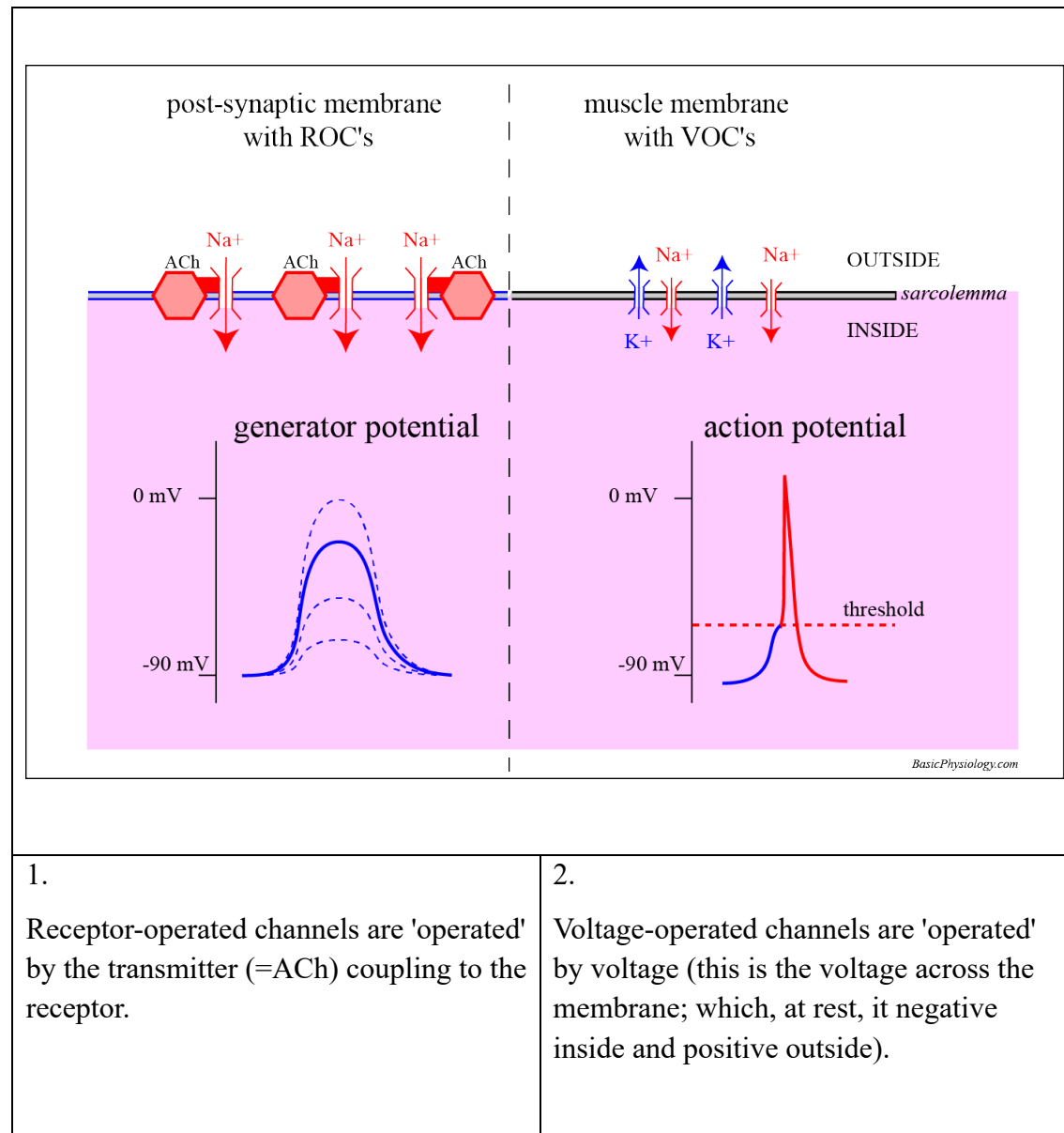
1. In the synaptic cleft, between the pre- and post-synaptic cleft, there is an enzyme, called acetylcholinesterase (= AChE)	2. This acetylcholinesterase breaks down the acetylcholine.
3. This breaking-down is a necessary step to stop the ACh from coupling continuously to the ACh-receptors.	4. Without this enzyme, the post-synaptic membrane would be constantly depolarized which will no longer induce new action potentials.

D. Curare and Curare-mimetica:

1. It is important to realize that the breaking-down of the transmitter takes place in the synaptic cleft. This is actually extracellular space (= outside the cell).	2. This makes it easy to influence this mechanism by poisons or drugs.
3. For example, curare is a well-known poison that competes with acetylcholine	4.

(ACh) to occupy the receptor-operated channels.	But, in contrast to ACh, curare does not open the channels and therefore does not induce a generator potential.
5. As curare does not induce a generator potential, it does not induce action potentials and therefore there will be no contractions. Effectively, curare induces paralysis!.	6. Curare was used by the South American Indians to kill their preys (and humans too!). The question now is how does curare kill a mammalian organism (like humans)?
7. At this point, students will often say that curare also blocks the heart .	8. But the heart is not a skeletal muscle, does not have motor-end plates, so curare cannot block these non-existing ACh-receptors.
9. But the respiration in the body is performed by contracting the muscles attached to the bones of the chest. And these are skeletal muscles.	10. So, curare paralyses the muscles of the respiration and therefore the unlucky victim is killed by suffocation!!
11. Nowadays, the pharmaceutical industry has developed curera-mimetica (mimetica = works like curare).	12. With these drugs, one can temporarily block all skeletal muscle activity. This is useful for example during surgery .
13. But then of course, one must also make sure that the respiration is not stopped. As the respiratory muscles are paralyzed, respiration is taken over by a mechanical ventilator .	14. Probably, even more important, is to make the patient unconscious .
15. Because, if the patient during surgery is not unconscious, he is effectively paralysed, and cannot scream, move or talk!	16. This is the stuff of nightmares! 

E. Difference between ROC's and VOC's:



F. Comparing a generator potential to an action potential:

1. The generator potential does not propagate and is therefore a local phenomenon (whereas the action potentials can and do propagate).	2. A generator potential is graded; it is small when only a few transmitter molecules are coupled to their receptors and becomes larger when a lot of transmitters are attached (so, not restricted by the famous All-or-None law!).
3. Therefore, if the generator potential does not reach the threshold, then there will be no action potential.	4. The generator potential also does not have a refractory period whereas the action potential does.

G. Comparing a motor end-plate to a chemical synapse:

1. In a previous page, we saw the structure and function of a <i>chemical synapse</i> ; the connection between two nerve cells.	2. In this page, we have introduced another type of chemical synapse, the motor end-plate, which connects a nerve cell to a skeletal muscle cell.
3. There are several important differences between these two structures that we need to discuss here.	4. The major structural difference is that the post-synaptic membrane in the motor end-plate is folded (<i>why?</i>) which is usually not the case in a synapse.

Motor End-plate Synaps pre-synaptic membrane synaptic cleft post-synaptic membrane Vesicles BasicPhysiology.com	
5. Crucial differences between synapse and motor end-plate: a. Transmitters b. 1:1 c. Generator potential vs. IPSP or EPSP	6. In a motor end plate, the transmitter is always acetylcholine (= ACh). In a synapse, it can be one of numerous (neuro-) transmitters (ACh, adrenaline, DOPA, etc).
7. In a motor end-plate, the transmitters always create a generator potential that depolarizes the membrane towards threshold.	8. In the chemical synapse, depending on the type of transmitter, either depolarizing (=EPSP) or hyperpolarizing (IPSP) currents are generated (See: '<i>Chemical Synapse</i>')

9. Finally, in the motor end plate, induction of a generator potential always reaches threshold (and therefore initiates an action potential in the muscle cell). Therefore, transmission of an action potential to a skeletal muscle cell is always successful. The ratio is therefore 1:1.	10. As discussed ('<i>Chemical Synapse</i> '), this is not the case in the synapse where a ratio of pre- to post-synaptic action potentials is typically 1:10.
--	---

H. Why is the post-synaptic membrane in the motor end plate folded?

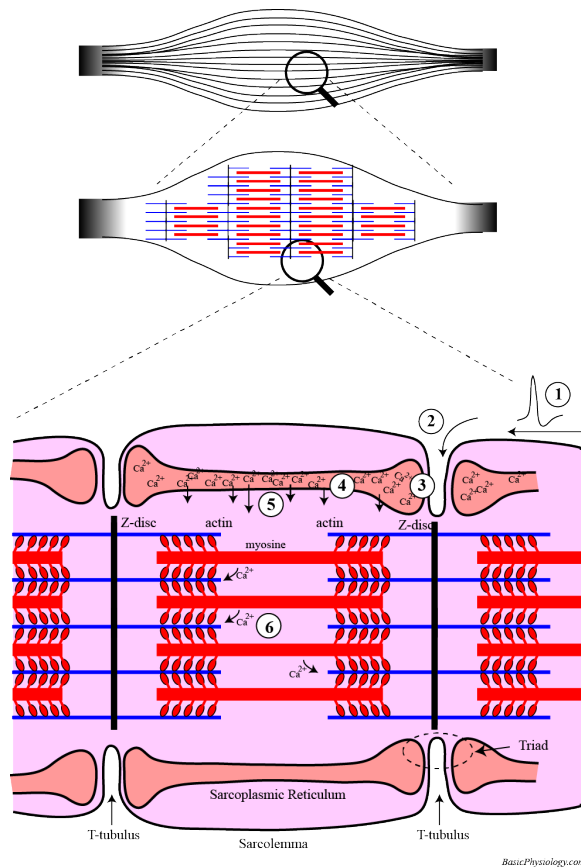
1. By folding the membrane at that location, the surface area of that part of the membrane is increased.	2. A larger surface area means that more ROC's can be located on this membrane.
3. Therefore, when ACh diffuses from the pre-synaptic membrane into the synaptic cleft, this transmitter can couple to more available ROC's.	4. This in turn will create a larger Na⁺ influx and therefore a larger generator potential.
5. This will make sure that an action potential is always created in the muscle cell.	6. In short, this folding of the membrane makes this type of synapse more sensitive!

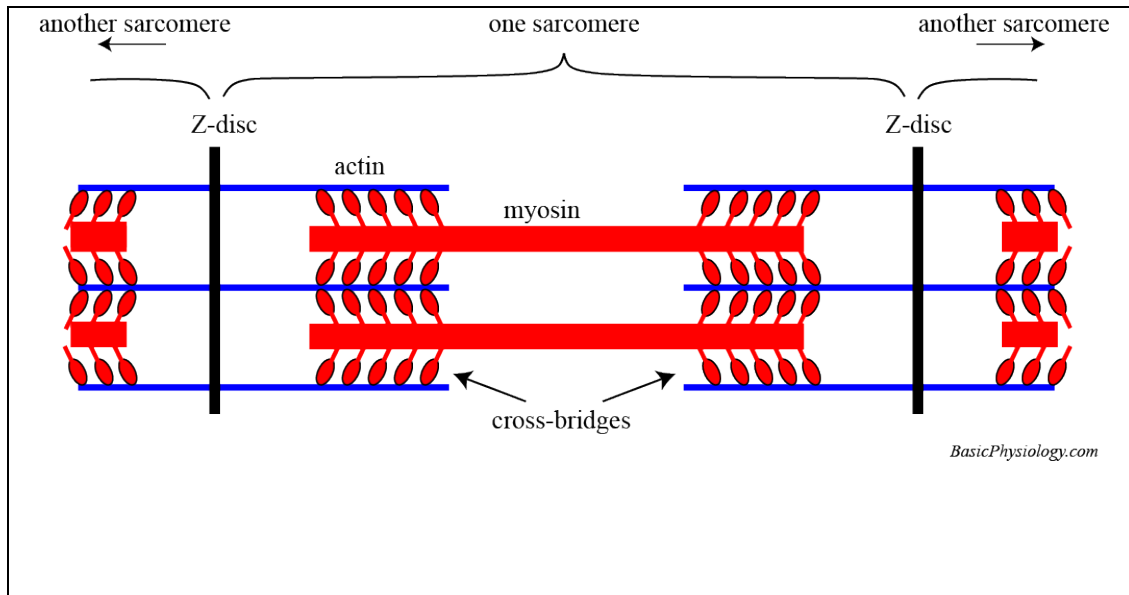
A.4.3. The Sarcomere

Introduction: The sarcomere is the fundamental unit in the skeletal muscle that makes the contraction happen.

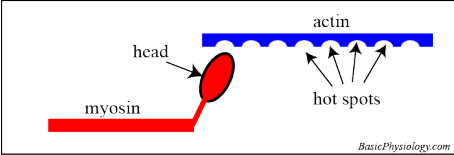
A. Definitions and Structural components required:

7. The sarcomere is the space that runs from one Z-disc to the next Z-disc
8. the sarcomere contains myosin and actin molecules, which are long and thin molecules
9. the actin molecules are attached to the Z-disc
10. the myosin molecules are arranged in the middle of the sarcomere and between the actin molecules
11. from the myosin molecules, cross-bridges extend towards the actin molecules
12. there is also a sarcoplasmic reticulum that stores Ca^{2+}
13. and there are transverse tubuli (singular: *tubule*). These are invaginations of the cell membrane (= sarcolemma) that come close to the sarcoplasmic reticulum.





B. Functional Steps:

1. A muscle action potential propagates from the motor end-plate along the cell membrane, thereby activating (=exciting) the whole cell membrane.	2. Because the transversal tubuli are continuations of the cell membrane, the action potential also propagates into these tubuli.
3. The action potential at the end of the transversal tubuli have an effect on the neighbouring sarcoplasmic reticulum.	4. This will open the Ca²⁺ channels that are located in the membrane of the sarcoplasmic reticulum (= SR).
5. Because there is much more Ca²⁺ inside the SR then in the rest of the sarcomere, there will be Ca²⁺ diffusion into the cell (along its concentration gradient) and the Ca²⁺ concentration in the sarcomere will rapidly increase.	6. The Ca²⁺ ions will influence the actin molecules to open their hot spots. 

7. Once these hot spots are available, the head of the nearest cross-bridge will attach to the hot spot.	8. It is important to note that the cross-bridges are a part of the myosin molecule. So, when the cross-bridges attach to the hot spots, then effectively the myosin molecule is linked to the actin molecule.
9. Once the head is attached to the actin molecule, the head will rotate a little (<i>see animation</i>). The rotation is always towards the centre of the sarcomere.	10. The rotation of the head will therefore pull the actin molecule a little towards the centre of the sarcomere.
11. The head will then de-tach from the actin molecule and rotate back towards its original position. This step requires energy (one ATP molecule).	12. Now repeat the previous steps; the head will attach again to the next hot spot, turn and pull again at the actin molecule.
13. In this manner, step-by-step, the actin molecule is pulled towards the middle of the sarcomere, thereby pulling the Z-discs closer to each other.	14. As the same thing is happening in all the other sarcomere along the muscle fibre, the whole fibre becomes shorter; this is the contraction.

C. The Cross-Bridge Dance:

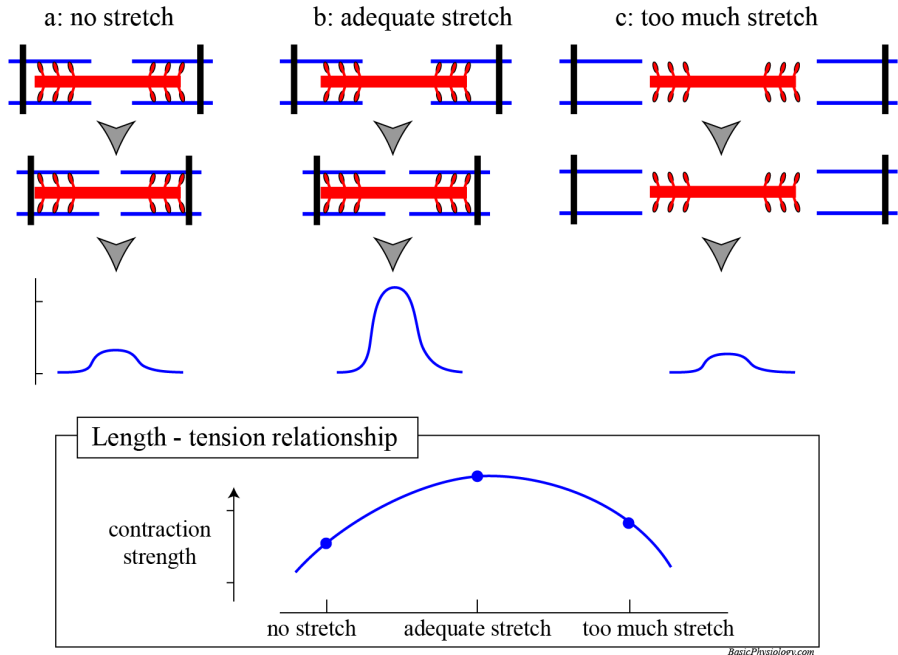
1. In summary; once Ca^{2+} ions have opened the hot-spots on the surface of the actin molecules, the head of the cross bridges will start, what I call, the “cross-bridge dance” (animation). This dance consists of four steps:	2. These are the four steps of the Cross-Bridge Dance: 1. attach (myosin head to actin hot-spot) 2. turn (towards the middle of the sarcomere) 3. detach (this requires energy in the form of ATP) 4. turn back
	The diagram shows a red myosin filament and a blue actin filament. 1. Turn back: The myosin head is at the end of the filament, pointing away from the actin. 2. Attach: The myosin head binds to the actin filament. 3. Turn: The myosin head pivots, pulling the actin filament towards the center. 4. Detach: The myosin head releases the actin filament, a process that requires energy from ATP (indicated by a red star labeled ATP). The source 'BasicPhysiology.com' is noted at the bottom right.

D. Additional Notes:

1. Triad: this is the name of the structure at the end of the transversal tubules. There, the cell membrane is close to the membranes of two sarcoplasmic reticula (plural of reticulum). The proximity of three membranes together is called a Triad (= three). The diagram shows a cross-section of a muscle cell. The pink area is labeled 'inside the cell' and the white area is 'outside the cell'. A red structure is the 'Sarcoplasmic Reticulum', a thin line is the 'Sarcolemma', and a vertical line is the 'T-tubulus'. The junction of these three is labeled 'Triad'. The source 'BasicPhysiology.com' is noted at the bottom right.	2. Actin hot-spots: Ca^{2+} ions have a complicated effect on the actin molecule. There is actually an interplay between three molecules: actin, troponin and tropomyosin. For more (technical) information, go to your Physiology textbook (<i>not very important</i>)
---	---

3. Head rotation is a bit of an exaggeration. In reality, the head movement is more like a “tilting” towards the middle of the sarcomere and, during the fourth step of the dance; the head tilts back to its starting position. It is more like the wipers on your car windshield that swipe back and forth. 	4. Million repeats: During a typical contraction, this cross-bridge tilting will happen millions of times, at all the thousands of cross bridges in the sarcomere, and in all the thousands of sarcomere strung along a muscle fibre.
5. End of contraction: the cross-bridge dance continues as long as Ca^{2+} keeps the hot-spots on the actin molecule open. But, at the same time that the contraction takes place, Ca^{2+} is being pumped back into the sarcoplasmic reticulum (active transport).	6. This pumping back will decrease the calcium-concentration in the neighbourhood of the sarcomere. As soon as the Ca^{2+} concentration is low enough, the hot spots will be closed and no longer available for the cross bridges. This will stop the contraction.
7. Sliding Filament Theory: This process of the cross-bridge heads pulling the actin along the myosin molecules, makes the actin slide along the myosin molecule (= filaments).	8. In the early days of this research, no one could actually see these cross bridges work and the idea of this mechanism was based on indirect evidence. But that evidence was enough to deduce the 'sliding' of the actin along the myosine molecule; hence the term “sliding filament theory”.

E. The Stretch-Contraction relationship. Also called the Force-Length relation.

1. This is an important phenomenon in physiology	2. If the muscle is stretched before the muscle is stimulated (by pulling at the tendons for example), then the contraction will be stronger.
3. But if you stretch too much, then the contraction will become weaker!	4. The explanation of this phenomenon is shown in the diagram and in the following steps:
 The diagram illustrates the Length-tension relationship in a sarcomere. It shows three scenarios: (a) no stretch, (b) adequate stretch, and (c) too much stretch. Each scenario includes a diagram of the sarcomere with actin (red) and myosin (blue) filaments, a corresponding tension curve, and a point on a larger 'Length - tension relationship' graph. In (a), the filaments overlap too much, resulting in a small contraction. In (b), the filaments have optimal overlap, resulting in a strong contraction. In (c), the filaments are too stretched, resulting in a small contraction. The graph shows a bell-shaped curve where contraction strength is highest at adequate stretch and lowest at no stretch or too much stretch.	
5. If the actin and myosin overlap a lot (as in the 'no stretch' situation in "a", then there will be a small contraction.	6. The contraction cannot be stronger because the myosin molecules are quickly stopped ('bump') against the Z-lines.
7. If the sarcomere (= the muscle) is more stretched (situation "b"), then the myofilaments can slide more before the Z-lines are reached and the contraction force will therefore increase.	8. So, if you stretch the muscles more and more, then the filaments will slide more and more and the contraction force will increase.

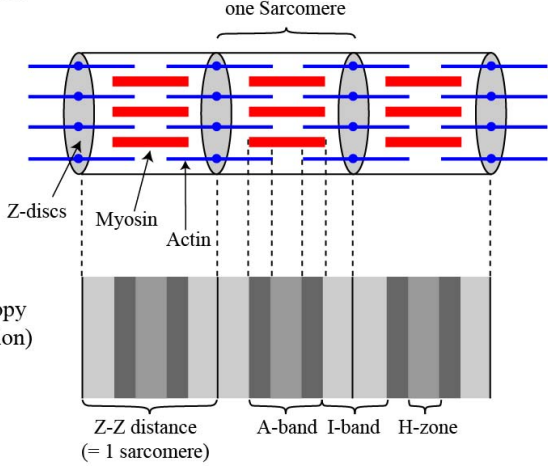
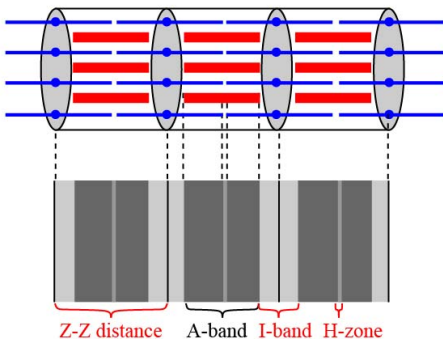
9. But there is a limit to the amount of stretching. If you stretch too much (situation “c”), then the actin and myosin filaments are no longer in each others neighbourhood, and the distance will be too much for the cross-bridges to connect to the actin molecules. This will reduce the contraction force.	10. This effect of pre-stretch is also very important in the heart (it is there called the Frank-Starling mechanism) and in all other muscles.
11. In practice, the length of the skeletal muscles (and therefore the stretch of the sarcomeres) is determined by the position of the joints in the body.	12. For example, the biceps muscles attach the lower arm to the upper arm. If the arm is fully flexed, then contraction will be small and when the arm is fully extended, it is more difficult to contract against a large force.
13. The optimal length of the biceps is at an angle of the elbow joint of about ninety degrees. This is the angle that most sportsman will use when having to lift heavy weights for examples (weight lifters).	

F. Rigor Mortis ("stiffness in death"):

Question: When a person dies, the body, after a few hours, will become stiff. Why?	
1. Contraction requires energy (ATP). Specifically, the ATP is required to de-tach the cross-bridge head from the actin molecule (step 4 in the “cross-bridge dance”!)	2. But, when a person dies, the normal repair mechanisms of the cells have stopped functioning. This means that the cells will start to deteriorate. One of the first signs of this deterioration is that membranes will start to fall apart.
3. Therefore, the membrane of the sarcoplasmic reticulum, which contains a lot of calcium ions, will break open and holes will appear in the membrane.	4. This will lead to a flow of Ca^{2+} ions from the sarcoplasmic reticulum into the sarcomere, and this will open the hotspots on the actin molecules.
5. Once the hotspots are open, the heads of the cross-bridges will automatically attach to the actin molecules.	6. But; because there is no ATP (<i>the person is dead remember?</i>), the heads will no longer be able to detach from the actin.
7. Therefore, the myosin and the actin molecules are now locked together forever.	8. Because this process happens in all skeletal muscles at more or less the same time, the corpse becomes very stiff .
9. What happens next? (<i>Will the body remain stiff forever?</i>)	

No. After some time, more membranes and filaments will break down in the body. Therefore, in time, the long actin and the long myosin molecules will also start to break down, thereby terminating the bonding between the two filament types. Therefore the muscles will again become less stiff and rigor mortis will disappear.

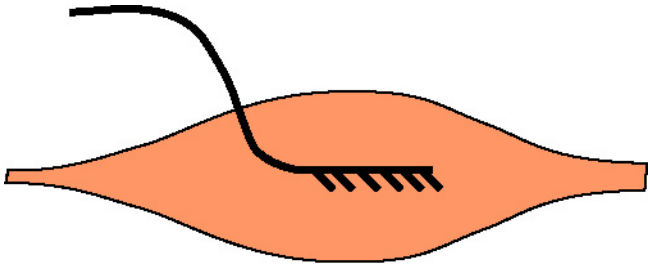
G. Behaviour of the striation pattern (= anisotropy) during contraction:

A: Relaxed  B: Contracting 	
1.	2.
When the muscle contracts , this means that the actin and myosin molecules slide into each other (= sliding filament theory)	Therefore the Z-disks (Z-lines) will move towards each other.
3.	4.
The A-band however will remain the same, as the myosin molecules do not shorten.	The H-zone (if visible) will become shorter and may even disappear as the actin molecules move towards the centre of the sarcomere.
5.	
Summary: When a muscle contract, then the Z-Z distance becomes shorter , the I-band shorter , the H-zone shorter , but the A-band does not change its length.	

A.4.4. Twitch & Tetanus

Purpose: To make a muscle contract in a sensible and useful manner.

A. Definitions and Structural components required:

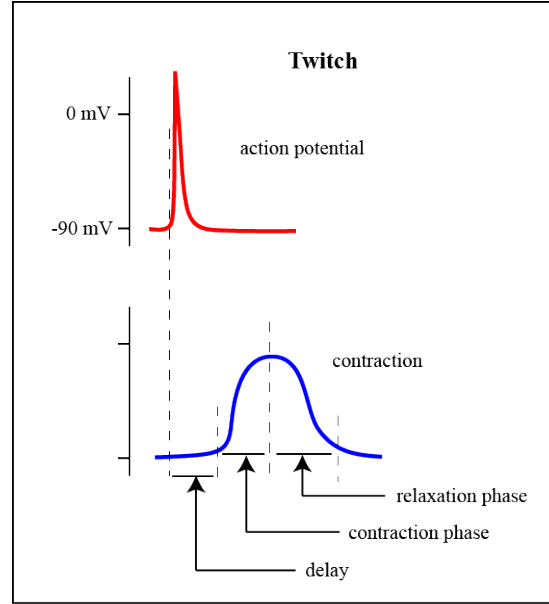
14. A skeletal muscle; this can be either a small muscle, like those that contract our eyelids, or a large muscle, such as in the upper leg (the rectus femoris for example). 15. These muscles consist of thousands of fibres (=cells) and millions of sarcomeres. 16. Nerve endings (=motor end-plates) that innervate all these muscle fibres.	 A diagram of a single skeletal muscle fiber, which is elongated and spindle-shaped, colored orange. A black line representing a nerve ending (motor end-plate) enters the fiber from the top left and terminates in a series of diagonal lines on the inner surface of the fiber.
--	--

B. The Twitch:

1. If there is only one action potential in the nerve that excites the muscle, then the muscle will contract only once. This is called a twitch. It is the minimum contraction for the whole muscle.	2. Notice that the duration of the contraction, the twitch, is much longer than the duration of the action potential.
In fact, the twitch has three phases: 1. The delay. This is the time between the arrival of the action potential at the motor end-plate and the beginning of the contraction. This time includes diffusion of acetylcholine, the propagation of the muscle action potential throughout the	

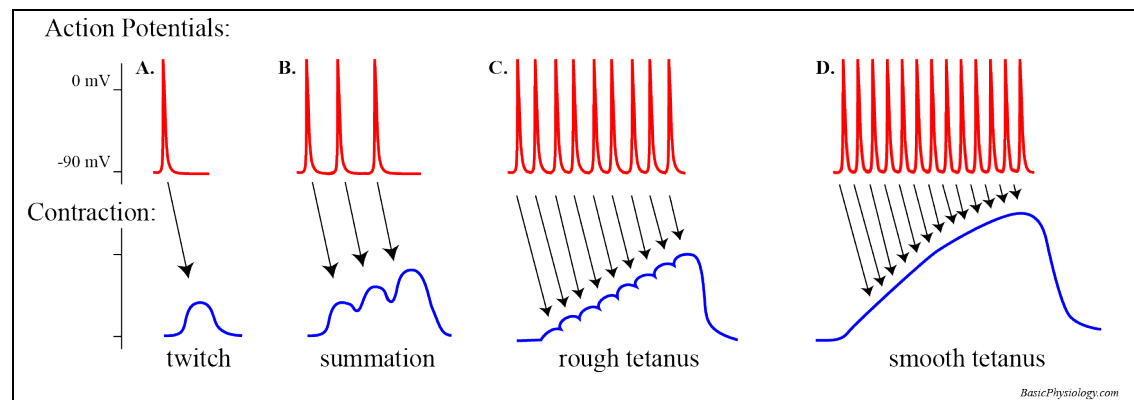
muscle, release of calcium ions from the sarcoplasmic reticulum etc.

2. The **contraction phase**: this is when the actin molecules bind to the myosin fibres and the head of the cross-bridges turn in cycles.
3. The **relaxation phase**; the contraction is over, calcium-ions are pumped back into the sarcoplasmic reticulum, the cross-bridges are no longer formed and the muscle relaxes.



BasicPhysiology.com

C. From Twitch to Tetanus:



BasicPhysiology.com

1.
If we only had twitches, we would have **difficulty** in moving around (moving around in 'jerks'!). We need many twitches (and therefore many action potentials) to make a proper movement.

2.
Remember that the duration of the twitch contraction is much **longer** than the duration of the action potential.

3.
If, after the first twitch, a **second** action potential excites the muscle, this will then generate a **second** twitch.

4.
If the time between the first and the second action potential is **short** then the second contraction will start while the first contraction is still going on (see panel B).

5. Therefore, the second contraction will start at a higher level and reaches a higher peak. This phenomenon in which one contraction gets a "lift" from a previous contraction is called summation.	6. In the figure above, in panel B, a third action potential was also generated earlier, exiting a third contraction, which induced additional summation. After this third action potential, the nerve became quiet and contraction force returned to the original level.
7. If the time between the successive action potentials is made even shorter, then the individual twitches will summate on top of each other even more and the total force of contraction of the whole muscle will further increase (figure, panel C, rough tetanus)	8. With a further increase in action potential frequency, the individual twitches will “blur” into each other, creating a smooth tetanus, a smooth contraction (panel D). This is what we want!

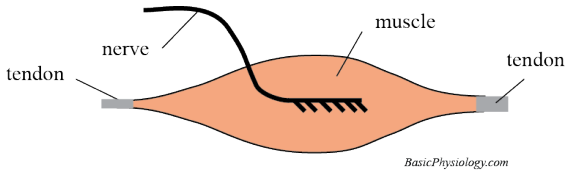
D. Additional Notes:

1. In daily and normal life, ALL contractions of our skeletal muscles are smooth tetani (= plural for tetanus). Examples of these are walking, writing, turning your head etc. Possibly the only example of a twitch is the blinking of an eyelid (lasts about 0.1 second).	2. In pathological situations however, when there is a problem with the coordination between nerves and muscles, it is possible for rough tetanus to become visible. Examples of such abnormal contractions are shaking, tremors and spasms.
3. The whole principle of summation depends on the fact that the action potential duration (and its refractory period) is much shorter than the duration of the ensuing contraction. A typical action potential in a skeletal muscle lasts 2-5 msec while a contraction may last from 100 to 1000 milliseconds.	4. If the action potential duration is increased, this will decrease the possibility of summation. This would be abnormal in the skeletal muscle and become visible as tremors.

A.4.5. Types of Skeletal Muscle Contractions

Purpose: To make a muscle contract in different ways.

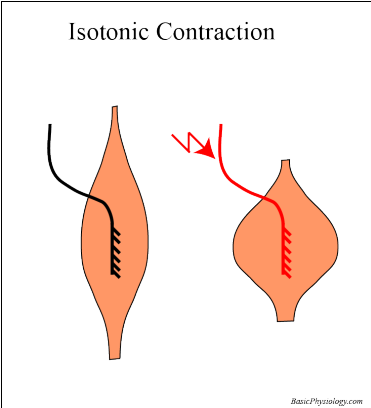
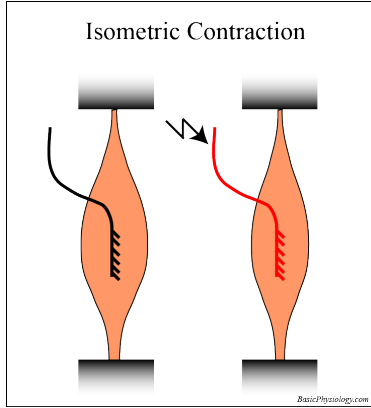
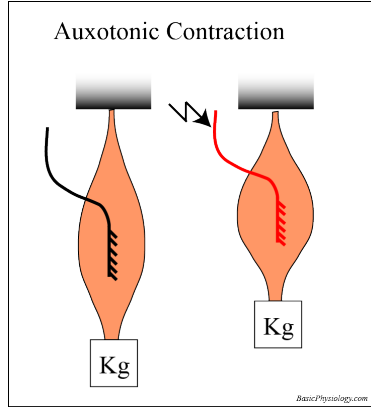
A. Definitions and Structural components required:

17. A skeletal muscle 18. A nerve innervating this muscle 19. Tendons at both ends of the muscle	
---	--

B. Muscle Length and Muscle Tone:

1. When a muscle contracts, two things can change in that muscle: the length of the muscle and/or the tone of the muscle.	2. But what is tone? A change in the length of the muscle is easy to understand but tone is maybe more difficult as most people don't know the meaning of the word "tone".
3. The easiest way to sense tone is to feel your muscles (such as your biceps in the upper arm) when it is relaxed and when it is contracting.	4. When contracting, the muscle feels 'stronger'. That is the tone.

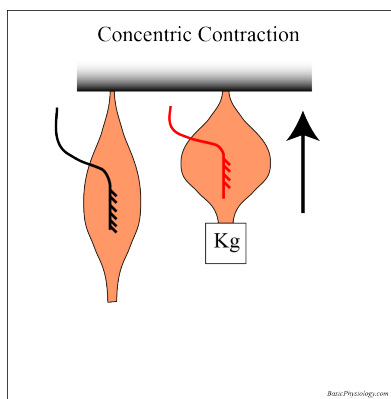
C. Types of Contractions:

1. Isotonic Contraction The most simple contraction is when the muscle contract without any or little attachment. The length of the muscle is then reduced but the tone has not changed. This is called isotonic (= same tone).	2. Isometric Contraction The opposite situation occurs when the muscle is fixed at both ends by its tendons. Then, when contraction occurs, the muscle cannot change its length but the tone will increase. This is called isometric (iso = same; metric = length).	3. Auxotonic Contraction Most contractions in daily life show some change in length and some change in tone; these are called auxotonic.
Isotonic Contraction  The diagram shows two muscle fibers. The left fiber is in a relaxed state with a black line representing the sarcomere. The right fiber is in a contracted state, shorter in length, with a red line representing the sarcomere. A red arrow points from the relaxed state to the contracted state, indicating a decrease in length.	Isometric Contraction  The diagram shows two muscle fibers fixed between two horizontal bars. The left fiber is in a relaxed state with a black line representing the sarcomere. The right fiber is in a contracted state, with a red line representing the sarcomere. A red arrow points from the relaxed state to the contracted state, indicating an increase in tone without a change in length.	Auxotonic Contraction  The diagram shows two muscle fibers, each with a weight (Kg) attached to its bottom. The left fiber is in a relaxed state with a black line representing the sarcomere. The right fiber is in a contracted state, shorter in length, with a red line representing the sarcomere. A red arrow points from the relaxed state to the contracted state, indicating both a change in length and a change in tone.
4. An example of an isotonic contraction is ‘waving your hand’ (like the royalties!) or waving your finger at a bad student!	5. An example of an isometric contraction is pushing your hand and arms against a wall (which will not budge), or, carrying a football in your hand with your arm flexed.	6. Since most daily contraction involves both changes in tone and in length, nearly all contractions are auxotonic.

D. Another type of Contraction:

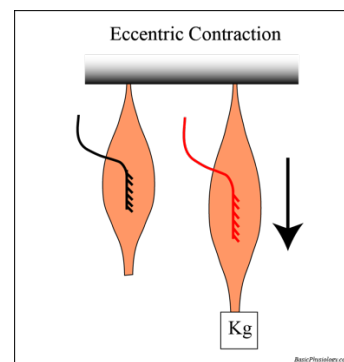
1. Concentric Contractions

Usually, when a muscle contracts, the length of the muscle decreases; this is called a **concentric** contraction. This is often used to flex a joint. For example, when you lift a suitcase from the floor.



2. Eccentric Contractions

But sometimes, you use your muscles to control **extension**, such as when you carefully lower a suitcase back onto the floor; then the muscle length increases while contracting at the same time. This is called an **eccentric** contraction.



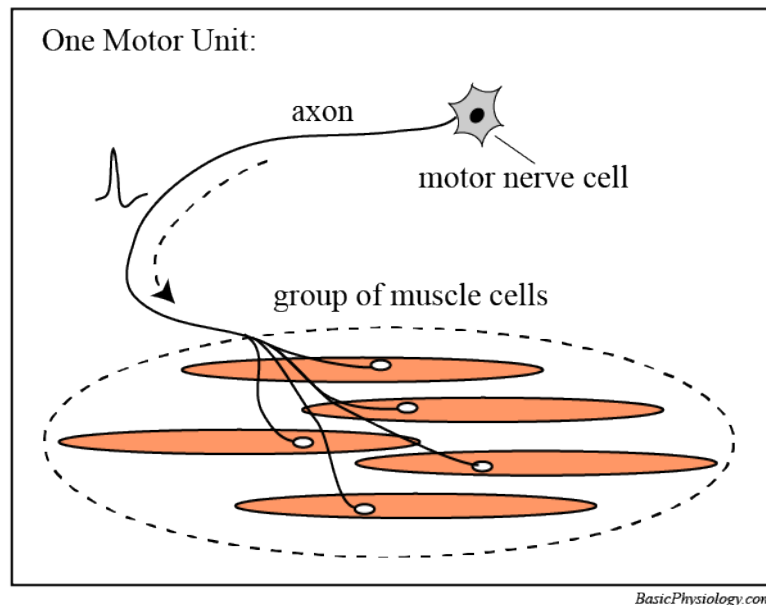
E. Contractions Types: Another way is to look at the rhythm of the contractions

1. Phasic Contractions When the muscle contracts and relaxes in a rhythmic manner; this is called phasic contraction. This occurs for example when you are walking. Your leg muscles alternatively contracts and relax while you walk.	2. Tonic Contractions The opposite situation occurs when the muscle is contracting all the time but only varies in tone. This is called tonic contraction. Typical muscles that perform tonic contractions are the muscles in the back . They hold the vertebra column (and therefore your back) upright all the time.
3. Tonic + Phasic contractions Many muscles, depending upon the situation, can also perform tonic and phasic contractions simultaneously . For example, when you hold a ball in your hand with your elbow bend at ninety degrees (tonic contraction) and you also, at the same time, move your lower arm up and down (phasic contraction).	The figure displays three vertically stacked line graphs illustrating different muscle contraction patterns. Each graph has a vertical axis with tick marks and a horizontal dashed baseline. The top graph, titled 'Phasic Contractions', shows four distinct, sharp peaks that rise from the baseline and return to it. The middle graph, titled 'Tonic Contractions', shows a continuous, low-amplitude, wavy line that remains above the baseline. The bottom graph, titled 'Tonic + Phasic Contractions', shows a continuous, low-amplitude, wavy line (representing the tonic component) with three sharp peaks (representing the phasic component) superimposed on it. A small watermark 'BasicPhysiology.com' is visible in the bottom right corner of the graph area.

A.4.6. Motor Units

Introduction: The motor unit is the only connection between the central nervous system (= the brain) and the skeletal muscles.

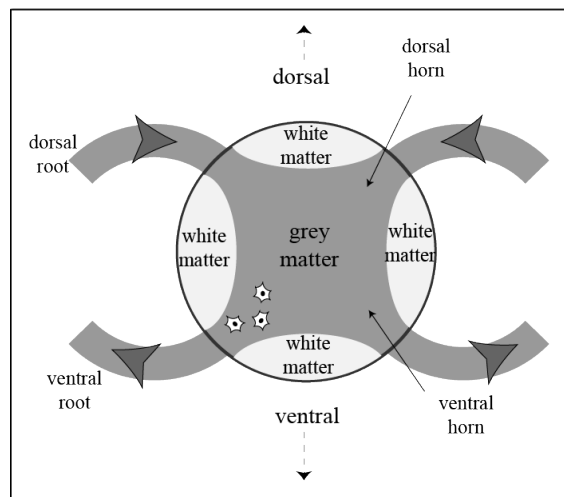
A. Definitions and Structural components required:



1. A motor unit consists of:	2.	3.
1. a motor nerve cell which is located in the spinal cord. 2. an axon that goes from the nerve cell to a skeletal muscle. 3. several skeletal muscle fibres that are innervated by this particular motor axon.	The axon can be very short or very long, depending upon the distance from the spinal cord to the muscle. For example, in the case of the muscles in your big toe, the axon has to go through the length of your leg; about one meter! (approx. 3 feet)	In the figure above, the motor nerve is connected to 5 muscle fibres. This is actually a small motor unit. Usually, a motor unit will connect (=innervate) many more muscle fibres. Typically, a few hundred to a few thousand muscle fibres (=cells) are connected to one single motor nerve.

B. A bit of information about the spinal cord:

1. The spinal cord is a part of the central nervous system . It is located in the vertebral column and runs from the head down to the sacral region (= your butt!).	2. In this cross section (figure), the spinal cord consists of two parts; the grey matter and the white matter .	3. Make sure you understand the orientation of the spinal cord in this cross section; the upper part is dorsal (pointing towards the back) and the lower part is ventral (pointing towards the front).
4. Inside the spinal cord, there are two types of tissues; the white matter and the grey matter (matter = tissue).	5. The white matter consists of myelinated nerve fibres. They form tracks that go up (= to the brain) and down (=from the brain). It is white because of the myelination. The grey matter consists mainly of nerve cell bodies (= soma), hence the greyish colour.	6. The spinal cord is connected to the body by the spinal roots .



BasicPhysiology.com

7. Between every pair of vertebra there are two roots coming into the spinal cord (at the dorsal side) and two roots going out of the spinal cord (at the ventral side).	8. The dorsal roots (incoming) contain the axons from sensors in the body. The ventral roots (outgoing) contain the axons that are connected to the 'effectors' in the body, mainly muscles and glands.	9. Therefore the incoming nerves are called sensory nerves and the outgoing nerves are called motor nerves .
10. Those parts of the grey zones in the spine that are close to the in- or outgoing roots are called the horns .	11. Because of the Ventral-Dorsal orientation, these horns are therefore called respectively the ventral horns and the dorsal horns .	12. The ventral horn is the home of the motor nerve cell bodies (that is their soma). The axons of these cells go out of the spinal cord through the ventral roots and to the muscle cells that they innervate.

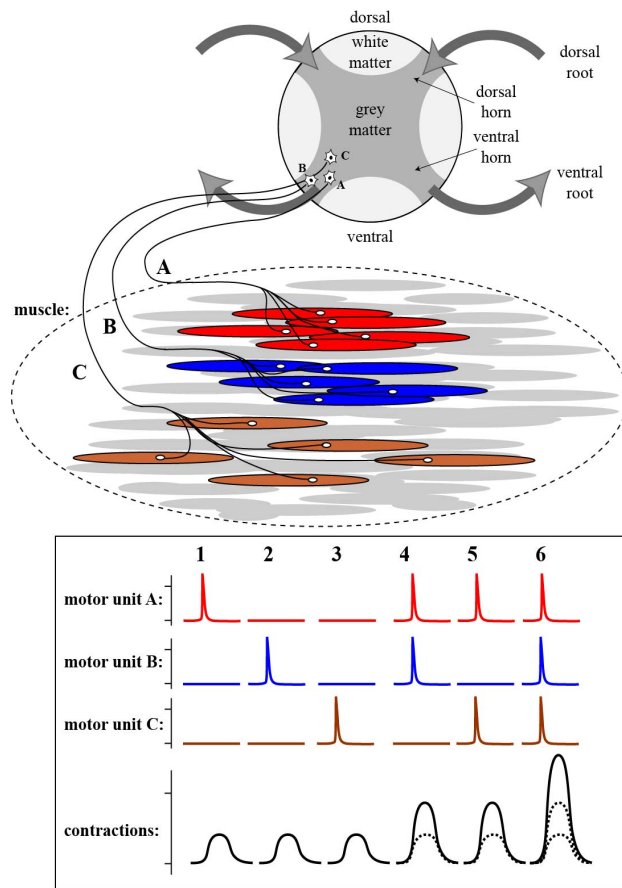
C. A bit more information about the motor unit:

1. The motor unit is a functional system that consists of a motor nerve together with the muscle fibres that are innervated by that same nerve.	2. A motor nerve is a nerve that initiates a skeletal muscle contraction. Its soma (= cell body) is located in the ventral horn of the spinal cord and its axon projects from the soma, through the ventral root, out of the spinal cord, to several muscle fibres in the muscle.
3. A motor unit does NOT innervate ALL the muscle fibres in a muscle. If that were the case, every action potential from this motor neuron would cause a massive and unregulated contraction of the whole muscle; i.e. a huge twitch.	4. A motor unit typically innervates 10-1000 muscle fibres. This depends on the type of muscles. Small muscles that are very delicate (like the small muscles in the fingers) innervate small size motor units

	(50-500 muscle fibres) whereas large muscles that do not need a lot of regulation (such as the large muscles in the legs) have motor units of 1,000 to 10,000 muscle fibres.
--	--

D. How does a motor unit work?

1. An example of several motor units is shown in the figure. In this case, three motor units are shown (three motor neurons A, B and C and their respective muscle fibres; red, blue and brown), all located in the same muscle.	2. If motor neuron A fires, then the red muscle fibres will contract. If motor neuron B or C fires, then the blue or the brown fibres will contract. This is shown in the graph in situations 1, 2 and 3.
3. If two neurons fire simultaneously, (situations 4 and 5) then both groups of muscle fibres will contract, causing a stronger contraction. This effect is called summation. If all three neurons fire simultaneously (situation 6), then the contraction amplitude will further increase.	4. You must realize that the motor neuron is the boss. The muscle fibres have absolutely no say in this. If the motor neuron induces an action potential, then that action potential will always propagate to the muscle fibres that are innervated by that axon.



5.

This is because transmission across the motor-end plate, the connection between the nerve axon and the muscle cell is always successful (*Link: remember?*). Therefore, if there is an action potential in the motor nerve, then there will always be action potentials travelling towards the connected muscle fibres and therefore contraction in those fibres. You could say that the muscle fibres are the ‘slaves’ of the motor neurons.

E. Spatial and Temporal Summation:

1. The summation discussed above, in which several motor neurons work together to induce stronger contractions, is called spatial summation. The term “spatial” refers to the fact that muscle fibres from different regions in the same muscle are activated together and contract together.	2. In a previous page, we have also discussed a different type of summation (see: <i>Twitch & Tetanus</i>). In that situation, one single motor unit was repeatedly activated. This also induced summation and this type of summation can now be called temporal summation (=summation in time; ‘tempor’ = time).	3. In daily life, both types of summation, spatial and temporal, are simultaneously active and work together to perform smooth contractions and movements of our skeleton.
--	---	---

F. Why do we need motor units? Would it not be simpler if a motor neuron would innervate and activate one single muscle fibre?

1. If every muscle fibre were connected to its own nerve cell, then there would be as many motor neurons as there are muscle fibres in our body.	2. The problem is that there are too many muscle fibres in the body. If every muscle fibre had its own motor neuron, then there would be an enormous increase in the number of motor neurons and hence in the size of the spinal cord . The spinal cord would then be very much larger (wider) than it now is.
3. So, to be more efficient, one motor neuron typically innervates 100-10,000 motor fibres.	4. In fact, the ventral horns (those that contain the motor neurons) are indeed larger in two areas along the spinal cord; namely at those locations where the motor neurons innervate the upper and the lower limbs . In those locations, more motor neurons are required to innervate more muscles, in the limbs, than in other parts of the body (such as thorax or abdomen).

G. A few more notes on motor units:

1. Motor units provide for a more efficient way of stimulating and contracting muscles. If the brain needs a lot of control to perform delicate movements, then there will be many neurons involved in this contraction and hence the motor units will be small (less muscle fibres connected to each motor neuron).	2. However, if in some muscles, the brain does not need a lot of control, then less motor neurons will be dedicated to these muscles.	3. This is often the case in large muscles such as in the legs or in the abdomen. Motor neurons that control these muscles often connect to thousands of muscle fibres each.
4. Motor units also provide the possibility of sustaining contractions for longer periods of time.	5. In the diagram for example, if motor units A alternate with B and C, then contraction of the whole muscle would be summated in time and each motor unit, in turn, gets some rest while the others are working.	6. This story about the motor units and the regulation of contraction is only true for skeletal muscles . The situation is very different in cardiac muscles and in smooth muscles .

A.4.7. The Cardiac Muscle

Introduction: The heart muscle is the muscle that is responsible for the pumping of the heart. (heart = cardia, cardiac = from the heart, cordial = from the heart, pre-cordial = before the heart; i.e. the chest)

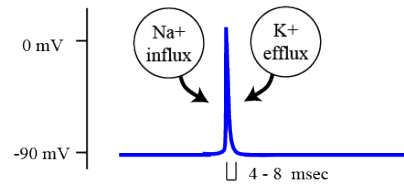
A. Comparing a Skeletal action potential with a Cardiac action potential:

1. The action potential of the cardiac muscle is similar on many points with the action potential of the skeletal muscle but also differs on a few important points.	2. The upstroke of the cardiac action potential (= depolarization) is caused by the opening of the sodium-channels and the influx of sodium-ions into the cardiac cell. This is similar to what occurs in the skeletal muscle.
3. The down stroke of the cardiac action potential (= repolarization) is caused by the opening of the potassium -channels and the efflux of potassium-ions out of the cardiac cell. This is also similar to what occurs in the skeletal muscle.	4. Between the depolarization and the repolarization, the potential stays at about 0 mV for a relatively long time, approximately 100-300 milliseconds (0.1 - 0.3 seconds). This potential that lasts between the de- and the re-polarization is called the “plateau” (pronounced “pla-too”; originally a French word which means a flat area on top of a mountain).
5. During this plateau-phase, the calcium channels are opened and there is a calcium-influx. This calcium is used in the subsequent contraction of the muscle to bind the myosin cross-bridges to the actin molecules.	

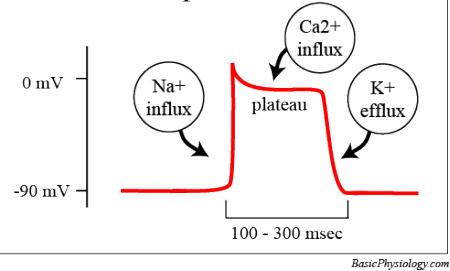
6.

In other words, in the heart, the calcium-ions necessary for the contraction, come from outside the cell (remember; in the skeletal muscle cell, the calcium ions come from the sarcoplasmic reticulum located inside the cell)

Skeletal action potential:



Cardiac action potential:



B. Cardiac Action Potential and Cardiac Contraction:

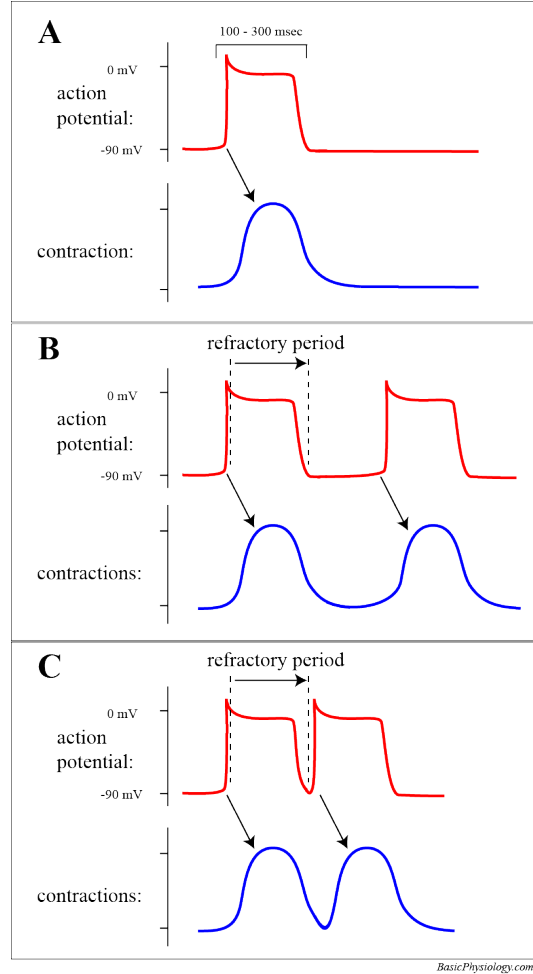
1. As with skeletal muscle, the action potential in a heart cell will initiate a contraction in that cell.	2. One important consequence of a plateau in the heart action potential is that the action potential duration is much longer than in skeletal muscles.
3. The cardiac action potential can range between 100 and 300 msec (=milliseconds) instead of 4-8 msec in a typical skeletal muscle cell.	4. As shown in figure A, the contraction in the heart muscle occurs during the action potential (while in skeletal muscles the contraction occurs after the action potential).
5. An important consequence of the long action potential duration is that the refractory period of the cardiac action potential is much longer than in skeletal muscles. Instead of 4-8 milliseconds, the refractory period in the heart may last as long as 300 milliseconds.	
6. Therefore, in the heart, the contraction is finished before a second action potential can be generated, as shown in figure B.	

7.

In figure C, the second action potential is initiated immediately after the refractory period of the first action potential and even then, the contraction of the first is finished before the beginning of the second.

8.

In other words, the contractions in the heart cannot summate! (as they can in skeletal muscles; *link: temporal summation*).



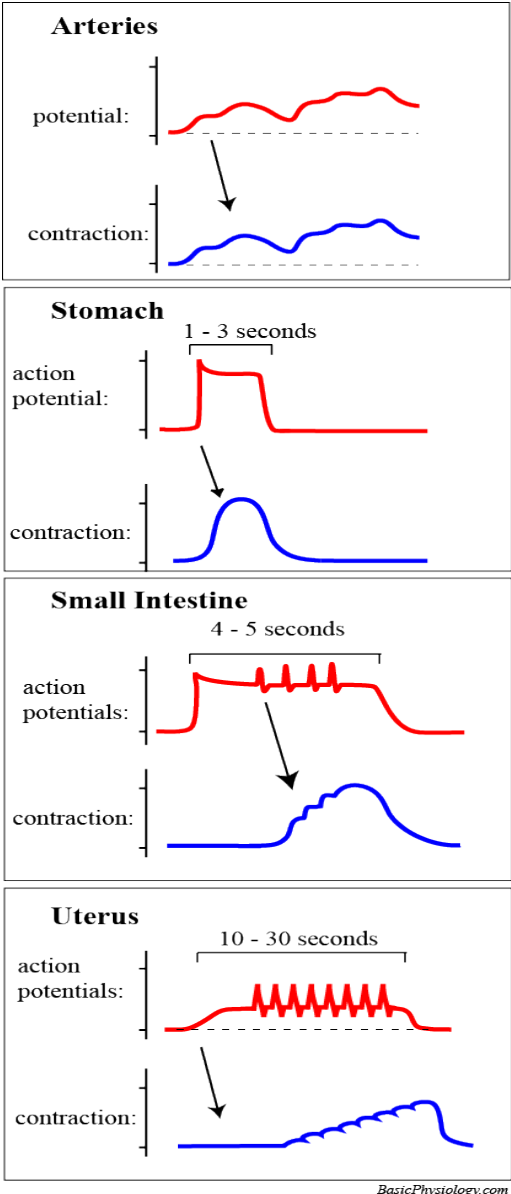
C. Some additional notes relating to cardiac muscle:

1. There are therefore in cardiac muscles at least three different ion-channels : Na^+ , K^+ and Ca^{2+} channels involved in creating an action potential.	2. And, as in other excitable tissues, the K^+ channels are mainly responsible for the resting potential .
3. Because there is no temporal summation in cardiac muscles, there can be no tetanic contractions in cardiac muscle.	4. There are also no motor units in the heart. In fact the action potentials in the heart do not come from the nerve cells at all but are self-generated in a specialized area of the heart called the sinus node. This is the pacemaker of the heart.
5. By the way, cardiac muscles, under the microscope, also show a striated pattern (= anisotropy), similar to skeletal muscle cells.	6. Please note that this is only a very brief introduction to the cardiac muscle. A much more elaborate presentation will be presented at a later time (<i>Chapter B: The Cardiovascular System</i>).

A.4.8. The Smooth Muscle

Purpose: To understand the major differences in action potentials and contractions in the smooth muscles.

A. Different Types of Smooth Muscle Action Potentials

1. There are many types of smooth muscles in the body and they all display different types of (action) potentials and contractions.	 The figure consists of four vertically stacked panels, each representing a different smooth muscle tissue. Each panel contains two vertically aligned graphs. The top graph in each panel is labeled 'potential:' and shows a red line representing the membrane potential. The bottom graph is labeled 'contraction:' and shows a blue line representing the level of contraction. An arrow points from the peak of the action potential to the corresponding contraction curve. Arteries: The potential graph shows a red line with small, frequent depolarizations and repolarizations. The contraction graph shows a blue line with corresponding small, frequent peaks. Stomach: The potential graph shows a single, sharp action potential that lasts for 1-3 seconds. The contraction graph shows a single, broad peak of contraction that occurs during the action potential. Small Intestine: The potential graph shows a burst of action potentials that lasts for 4-5 seconds. The contraction graph shows a broad peak of contraction that occurs during the burst of action potentials. Uterus: The potential graph shows a burst of action potentials that lasts for 10-30 seconds. The contraction graph shows a broad peak of contraction that occurs during the burst of action potentials. BasicPhysiology.com
2. Some smooth muscles, such as the smooth muscles in the walls of blood vessels (the arteries and the veins) do not even display an action potential at all! But they do show slow depolarization and repolarizations, the level of which is determined by the action of local nerve endings.	
3. Other smooth muscles resemble the heart, such as the stomach, with a pacemaker region, an action potential that propagates in the wall of the organ and a resulting contraction. Note that the stomach action potential lasts much longer than the cardiac action potential (5-10x).	

4. Smooth muscle action potentials in the gastrointestinal system often last very long. In the small intestine they can have a plateau that lasts for many seconds. Note here that it is the "spikes" that induce the contraction, not the action potential itself. These spikes occur in the plateau phase of the action potential.	
5. Other smooth muscles, such as the uterus and the bladder, show very brief action potentials, also called "spikes". Often, these spikes occur in bursts and will lead to summation of contractions (temporal summation).	
6. The major ion channels in smooth muscles are Calcium-channels (for influx and depolarization) and Potassium-channels (for efflux and repolarization). Sodium and sodium channels do occur in smooth muscles but do not seem to be very important.	
7. Please note that this is only a very brief introduction in smooth muscles. A much more elaborate presentation will be given at a later time (<i>Link</i>).	

Basic Physiology Info:

This book collects the text and figures from my website: *BasicPhysiology.org*. This may be useful for anyone who either wants all that info in the same document, a pdf in this case, away from the internet or for any other reason.

What is this book about?

1. This is a simple book, dedicated to teaching the basics of physiology.	2. I have used a similar site for many years, teaching human medical physiology in several medical and para-medical schools.
5. While I am (still) expanding and upgrading this and future chapters, I most certainly welcome your comments, suggestions and/or questions. Feel free to contact me: wlammers@smoothmap.org	<i>Thank you for your interest!</i>  <i>Wim Lammers</i>

NO Copyright and NO Cookies!

1. YES!! This site does not want any copyrights. It is totally FREE . You can use any of its contents, texts, images, animations etc. for your own purpose such as in your dissertations, lectures, or whatever.	2. I do appreciate, if you use some of these contents if you could let me know, by email (wlammers@smoothmap.org). And ... if you have criticism or your discovered something wrong, please let me know!
3. Finally, this site does also not like and use Cookies ! I mean these data links to your computer or mobile (not the real thing of course; I actually love real cookies, especially those made with chocolate!).	