Chapter 3.4 Operating an Organism

Introduction

In the previous chapters we discussed the storage, transfer and use of the genetic information required to build a new organism. Genetic information is digital and is stored in large polymers as a sequence composed of four different bases: its alphabet. The reliable storage of genetic information is essential for the survival of a species; this data is the family jewels. Genetic information is transferred from parents to children using a random selection from each parent which ensures diversity among the progeny.

However, the information needed to operate and control an existing organism on a time scale of milliseconds to days isn't permanently stored, rather it consists of fairly immediate detection of conditions in the organism and its environment and commands to respond to these conditions. This operational information is analog in nature. Multiple channels can be represented by multiple species of molecules. The structure of these molecules keeps the channels distinct, but the actual information is encoded in the concentration of each of the molecular species, and there are a sufficient number of molecules of each species that the information is effectively continuous in nature. Other information channels are defined by groups of neurons, with information carried by voltage pulses across the neural membrane. The information is encoded in the frequency of pulses, and again is thus intrinsically analog in nature.

The operational information system will be illustrated by a series of specific examples, starting with the most short ranged information transfer, within a molecule, and ending with examples of communication throughout a large organism, ourselves, over distances of more than a meter. The first example is hemoglobin, a protein we are already familiar with.

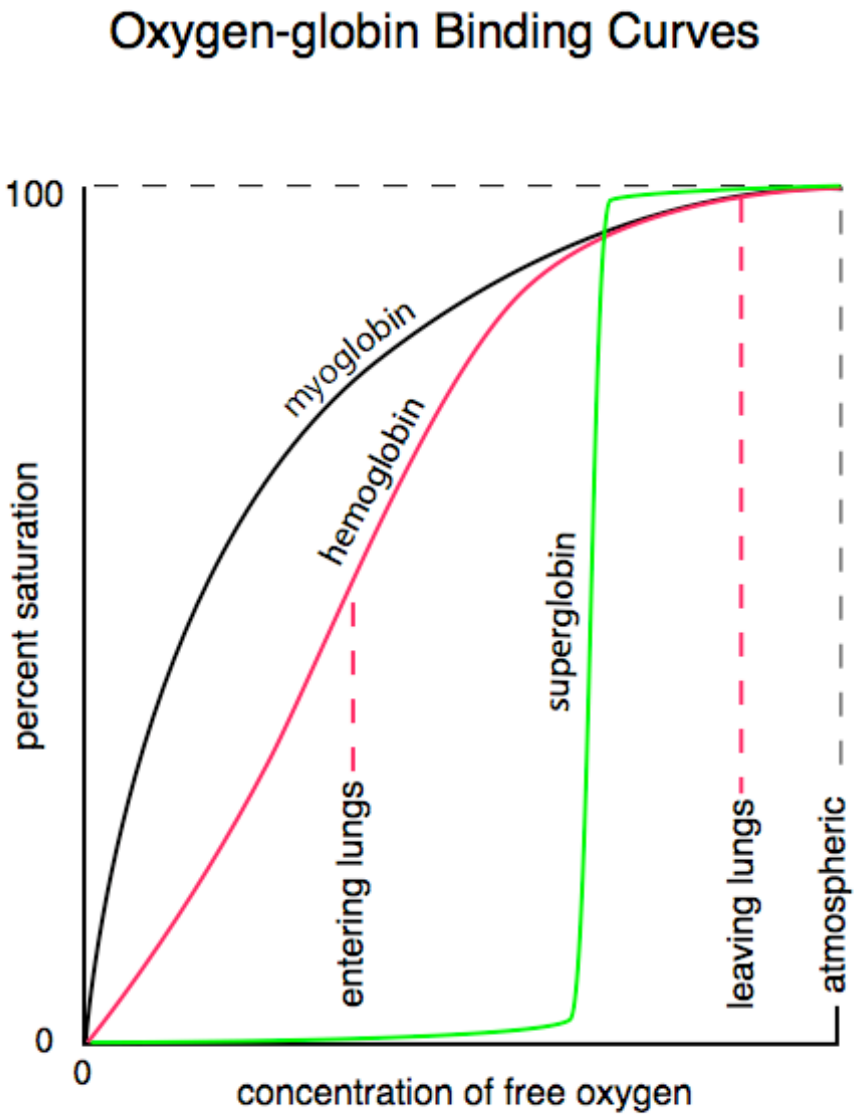
Intramolecular communication: hemoglobin

A major function of hemoglobin is to absorb oxygen from air in the lungs, carry oxygen while in the blood, and then release oxygen to all the tissues of the body, where the oxygen reacts with nutrients and provide energy. To do this most effectively, hemoglobin should bind oxygen maximally in the lungs where the oxygen concentration is high, but then be capable of releasing most of that oxygen in tissue where the oxygen concentration is lower. This would be no problem if it was acceptable to have a low oxygen concentration in tissue, because any oxygen binding substance would release oxygen if the oxygen concentration in the surrounding environment was sufficiently low. The problem is that it is desirable to have a high oxygen concentration in tissue. The higher the concentration of oxygen in tissue the greater the rate of oxidation of nutrient to generate energy production. Thus the design goal for hemoglobin is to become essentially saturated with oxygen in the lungs but to release a large fraction of that oxygen in tissues at only a modestly lower oxygen concentration.

Oxygen binding curves

Before explaining how hemoglobin accomplishes the goal let's look at a graph that describes the performance of three oxygen carrying proteins. In Figure HbO_binding percent oxygen bound is plotted against the concentration of free oxygen.

Figure HbO_binding



HbO_binding

Legend HbO_binding. The amount of oxygen bound to three proteins, as percent of maximum, is plotted against the concentration of oxygen in their environment. Myoglobin has a simple binding curve. At first, as the external oxygen concentration drops from the saturation level, myoglobin releases a small percent of bound oxygen. As the oxygen concentration progressively decreases myoglobin releases an increasing fraction of its bound oxygen. The whimsical protein superglobin releases all oxygen when the oxygen concentration drops below a critical level. Hemoglobin has an intermediate binding curve, at an intermediate oxygen concentration it releases more oxygen than myoglobin, but not as much as superglobin.

The black curve describes the performance of myoglobin. Starting at a high oxygen concentration, atmospheric, myoglobin at first releases a small percent of its oxygen as the oxygen concentration decreases. As the oxygen concentration decreases a progressively larger fraction of oxygen is release for each decrease in the oxygen concentration of the environment.

At low oxygen concentrations the slope of the binding curve is high; a small increase in oxygen concentration results in a large increase in bound oxygen. This initial slope is known as the affinity of the protein for oxygen. The decrease in the slope of the binding curve when most myoglobin molecules contain oxygen is not due to any intrinsic change in the myoglobin molecules that are empty, the only molecules that can bind oxygen, rather there are just fewer of them. The oxygen binding curve of myoglobin is exactly what you would expect if there was no funny business; it's the default.

The green line is the binding curve of the hypothetical protein superglobin. At oxygen concentrations found in the lungs superglobin is saturated, but when the oxygen concentration drops to 70 percent of atmospheric all the oxygen is released. Thus, as long as the oxygen concentration in the lungs is above 70 percent, superglobin will pick up as much oxygen from the air as it can, while in the other tissues of the body the oxygen concentration will always be at least 70 percent as long as superglobin carries any oxygen at all. This whimsical oxygen carrier does the best possible.

The red curve describes the performance of hemoglobin. It's intermediate between myoglobin and superglobin. A much larger amount of oxygen is released in the internal tissues than would be accomplished if myoglobin was the oxygen carrier in the blood. The dashed red lines indicate typical values of hemoglobin saturation in blood flowing out of the lungs into the rest of the tissues and saturation when it has returned. The difference in saturation is the amount of oxygen transported during this cycle. The difference in saturation between myoglobin and hemoglobin at the lower free oxygen concentration (left dashed line) is the advantage of hemoglobin over myoglobin.

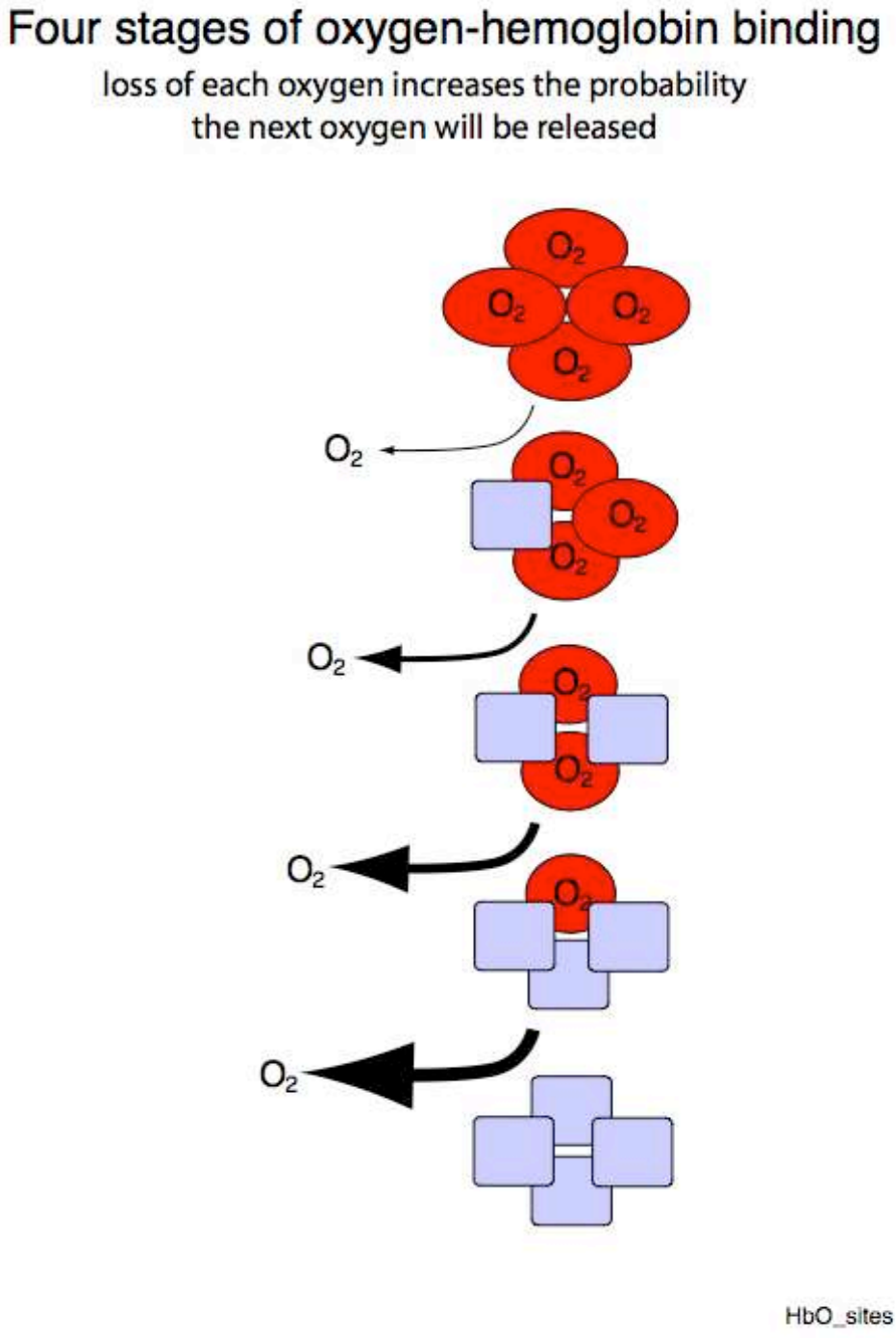
Subunits transmit information

We now know the extent to which hemoglobin is an improvement over myoglobin, but how does hemoglobin do it? A clue is that while the myoglobin molecule is only one unit containing a globin protein chain and a heme group, the hemoglobin molecule has four protein subunits, each with a heme group and oxygen binding site. Since hemoglobin has four subunits that are in contact, the subunits are able to

communicate with each other. Specifically, one subunit can signal the other subunits that it has lost an oxygen molecule by changing its shape.

Let's follow a hemoglobin molecule as it leaves the lungs fully oxygenated. When it is near tissue that has a low oxygen concentration there is a certain probability that one subunit will loose an oxygen molecule which will then be transferred to the tissue by diffusion. The subunit that looses oxygen changes shape, and that change then changes the shape of the other subunits which increases the probability they will loose oxygen. This induced shape change thus constitutes an information transmission mechanism which produces the "S" shaped binding curve.

Figure HbO_sites



Legend HbO_sites. Each of the four subunits of hemoglobin can bind one oxygen molecule (the color of the heme is red when an oxygen is bound and light blue when empty). When an oxygen molecule is released from a subunit the shape of the subunit changes (symbolized as a square in the Figure). This shape change causes a change in the shape of the other subunits (symbolized as becoming less elliptical), decreasing their affinity to oxygen. The interaction between subunits represents information transfer; one subunit "knows" if other subunits have an oxygen molecule. This progressive decrease in affinity generates the characteristic "S" shaped binding curve.

This type of regulation is called allosteric (allo = other; steric = spatial), in contrast to a steric effect, in which, for example one oxygen molecule would interfere with the binding of another oxygen binding by directly blocking the binding site.

Digital or analog?

At the start of this chapter I claimed that operational information was analog in nature. However, the number of oxygen molecules bound to one hemoglobin molecule at any one time is an integer; 0, 1, 2, 3, or 4. Thus the affinity of one hemoglobin molecule must be one of 5 discrete values. Isn't this a digital system?

It is an analog system because the effective oxygen affinity of blood is an average over both time and an immense number of hemoglobin molecules. Oxygen molecules are rapidly binding and disassociating from hemoglobin molecules, with time constants of much less than a second. In addition, there are more than 10^{18} molecules in each ml of blood. Thus the state of one hemoglobin molecule at one instant of time only has an infinitesimal contribution to the oxygen concentration seen by tissue. In contrast, genetic information, e.g. the nucleotide sequence that represents a gene, is present in a cell as one copy, and it is stable over a time scale of years. That is a digital message.

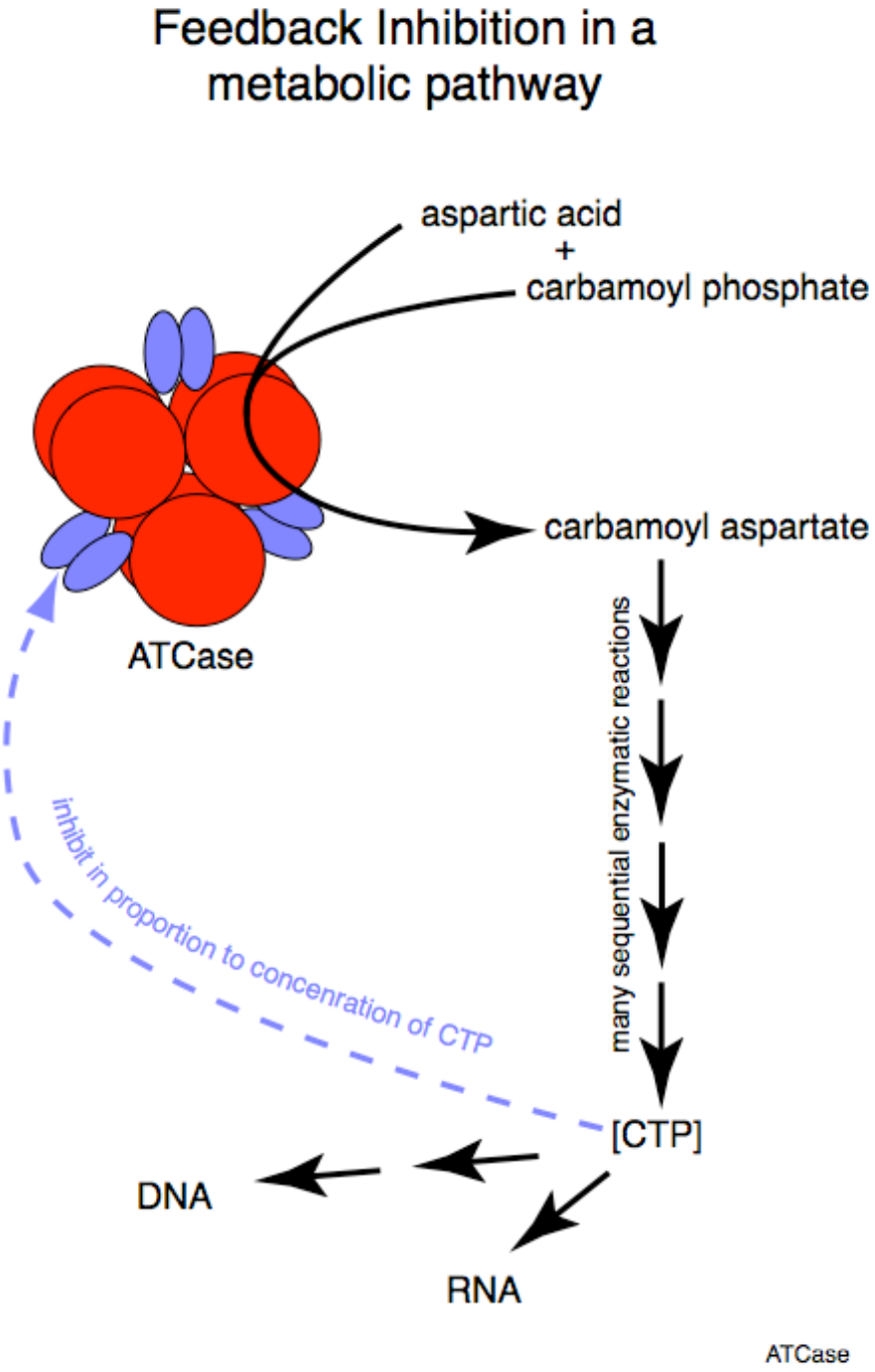
Chemical pathway communication: ATCase

Chemical factories, which break down nutrients to generate energy or assemble small molecules into larger ones are an important part of living cells. A chemical factory uses a sequence of reactions acting on a series of chemical intermediates to produce the final product; biochemists call this a chemical or metabolic pathway. The rates of the intermediate reactions must be controlled to prevent accumulation of intermediates, and of course the overall rate must be controlled so production equals demand.

A common system used by human engineers and by the cell to solve this problem is feedback inhibition; product inhibits an earlier process in the pathway. Thus, if the concentration of product becomes large it decreases the rate of its synthesis which tends to constrain a further increase. In a properly tuned factory the concentration of product is thus stabilized at an optimal level.

In our example a series of sequential chemical reactions produces one of the building blocks used in the synthesis of nucleic acid. In the absence of control the building block would be made at maximum rate, faster than it could be used, and it would accumulate until it crowded out everything else.

Figure ATCase



Legend ATCase. Cytosine triphosphate (CTP) is made in the cell by a series of sequential reactions catalyzed by specific enzymes. The enzyme ATCase carries out the first reaction in that series. ATCase is composed of six subunits that actually catalyze the reaction, and six subunits the bind the final product, CTP, and change shape as a result. The change in shape of these regulatory subunits is transmitted to the catalytic subunits, greatly decreasing their activity. This feedback loop maintains a relatively constant level of CTP in the cell.

Cytidine triphosphate (CTP) is one of the four nucleotides required to make RNA and DNA. The first unique step in the synthesis of CTP is the combination of the amino acid aspartic acid with carbamoyl phosphate. As diagramed in Figure ATCase, this chemical reaction is catalyzed by aspartate transcarbamoylase (ATCase), an enzyme which is inhibited by CTP. Thus, if the concentration of CTP is low the enzyme works at full speed to make product, but as the concentration of CTP increases the rate of production decreases until it equals the rate CTP is being used so a steady state is achieved

The implementation of feedback inhibition of ATCase has some similarity to the mechanism of control of oxygen binding by hemoglobin; changes in the shape of one subunit change the properties of another subunit in the protein. However, in the case of ATCase, the small molecule which must regulate the activity of ATCase, is neither the substrate or product of the reaction, and it has little structural resemblance to them. The solution to this problem is a separate protein subunit that binds CTP, and changes its structure as a result of the binding.

The subunit that binds CTP is very different than the subunit that binds aspartic acid and carbamoyl phosphate to catalyze the production of carbamoyl phosphate. There are 6 identical regulatory subunits that bind CTP and 6 identical catalytic subunits that carry out the synthesis. However, as seen in Figure ATCase, the size of the two types of subunits and geometric arrangement in the protein are quite distinct.

Remarkably, in the laboratory it is possible to dissociate this large enzyme into subunits, and make pure preparations of each type. Furthermore, the regulatory subunits bind CTP, but don't catalyze a reaction while the catalytic subunits carry out the synthetic reaction, but are not inhibited by CTP. You can imagine that the separation of functions like these might facilitate the evolution of complex proteins. The amino acid sequence that accomplishes one task need not be specified by the same gene that accomplishes the other task. If they are in the same gene, either they have to be joined at the ends of the amino acid chains or the structures of the two must be similar enough to function as a chimera. Rather, as distinct subunits, the two proteins need only change so they bind to each other and transmit information by change in shape. In addition, the regulatory subunits can evolve from other proteins that bind CTP.

The ATCase system is analog for the same reasons the hemoglobin system is analog. However, the information is transmitted over a greater distance, since a change in the concentration of CTP throughout the cell must control all the ATCase proteins in that cell. Since cells are typically about 10 μm in diameter, we have been describing information transfer over this distance. Passive diffusion distributes CTP throughout the cell in just a few seconds.

The cell wall functions to isolate and protect internal molecules from the external environment. However, the internal machinery of a cell must respond to some of the

changes in the external environment, and thus information must pass through the cell wall. In the next section we describe a cell in more detail and examine an example of information transfer across the cell wall.

The cell

The cell is the basic unit of living organisms. We have used the term several times previously, but now we need to describe a cell in more detail.

Single cell organisms

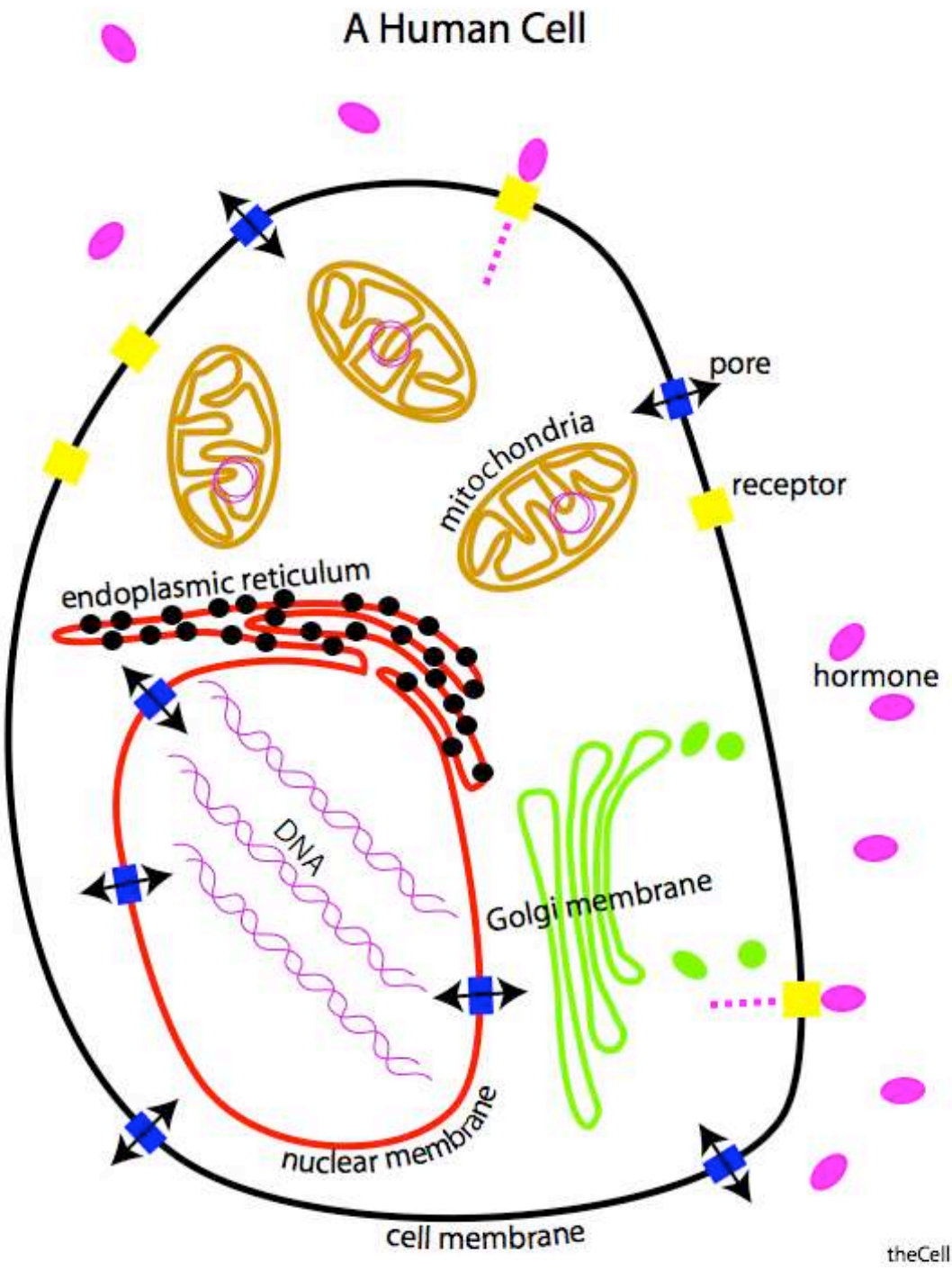
The single cell organisms, e.g. bacteria and yeast, need to isolate themselves from the environment. All the small and large molecules of the cell, at least all those that are not tied together, would just diffuse away without a wall to contain them. The environment inside and outside the cell is aqueous, and thus a lipid (the scientific name for fat or oil) layer provides an effective barrier, since hydrophilic molecules do not dissolve in or penetrate lipid layers. All cells are enclosed by a lipid layer, but single celled organisms also require the cell wall to have considerable mechanical strength also. This is supplied by a polysaccharide wall outside the lipid membrane. This wall is also strengthened by polypeptides, often containing "unusual" amino acids, e.g. different from the ones used by out to make our proteins. This fact is the basis for the selective activity of some antibiotics.

The wall of single celled organisms contain many pores that selectively allow molecules to pass in or out of the cell. This wall also contains receptors that bind to specific molecules and transmit this binding inside the cell. However, our example of information transfer occurs in the cell wall of a multicellular organism.

Multicellular organisms

Most multicellular organisms are enclosed by specialized material, e.g. skin or shell, that provides mechanical protection from the environment. Thus the outer cell wall of a single cell organism is not needed. However, the cells still must be isolated chemically from their environment, even if the environment fairly constant and benign, e.g. blood. The lipid membrane provides that function.

Figure theCell



Legend theCell. The cell is the physical unit of a living organism. The cell membrane isolateds the internal components from the exterior environment. Organisms that evolved early consisted of only one cell, and thus the cell membrane (or in this case a cell wall, since there are several layers protecting the cell) keeps all the internal molecules from leaking out into the external world. The cell wall also establishes an internal, constant chemical environment that enables the molecular machines to operate. Much of the interior volume of the cell is filled with membrane structures. The nucleus contains the DNA, while an evagination of the nucleus, the endoplasmic reticulum, is the site of most of the protein synthesis. The Golgi membrane transports a class of proteins to the cell surface where they can be secreted. The mitochondria are the sites of the final stages of conversion of nutrients to energy.

Figure theCell is a simplified diagram of a human cell. Most of the DNA is inside a nucleus defined by a membrane. Molecules pass from nucleus to cytoplasm and visa versa by way of nuclear pores. Most protein synthesis takes place on ribosomes that are embedded in extrusions of the nuclear membrane, the endoplasmic reticulum. Many proteins are processed to mature forms and transported to the cell surface on a stack of membrane vesicles called Golgi membranes. The mitochondria are double membrane structures that evolved from symbiotic, prokaryotic organisms. Mitochondria contain a small genome that codes for some of the their proteins, while other mitochondrial proteins are specified by genes in the nuclear DNA. The chemical environment inside mitochondria is different than the cytoplasm. The difference in pH across the mitochondrial membrane is generated by oxidation of nutrients and this difference in turn drives the conversion of ADP to ATP, the source of energy for the entire cell machinery.

Thus, the cell is hardly a homogenous bag of water, but instead contains many micro environments. The interior of the cell is aqueous in nature, but it also has some of the characteristics of a solid state machine, with many of the processes occurring on two dimensional membrane surfaces.

Like unicellular organism, the outer cell membranes of multicellular organism contain many species of pores and receptors. In multicellular organisms a major function of these membrane receptors is to transmit information between cells. This coordinates the activities of all the individual cells, and thus constitutes a major operations information network of the organism.

Control of cell growth and division

Single cell organisms must control growth and division. If the environment is favorable and there are sufficient nutrients cells must grow and then divide when they reach a characteristic size. Failure to grow at a high rate puts them at a competitive disadvantage to other organisms that can grow faster. However, if cells attempt to divide when conditions are unfavorable they risk running out of energy or material in the middle of a division. They also use up stores of energy which could better be used to maintain a basal level of function during hard times.

Multicellular organisms have an even more complex task of cellular growth regulation. The cells in developing embryos must constantly change their profile of gene expression in order to differentiate into the different tissues and organs of the adult. The different types of cells of the adult must adjust gene expression to maintain

a dynamic equilibrium, which to the uninformed observer might seem to be merely a static state.

Cancer

The importance of a control system can often be best appreciated when it fails. Cancer is the failure of a control system which then causes cells to grow and replicate in an inappropriate manner. Since there are many control systems that regulate the growth of many types of cells there are also many types of cancers. Thus cancer is more a symptom than a specific disease.

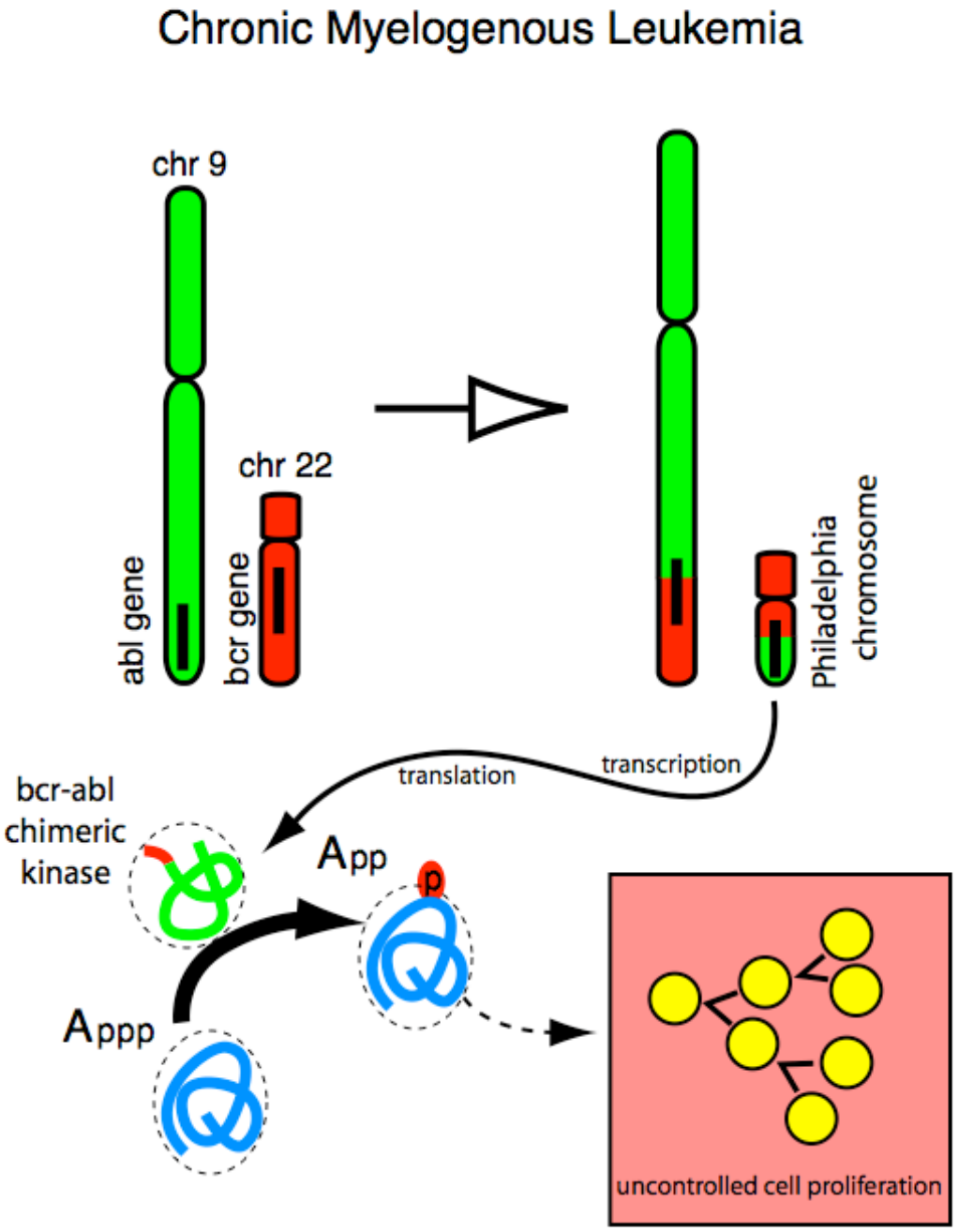
While cancers are diverse in effect the vast majority share a common cause: damage to the DNA genome. The damage can be a simple mutation, deletion, insertion, or a rearrangement of the genome. Here we look at one cancer as an example.

Chronic myelogenous leukemia

Cancers (and most other diseases) are named for their symptoms, since knowledge of causes come later than efforts at categorization. Chronic (as opposed to acute) means that the disease lasts for a long time; myelogenous means that the cancer cells originate in the bone marrow; leukemia means that the cancer cells are white blood cells which eventually crowd out all other cells in the blood.

The vast majority of CML is caused by a specific translocation between chromosome 9 and 22 which occurred in a granulocyte-platelet stem cell as it divided in the marrow. The translocation, or recombination, produces a dramatically smaller chromosome 22, which can be distinguished from normal under the microscope. In 1960 two researchers working in Philadelphia demonstrated the correlation between this truncated chromosome and CML. What became known as the Philadelphia chromosome was the first clear evidence that cancer in humans was caused by genetic damage.

Figure Cancer



Cancer

Figure Cancer. Recombination between DNA in chromosomes 9 and 22 generates two abnormal chromosomes. The new chromosome 22, the Philadelphia chromosome, contains a chimeric gene spanning the recombination point, and this gene produces a chimeric protein which retains the kinase activity of the abl kinase. However, a fragment of the bcr protein has replaced the segment of the abl kinase that normally inhibits activity when bound to other cell proteins. Thus the chimeric abl kinase is always maximally active. The phosphates it transfers to other proteins activates them and ultimately causes the cell to continually grow and divide, thus creating the leukemia.

The chimeric protein produced by the Philadelphia chromosome retains the protein kinase (catalyzing transfer of phosphate from ATP to proteins) activity of abl, but a segment at the beginning of the kinase has been replaced by a fragment of bcr. The lost abl segment normally inhibits kinase activity, at least when bound to other cell proteins. Without this segment the kinase continuously adds phosphates to proteins which in turn cause the cell to grow and divide without control. This uncontrolled growth is the leukemia.

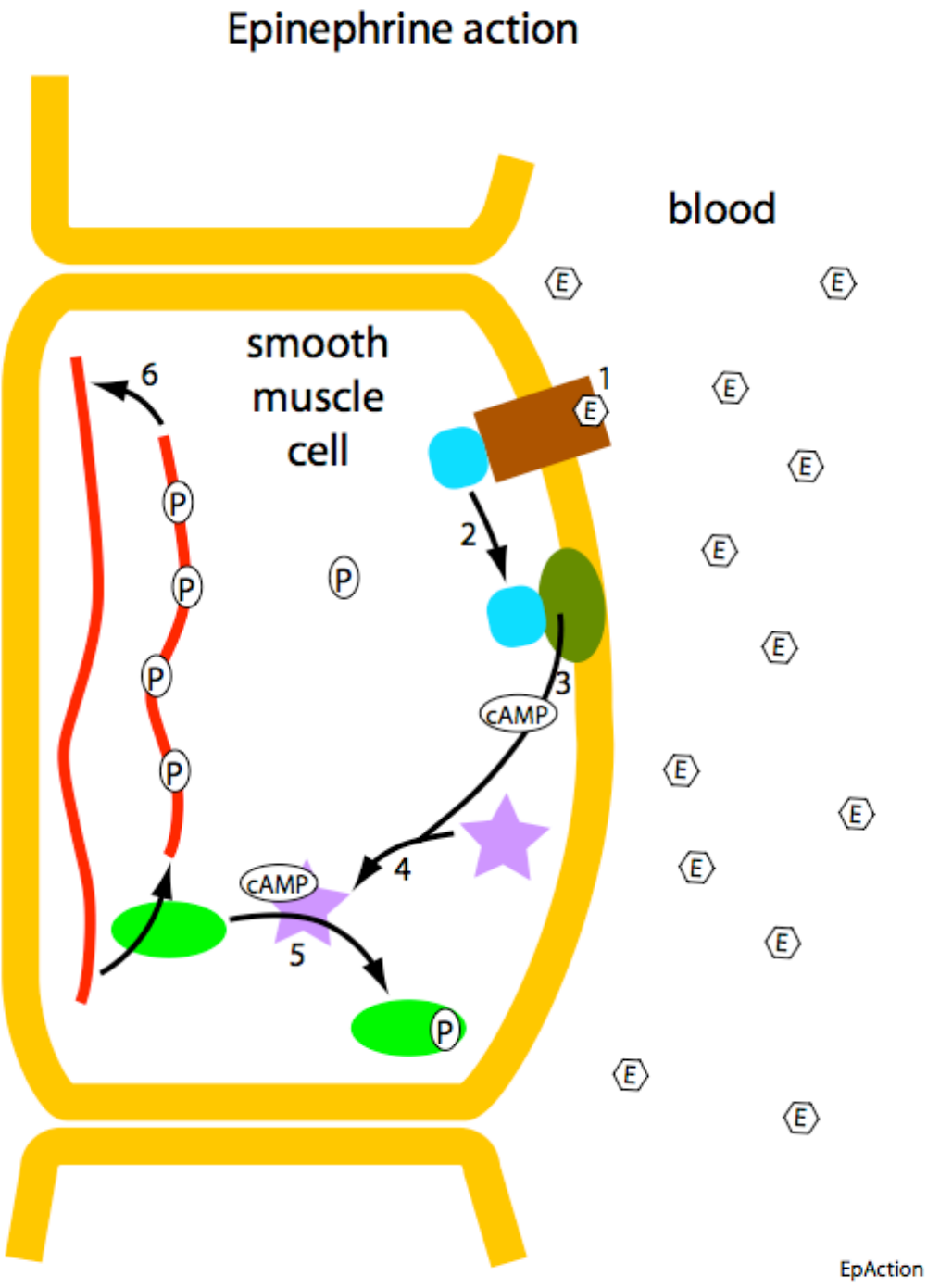
Recombination usually occurs only between very similar chromosomes (or DNA molecules), for example between the two versions of chromosome 9 in the cell, and thus the recombination event that generates the Philadelphia chromosome would seem to be an aberration. It is indeed a rare event, most people don't get CML even though their granulocyte stem cells divide millions of times during their lifetime. But there does seem to be something special about the regions around the Philadelphia breakpoints, because we don't observe a random collection of recombinations. Examination of the nucleotide sequence in these regions, {Saglio, 2002 #58} revealed the existence of similar duplicons (sequences present multiple times in chromosomes), which might be the cause of the aberrant pairing and recombination. While duplication of sequences often provides gene copies that can then evolve to perform new functions (as described in the previous chapter) duplications also represent a potential danger.

In the case of CML, but not for all cancers unfortunately, we know the exact molecule, the bcr-abl kinase, that is the cause of the uncontrolled cell growth. It thus might seem possible to develop an inhibitor for this enzyme which would then control the cancer. In fact it has been possible, and the drug, STI571 (Gleevec) developed and marketed by Norvartis, produces remission for CML in about 90 percent of patients. Development of the drug was not at all trivial however, because there are more than 100 other tyrosine kinases with similar active sites that perform other needed functions. Thus it is remarkable that STI571 has the needed specificity to halt the progression of the cancer without having unacceptable side effects. Unfortunately, the power of evolution here shows the other edge, as mutant kinases, not inhibited by STI571, frequently arise after a period of remission.

Communication between cells: epinephrine

To illustrate the transmission of information between cells I will use the epinephrine (aka adrenalin) system. We start in the middle of the transmission network and describe how the presence of epinephrine in the blood causes changes in the cell. In this example the cell is a smooth muscle cell that lines blood vessels and the change is relaxation. Relaxation increases the diameter of the vessel and allows more blood to flow through.

Figure EpAction



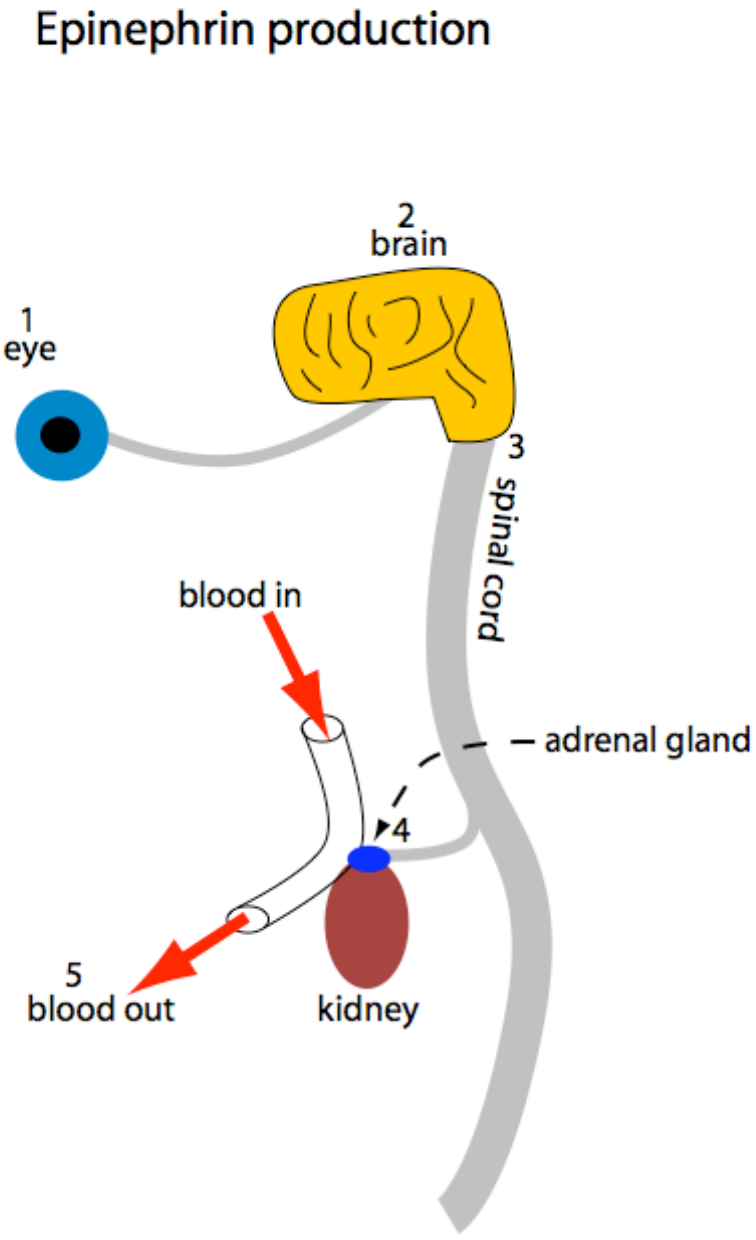
Legend EpAction. Epinephrine in the blood binds to specific receptors on the cell surface. The binding changes the shape of the receptor and causes the release of a subunit which diffuses along the interior of the cell membrane and activates the enzyme that produces cyclic AMP (c:AMP) which activate an enzyme that produces an inactive form of myosin kinase. In the absence of myosin kinase most of the myosin in the cell looses phosphates and relaxes.

Epinephrine action

Figure EpAction presents the series of events occurring after epinephrine appears in the blood. Step 1 is the binding of epinephrine to the β-adrenergic receptor protein. The receptor spans the cell membrane, exposed to both the outside and inside cell environments. Epinephrine binding producing a change in the shape of the entire receptor and this weakens its attachment to the α–subunit protein inside the cell. In step 2 the α–subunit is released and diffuses along the inside of the cell membrane where it binds to the adenylate cyclase enzyme and changes its shape. In step 3 the altered adenylate cyclase produces many molecules of cyclic AMP (cAMP) from ATP. In step 4 the cAMP diffuses in the cell and binds to protein kinase. In step 5 the cAMP:protein kinase complexes transfer phosphate from ATP to the myosin light chain kinase (MLCK). The phosphorylated MLCK is inactive.

Phosphates are constantly being removed from myosin. If MLCK is in the inactive form no phosphates are being added to myosin and the amount of phosphorylated myosin in the muscle decreases. Since it is the phosphorylated myosin that is contracted, the decrease of this form allows the cell to relax and the blood vessel to enlarge.

Figure EpProduction



EpProduction

Legend EpProduction. In this example the eyes see an image which is relayed to the brain. The brain determines that there is great danger, and sends signals down the spinal cord and then to the adrenal gland which releases epinephrine into the blood system.

Epinephrine production

Figure EpProduction describes some of the stages in the production of epinephrine. Step 1 is the acquisition of images by the eye that will eventually generate a "Fight or Flight" reaction. In our world this could be an oncoming automobile that almost collides with you. Partially processed images are transmitted to the brain where in step 2 they are evaluated to generate the "Fight or Flight" reaction. In many cases there will also be input from other sensors, e.g. ears and nose. The brain does the processing and in step 3 sends a specific message to the adrenal glands, on top of the kidneys, using a chain of nerve cells. So far the process has taken less than a second although the information has traveled more that a meter (in a human). The nervous system is obviously important in operations, and we will get to it in the next section. The adrenal glands have already made and stored epinephrine, which is a derivative of the amino acid tyrosine. Thus, in step 4 this epinephrine only needs to released into the blood and in step 5 it is carried throughout the body. Transport of the signal by the blood over a distance of a meter takes only a few seconds, as I can personally attest. I received an IM injection of epinephrine to ameliorate an allergic reaction. The nurse squeezed the syringe and asked me to count to 10; at a count of 6 I experienced a rush that almost blew my head off. Now the epinephrine is at the surface of the cells it will affect and we are at the start of the processes described in the previous section.

This system is far more complex than the ATCase system described previously. Like the ATCase system, interaction between protein subunits is an important part of the regulation pathway. However, there are many more steps in this pathway and in some information is transmitted over distances of several meters instead of several microns. The two big subsystems that make this possible are the circulatory and nervous systems.

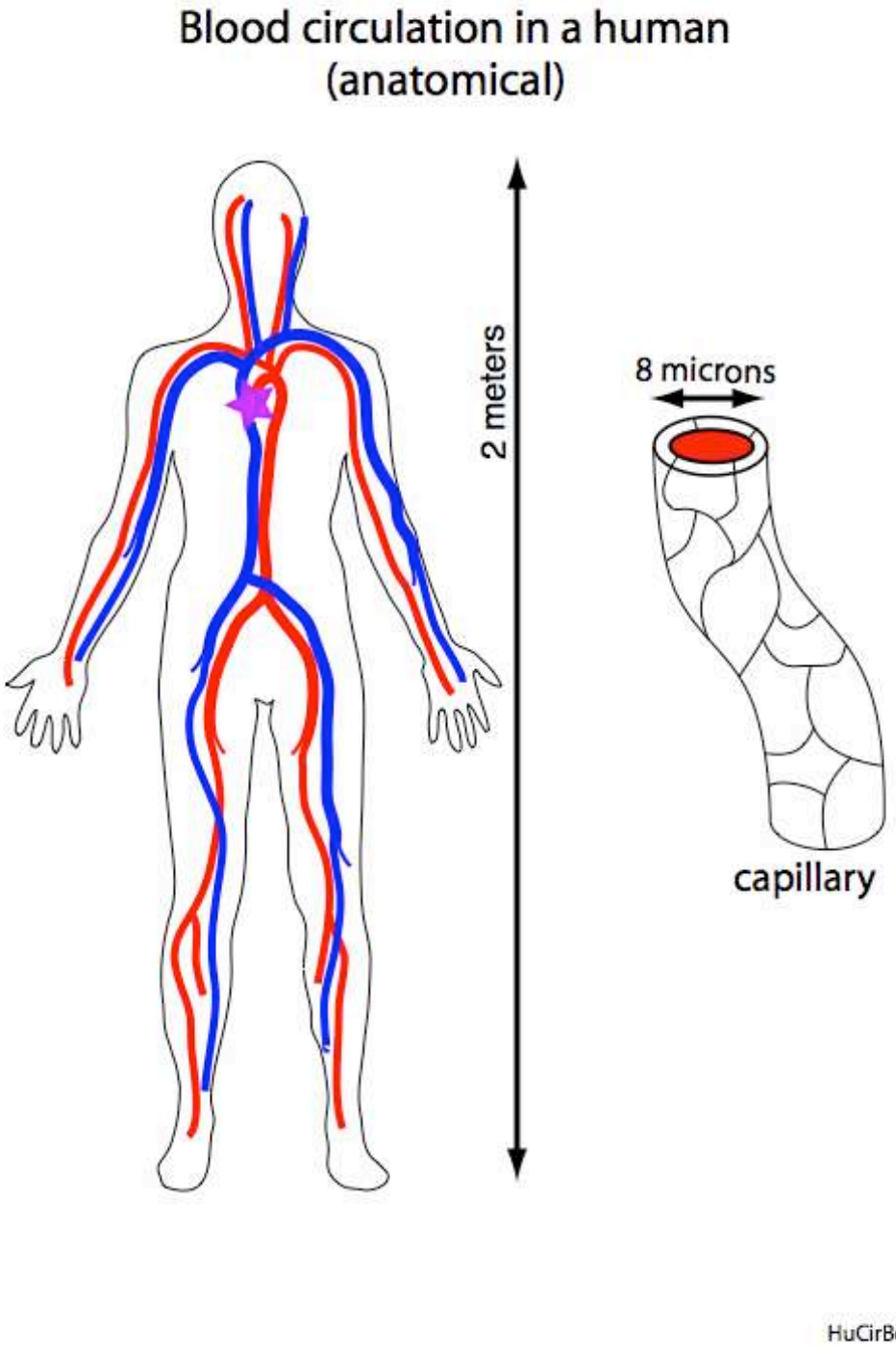
The circulatory system

Some multicellular organisms do not have an efficient mechanism for transporting material among the cells. However, as the number of cells, the size, and the rate of metabolic activity increases, a system for rapid transport of molecules throughout the organism become necessary.

The body

In Figure HuCirBody the basic plan of one loop of the human circulatory system is laid out. The aortic artery leaves the heart and radiates into all parts of the body, splitting into progressively smaller and smaller arterioles, finally becoming capillaries. The major transfer between blood and tissue occurs in capillaries, tiny tubes as small as 8 microns in diameter with walls only a single cell thick. Many capillaries are so small that red blood cells must be deformed in order to pass. Red blood cells containing the mutant sickle hemoglobin, which is semi-crystalline and relatively rigid, can occlude the capillary, causing tissue damage and intense pain.

Figure HuCirBody



Legend HuCirBody. The heart pumps blood from the veins into the arteries. The arteries branch out into the body, becoming smaller and smaller until they become capillaries. It is mainly in the capillaries that gases, nutrients, waste products, and hormones are effectively transported into and out of tissue.

The aorta has the greatest diameter of all arteries and blood flows through it at the greatest velocity, 330 mm/sec. As the diameters of the arterioles decrease their number increases more rapidly and thus the total vascular cross sectional area increases. As a result, the velocity of blood flow is about 100 fold lower, 0.3 mm/sec, in the capillaries. The slower the better in the capillaries because most of the exchange between blood and tissue occurs there, and diffusion takes time.

Blood flows from the capillaries into veins of increasing diameter, the inverse of the arteriole system. The pressure here is much lower than in the arteries, and the vascular walls are corresponding thinner. Finally the blood is returned to the heart in the vena cava.

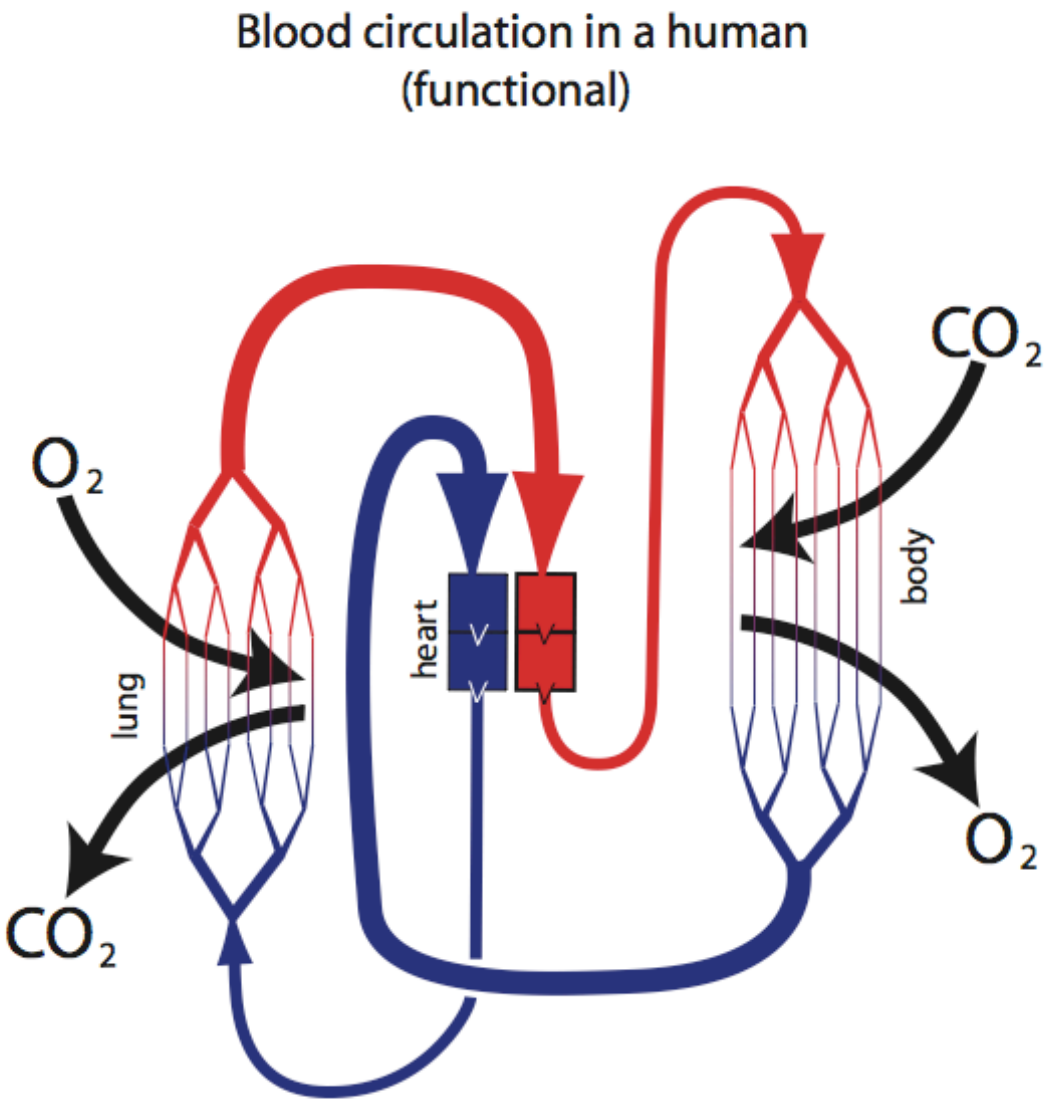
The lungs

Transport of oxygen and carbon dioxide is so important that a second circulatory system, in series with the loop just described, transports blood through the lungs where gasses can be exchanged with the atmosphere. Again, the arteries become smaller, feed into capillaries, and then the blood is collected into larger and larger veins to return to the heart.

The heart

There are two circulatory loops and two pumps in the heart which are fused into one muscle. Each pump has two chambers, a low pressure ventricle that receives blood from the veins and delivers blood to the high pressure atrium which then sends it into the artery. The four chambered pump and its relation to the two circulatory loops is diagramed in Figure HuCirFunct.

Figure HuCirFunct



HuCirFunct

Legend HuCirFunct. The human has two serial circulatory loops. First the blood is pumped by one half of the heart through the lungs and back to the other half of the heart. The other half of the heart then pumps the blood through the rest of the body. Each half of the heart has two chambers. The larger ventricles receive blood at low pressure from the veins and act as a reservoirs for the muscular ventricles that provide the major increase in pressure.

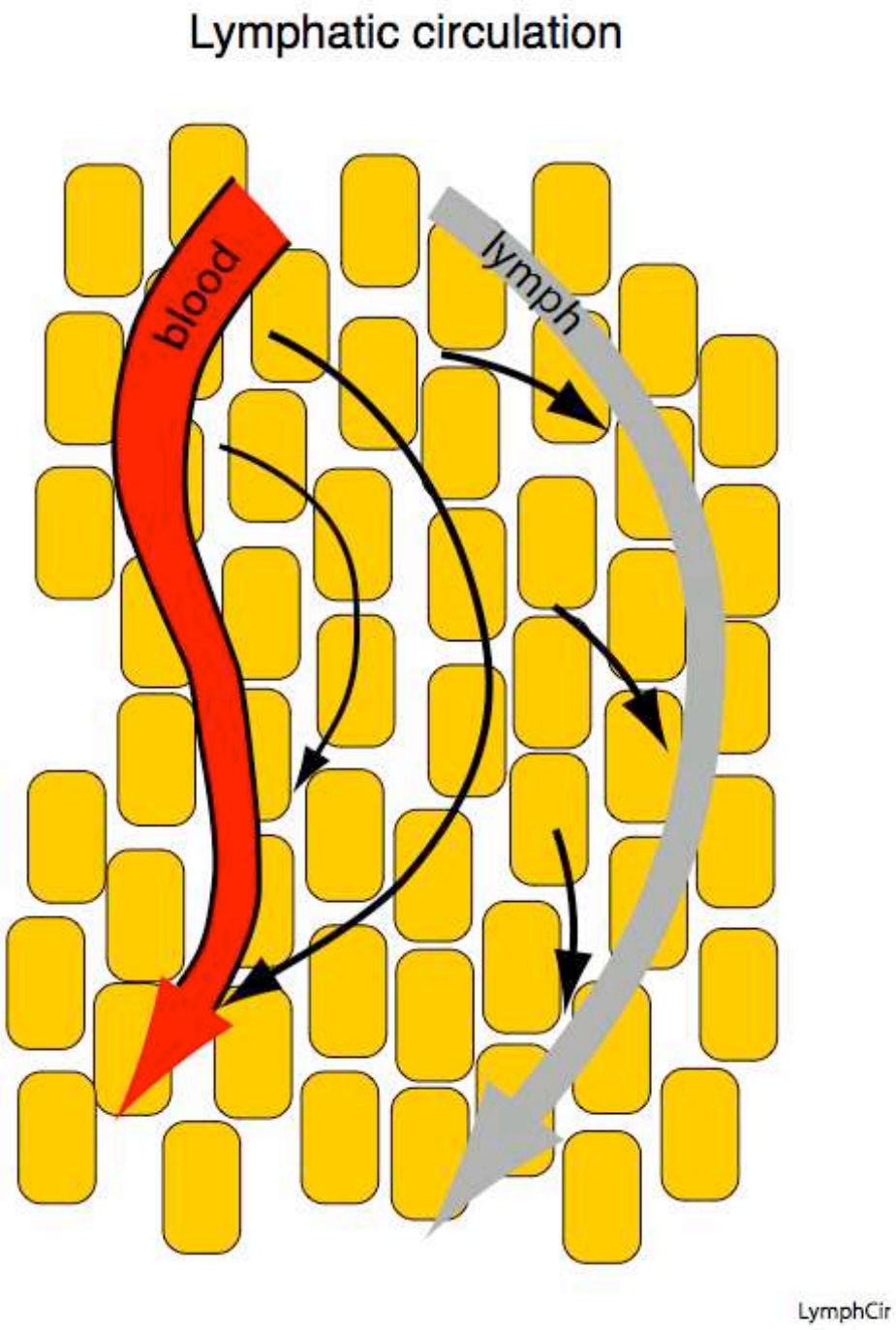
The lymph

There is such an immense number of capillaries in the human body that the average cell is only 20 cell diameters distant from one. However, there is an intermediate fluid system that transports material from capillaries to cells, the interstitial fluid or lymph.

The walls of capillaries are leaky. Small gaps between the epithelial cells that form the walls of the capillaries allow fluid to percolate into the tissue surrounding the capillary, and small leaks between the cells of the tissue allow fluid to continue to move deep into the tissue. The gaps that allow this leakage are so small that large molecules, e.g. antibodies, have difficulty squeezing through. Thus, the concentration of antibody in the lymph is less than the concentration of antibody in the blood. However, smaller molecules, e.g. hormones, pass freely.

The majority of the lymph that flows from capillaries into tissue returns to the blood by leaking back through the walls of veins. However, there is another path, the lymphatic system, a network of thin walled vessels which collect the lymph from tissue and return it to the venous system through the thoracic duct.

Figure LymphCir



Legend LymphCir. As blood flows through the capillaries, fluid and smaller molecules leak through the walls into the interstitial space. Most of this fluid, lymph, returns to the capillaries before they join the veins, where the fluid pressure is low. However, some lymph is collected in an independent network of vessels, the lymphatic network. The lymph is eventually returned to the blood at the thoracic portal.

The flow of lymph in this network is not driven by a dedicated pump, rather the normal movement of skeletal muscles in combination with valves in the lymphatic vessels pushes the fluid through the system. If you are inactive for some time, lymph can pool in tissue. This pooling is most obvious if you are standing, so that the force of gravity causes lymph to collect in your legs. Soldiers standing at attention, a very unnatural activity, are advised to periodically contact and relax their leg muscles to ameliorate this problem. For the same reason it can be beneficial for airline passengers to flex their muscles periodically and if possible get out of their seat and walk.

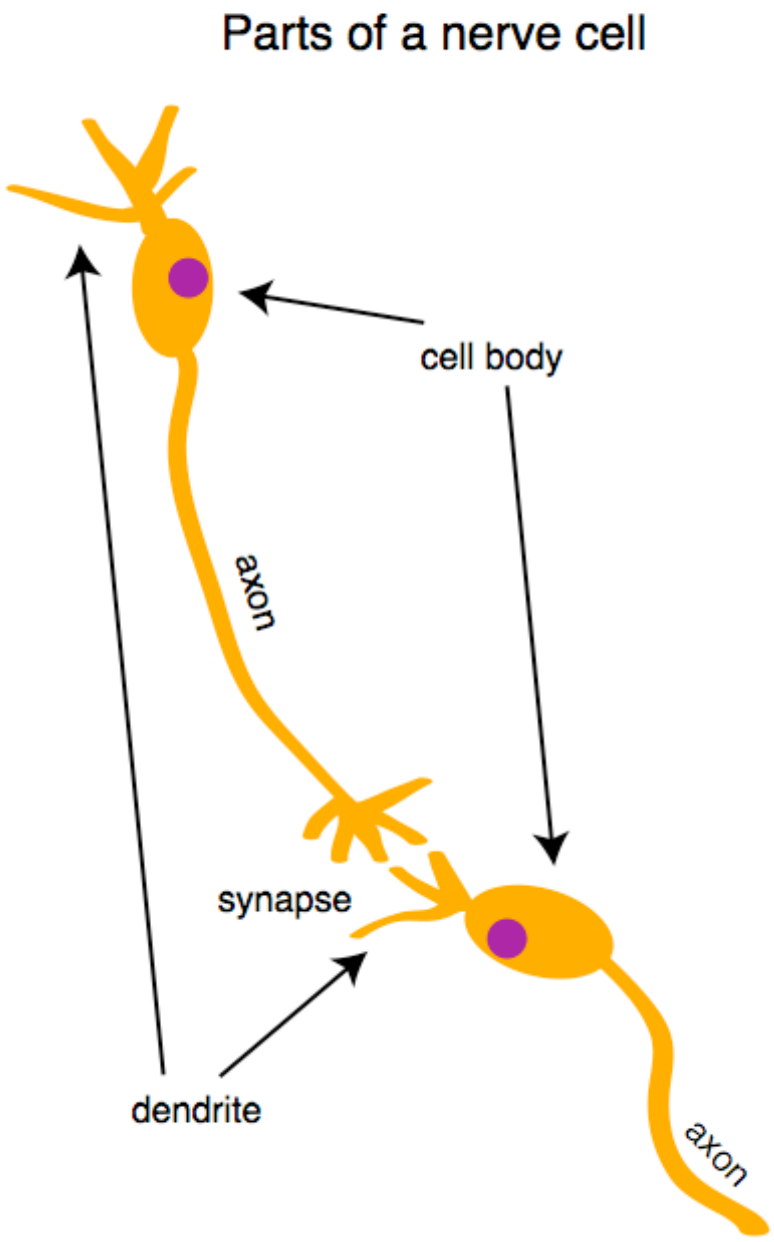
The nervous system

Our previous discussion of the transmission of the "Flight of Fight" message from the brain to the blood vessels only covered the distribution of epinephrine throughout the body over a period of a few seconds. However, the release of epinephrine into the blood requires messages to be sent from the eyes to the brain and then to the adrenal glands by way of the nervous system. Message transmission by nerves is by far the most rapid means of communication over large distances, requiring only 0.01 sec to cover a distance of one meter. In addition, only a nervous system has the potential to make an immensely complex network of connectivity that can be modified by experience; a brain.

The neuron

Nerves are built up of single cells, neurons. In Figure NerveA we see a prototype of a neuron. While there are several types, they all contain a cell body, dendrites, and an axon. The cell body contains the nucleus, mitochondria, and the rest of the metabolic machinery that carries out the housekeeping choirs of the neuron. Two specialized bundles of membranes, dendrites and the axon, project from opposite ends of the body. The message carried by the neuron, an electrical pulse, starts at the end of one of the dendrites. The pulse then travels through the cell body and moves down the axon at high speed, up to 100 m/sec.

Figure NerveA



NerveA

Legend NerveA. A signal enters a nerve cell at the end of one of the branching dendrites. It then passes across the cell body, which handles metabolic activities of the neuron, and enters the axon. The axon typically transmits the signal over the major distance.

The electrical pulse

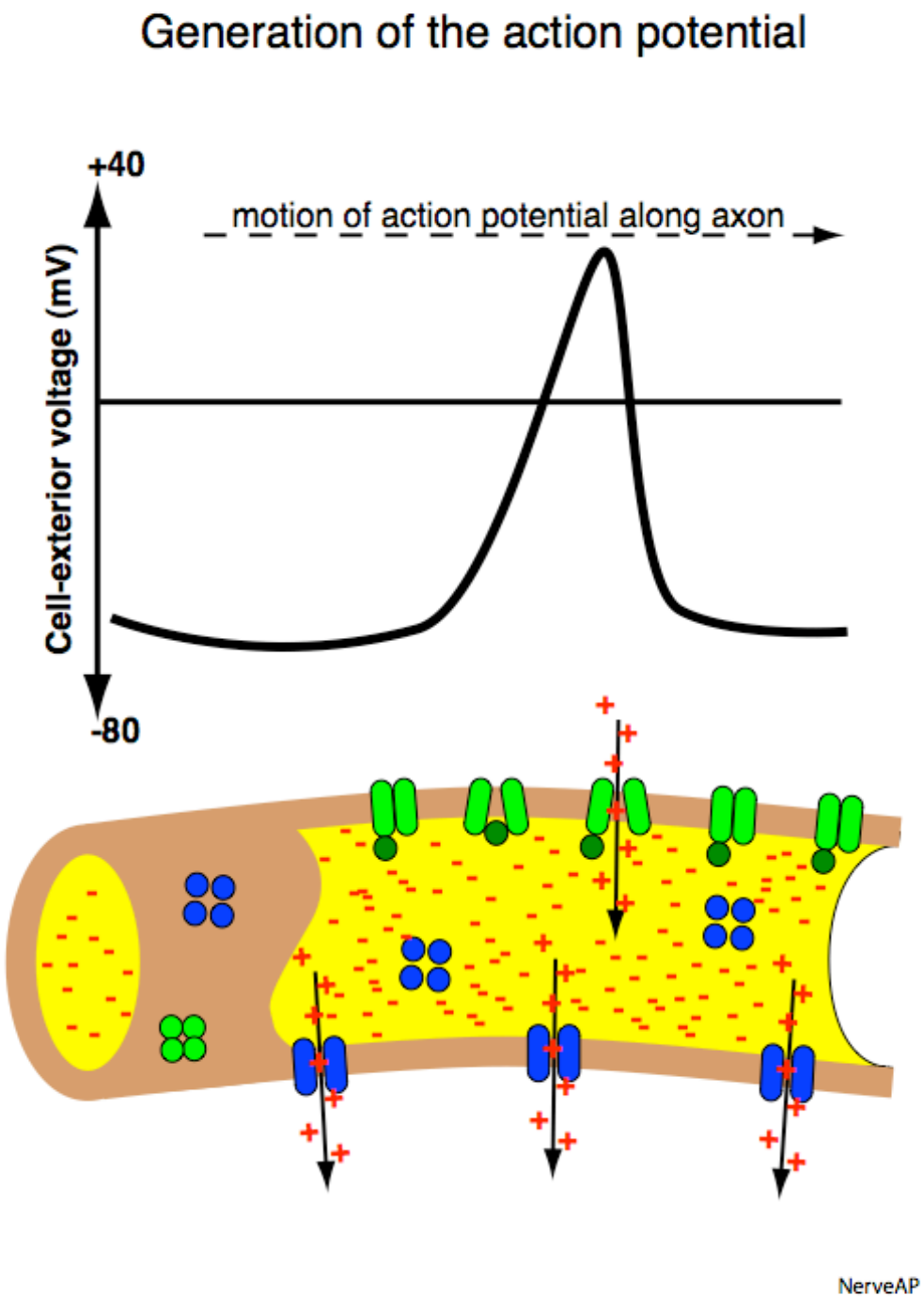
Transmission of an electrical pulse by the neuron utilizes the fact that the interior of a cell is at a negative electrical potential relative to the outside, a fact that we have not described previously. However, we have pointed out that the ionic environment inside a cell not the same as the outside, that the lipophilic cell wall isolates the two aqueous environments, and that the ionic imbalance is established and maintained by molecular pumps. The pumps of course require energy, usually provided by the hydrolysis of ATP to ADP.

The pumps in human cells produce a concentration of potassium ion (K^+) about 10 times higher inside the cell than outside, but a concentration of sodium ion (Na^+) 10 times lower inside the cell than outside. These concentration differences represent stored energy that can be converted into a difference in electrical potential by channels that selectively allow specific ions to flow with the concentration gradient. Specifically, a "resting potential" of about -0.07 volts (–70 mV) is generated by the resting K^+ channels in the membrane which allow a constant trickle of K^+ to pass from the interior to the exterior, but exclude movement of the negative Cl^- ions. The pumps that established the K^+ difference in the first place have to work constantly to maintain the K^+ concentration difference.

Suppose a sudden decrease in the negative voltage across the membrane occurred at one point on the axon, e.g. by allowing some of the excess Na^+ outside to enter. Before the resting channels could restore the potential, the excess Na^+ would move out from this disturbance spreading the voltage spike as a wave of diminishing size. Thus the axon is thus analogous to a wire, or more accurately a co-axial cable; two conductors separated by an insulating layer. However, the neuron has functional equivalence of distributed batteries which maintain a potential between inside and outside conductors. These batteries have sufficient internal resistance and the neuron has distributed capacity so that it takes a characteristic time to restore the potential after it has been disturbed, and the potential spreads out as a wave. While movement of ions down the axon generates the wave, the ions are linked by the electric field generated by their movement. As ions in one location start to move they effect the ions ahead by the electric field they generate, they don't have to actually bump into them. Thus the velocity of the wave can be faster than the actual velocity of the ions. This is analogous to movement of an electric pulse down a coaxial cable, with ions replacing electrons.

This spreading wave of depolarization is called passive, to distinguish it from an active wave, or action potential. The active wave, which moves in one direction and does not diminish in size as it propagates, requires a second type of channel, the voltage gated Na^+ channel. The relationship between propagation of the action potential and the two types of ion channels is shown in Figure NerveAP.

Figure NerveAP



Legend NerveAP. The voltage pulse that travels down the axon represents a transient interruption of the negative resting potential which is maintained by potassium channe. When the leading edge of the pulse reaches the voltage gated sodium channels, they open and amplify it, eventually forcing the voltage positive. At this time a fragment of the channel plugs the opening and stops the influx of positive sodium ions. Now the resting channels can take over and restore the potential. The pulse has passed.

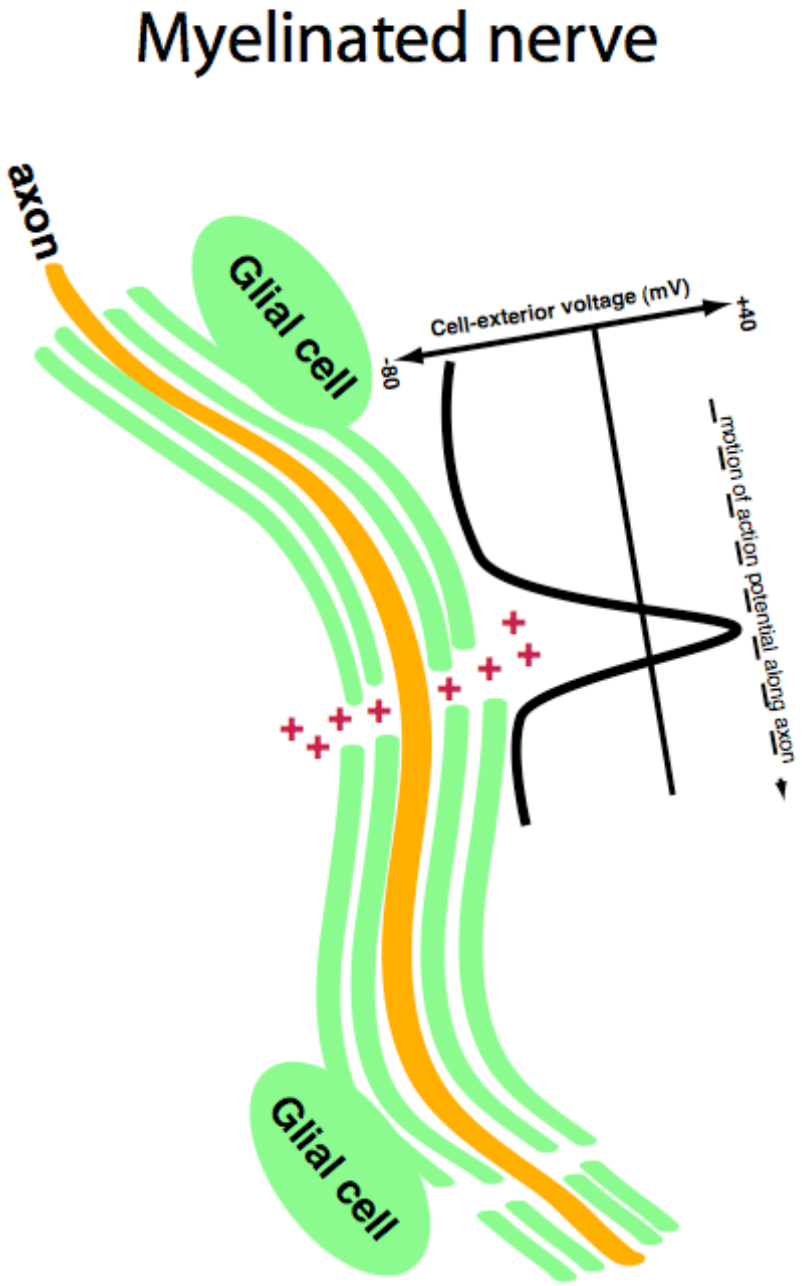
Both types of channels shown here have four subunits which span the lipid membrane. As we have described, the resting K^+ channels, the blue structures, allow a constant flow of positively charged potassium ions to flow out of the cell to maintain the resting potential. The voltage gated Na^+ channels, the green structures have three states. Normally they are closed, but if the voltage increases slightly they change to a second state, open, allowing Na^+ to enter the cell. This rapid influx of Na^+ causes the potential to become less negative, eventually reaching a positive value of +30 mV. However, a discrete fragment of the channel protein is only loosely anchored at the interior lip of the channel, and after a characteristic time it diffuses into the opening and plugs it, creating the third state. The resting channels are then able to restore the voltage differential across the membrane before the plug falls out of the gated channel, which remains closed.

The voltage gated Na^+ channels are thus amplifiers, and the characteristics of the plugs determine the length of the pulse as it moves down the axon. The velocity of the pulse is determined both by the speed of the "passive" movement of ions and by the kinetics of the response of voltage gated channels.

Myelinated neurons

Neurons that need to transmit pulses rapidly over a long distances have evolved to use the membranes of another cell type, the glial cells. The cell walls of the glial cells extend from their cell body to form flat, double membranes which wrap around the axons of the neuron, as seen in Figure NerveMS.

Figure NerveMS



NerveMS

Legend NerveMS. The myelinated nerve is covered by several layers of membrane from a gial cell. Each glial cell only covers the axon for a mm or less, and there are gaps between the membranes of sequential glial cells. Voltage gated sodium channels can only amplify the voltage pulse at these gaps. However, this is sufficient because between gaps the resting potassium channels also do not function, and thus pulse is not attenuated as rapidly as it would be in a non-myelinated axon. Since transmission speed is greater in the passive mode, a myelinated axon transmits voltage pulses much more rapidly than a non-myelinated axon.

The glial membranes are so tightly wrapped around the axon that they isolate it from the extracellular environment, except for short nodes between the membranes of the adjacent glial cells attached to an axon. When an action potential travels down a myelinated axon the ion channels can only act at a node, for it is only at a node that the external ionic environment is accessible. Between nodes the pulse must be propagated in the passive mode, however since this region is isolated from the external environment, the pulse suffers minimal attenuation by resting channels. The velocity of the voltage pulse in passive mode is actually much faster than the velocity when it is constantly shaped by the voltage gated channels. Thus, as long as the voltage gated channels localized at the node amplifies the pulse back to its nominal value before it enters the next myelinated sector, you have a functional high speed axon.

This seems analogous to the older fiber optic lines where periodically the attenuated pulse of photons was converted to an electrical signal, amplified, and then converted back to photons to continue on in the fiber.

The ends of neurons

Neurons can be connected together, end to end, to produce a longer functional unit. In this most simple case the axon end of one neuron contacts a dendrite of another. However, multiple axons can contact dendrites of one neuron, and one axon can link to dendrites of multiple cells. The dendrites of some neurons are functionally connected to sensory cells, e.g. the light receptors of the eye, the olfactory receptors of the nose, the auditory receptors of the ear, etc. The ends of the axons of some neurons must activate muscle cells, while as we have described, the ends of other axons must cause specialized cells to release hormones into the blood, e.g. epinephrine.

The area of functional contact between neurons or between neurons and the cells that send or receive messages to neurons, is called a synapse. The membranes are not actually in contact, although the separation is quite small, on the order of 0.1 micron. In the majority of cases the message is not transmitted as an electrical signal. Instead the incoming electrical signal causes small vesicles to release neurotransmitter molecules into the synaptic space, these diffuse to neurotransmitter rectors on the surface of the receiving cell, and an electric pulse is generated. Because the synaptic gap is so thin, the entire process can occur in less than a millisecond.

The minute to minute information flowing through the neural system consists of electrical pulses, but the connections between neurons represent information changing over a period of hours or days. Of course the outline of the network is determined by genetic information; it is coded in the DNA. We do not know the relation between nucleotide sequence and the topology of the neural network, except that it is very indirect. In fact, experimentally determining the topology of the neural network is generally not easy. If a dendrite and an axon end are far apart we know they are not connected, but if they are close they may or may not be functionally connected. The

only sure way to establish connectivity is to artificially generate a pulse in one axon and see if it is transmitted to the other. This type of analysis is extremely tedious.

Much of the network connectivity is changed in response to experience, it is in fact our memory and thus is mostly generated after birth. There are at least two very different types of memory, short (minutes to hours) and long term (days to years). A memory starts as short term and then may or may not be converted to a long term one, a transformation that requires protein synthesis. Injuries and diseases may result in loss of the ability to form long term memories, while leaving the formation of short term memory intact.

The neural message is analog

The description of the neural network so far would seem to define it as a digital information system. The action potential, the voltage pulse that constitutes the message, is all-or-none, like a digital system. However, unlike a true digital system, the time sequence of pulses does not constitute a code in which deletion or addition of one pulse could make a significant change in the meaning. Rather, the time average of the pulse rate constitutes an essentially continuous analog variable. The greater the number of pulses per unit time, the greater the magnitude of this continuous variable.

A discussion of neural coding must be somewhat limited here. Although we think we understand the coding in peripheral nerve systems, the details of neural activity in the brain, by far the most complex neural system, are still obscure. Compared to man-made electronic systems, the transmission speed of neural signals is very modest; 10^7 m/sec for electronics versus 10^2 m/sec for nerves. This factor of 10^5 is the ratio of motilities of electrons in metals to motilities of ions in aqueous solutions. However, 10^2 m/sec is sufficient to control our muscles, since our size and mass prevents significant changes in movements in times less than a few msec. Since the width of the neural pulse is never less than a msec, a nerve could not carry more than 1000 bits/sec., and since the coding is not digital, but rather frequency modulation, the true information rate must be even lower.

The brain

The human brain must contain a large number of neurons, perhaps as many as 10^{11}, and many of these neurons have many more synapses than a simple peripheral nerve, perhaps as many as 1,000. However, our brain is not very good at solving simple arithmetic problems rapidly. For example, we can only use a tiny fraction of the neurons in our brain for integer multiplication. Integer multiplication is not something evolution has selected for, it's just an artificial operation we have learned. Our fundamentally low speed neural system can't do multiplication rapidly with one unit and there is no massively parallel hardwired subsystem in our brain to do integer multiplication.

However, our brain carries out immensely complicated logical operations in just a few seconds. It is only fairly recently that even a very large computer has been able to been able to win in chess against a human, and chess is a very "logical" and defined problem compared to the normal activities of a human. The computer must evaluate potential moves by comparisons to classical games stored in memory and logical predictions of the outcomes of all possible moves.

The human uses these tools as well, but also looks for and evaluates patterns, sometimes by following "hunches" or "feelings" which represent logical "calculations" that the human can not define explicitly. The human carries out pattern analysis by large parallel processing, which the brain does well. The pattern processing used by humans to play chess must have some similarity to the pattern processing that solves everyday problems, e.g. identifying visual images in the context of memory. The number of logical operations that must be done when you are trying to find your wife or husband in the supermarket is immense. It not just that each visual field is complex, and you may have to analyze dozens per second as you move your head around, you also will not have seen your spouse at exactly the same angle and in the same lighting ever before. And yet you find them most of the time.

Part of the reason for the apparent discrepancy between the logical ability of humans and computers is due to fact that humans usually do not understand how they do many tasks; why should they? However, all the details are needed to enable a computer to do the task, because an explicit computer program must be written. It took many years to write computer programs that just enable a computer system to "read" printed text (optical character recognition) or translate text from one language to another (and computers do translation at a basic, literal level). We humans learn to do these things by a process that hides the actual logical operations. Indeed, writing a computer program that does something is the only way to prove that you do indeed understand all the required steps. It is the best way to learn how a problem is solved.

Our brains not only use larger numbers of units simultaneously to solve a problem compared to man made computers, the units are different in design, and are probably each running different programs. This is only possible because you don't need a team of hardware engineers to design and debug each type of neuron network, and you don't need a team of software engineers to write and debug a program for each group of synapses. The living computing machine evolved over millions of years, with the evolution of the parts occurring mostly in parallel. The software is the result of learning and training, but we don't know the details of the training.

Chapter summary

In order to respond to changes in environment the organism must exchange information between its components. The transmission times range from milliseconds to many minutes and the transmission distances range from a nanometer to several meters.

The structure of these systems and mechanism of action are extremely diverse, but they are all analog in nature, with information in different channels generally carried by different molecular species. The address for the information is specified by the structure of the molecules while concentration represents intensity. Four examples illustrate the range of operational controls.

Hemoglobin carries oxygen from the lungs to all the other tissues of the body. Hemoglobin must release oxygen to tissue when the oxygen concentration is low, and it is desirable to release more than would occur if hemoglobin had a simple oxygen binding curve. This is accomplished because the four subunits of hemoglobin communicate with each other. If one subunit looses oxygen its shape changes which

changes the shape of the other subunits to increase the probability they will also release oxygen.

Metabolic pathways produce substrates for growth by a series of chemical reactions catalyzed by specific enzymes. Production must be proportional to need. This control can be accomplished by feedback inhibition: the final product inhibits the initial reaction. The enzyme ATCase catalyzes the first step in the production of the nucleotide CTP. This reaction is accomplished by the catalytic subunit of the enzyme, while the regulatory subunit binds CTP and then changes shape to decrease the activity of the catalytic subunit.

Hormones are produced by specific tissues, released into the blood, carried long distances by the circulation to finally produce an effect by binding to specific receptors. Epinephrine is produced by adrenal glands attached to the kidneys. This hormone is then carried throughout the body by the circulation and binds to receptors on the surface of muscle cells lining blood vessels. The binding causes the receptor to change shape which releases another protein inside the cell. A chain of reactions finally leads to relaxation of the muscle which allows the blood vessel to expand and deliver a larger blood flow. This type of hormonal response travels a meter in several seconds.

The release of epinephrine is triggered by a signal from the brain which travels about a meter to the adrenal glands. Both the generation and the transmission of the signal requires electrical pulses to travel along nerve cells. These nerve cells have generated an electrical potential across the membrane, and thus between inside and outside, by differential pumping of charged ions. The electrical pulses represent transient changes in the permeability of the membrane of the nerve cell which allow a transient flow of ions across the membrane. Signals can travel along nerve fibers at speeds of 100 m/sec. Information is transmitted as groups of pulses, but is not coded in the exact height or timing of the pulses, but rather in the average frequency. Thus, as with the other operational systems, the nerve network is essentially an analog information system.