Introduction to Biochemistry

Next time you’re at the gym, think about the fact that all the cells in your body are working together to achieve your goals. Your muscles would rapidly fail without your liver sending out the sugar they need to contract. You could only last for a few minutes without your heart pumping oxygen-containing blood throughout your body. And without your brain sending signals to mastermind it all, you wouldn’t even make it out of the locker room.

One of the goals of this course is to understand how all the body’s organs work together during exercise. This is pretty complicated, as you can imagine, so before we can understand this cooperation between organs, we have to first discuss the building blocks of the organs, cells. We can reduce cells even further down to their components, the basic biological building blocks called lipids, carbohydrates, proteins, and nucleic acids. That’s what biochemistry is all about, trying to understand the whole from its parts.

Chemistry Review

If you were to take biochemistry, you would first have to take a semester of introductory biology and four semesters of chemistry. However, our goal in this course is to learn just enough about biochemistry to understand what’s going on at the cellular level when we exercise. Let’s first highlight some of the most important concepts from all those chemistry courses that you (probably) haven’t taken so that you can follow the rest of this chapter.

A. What is chemistry anyway?

Chemistry is the study of material substances and the changes they undergo. All materials are comprised of matter, which can be defined as anything that occupies space and has mass. Matter is composed of extremely small particles called atoms. There are about a hundred different kinds of atoms in nature. Each
A different variety of atom is called an element, and chemists arrange these in the periodic table of the elements (Figure 1). Not all the elements are represented equally, either on Earth itself or inside cells. All life forms are based on the element carbon (C), and they also contain relatively large amounts of hydrogen (H), nitrogen (N), oxygen (O), calcium (Ca), phosphorus (P), and sulfur (S).

Atoms are made up of even smaller particles: positively charged protons, negatively charged electrons, and neutral neutrons. The arrangement of these subatomic particles puts the protons and neutrons together in a massive nucleus with the much smaller electrons buzzing around in a cloud. Atoms have equal numbers of protons and electrons, which means that the charges cancel and they are electrically neutral.

Atoms can link together in different ways to form molecules, with the “glue” that holds them together called chemical bonds. Chemical bonds are often shared pairs of electrons. The arrangement of atoms in a molecule is called the structure, and chemists have developed some shorthand ways of representing structures.

As an example, let’s look at the molecule ethanol, which contains two atoms of carbon, six atoms of hydrogen, and one atom of oxygen. We can write a chemical
formula for ethanol as $C_2H_6O$, where the subscripts reveal how many of each type of atom is in a molecule. Usually, chemists would draw this molecule using a simple depiction with symbols for the atoms and lines for bonds (Figure 2C). This type of drawing can be further simplified by leaving out the explicit bonds between carbon and hydrogen, since there are so many carbon-hydrogen bonds in biological molecules (Figure 2D).

**B. Oxidation-Reduction Reactions Release Energy**

Chemical reactions occur when the atoms in molecules link up in new ways to produce new substances with different properties than the original materials, often releasing or consuming energy. Energy produced during chemical reactions can sometimes be harnessed to do useful work, such as lifting a big weight or throwing a ball.

An important type of chemical reaction in metabolism is the **oxidation-reduction** (or **redox** for short) reaction. Redox processes enable you to use the energy within fuel molecules and also provide the energy needed to power your Ipod and drive your car. Redox reactions involve the transfer of electrons from one substance to another. The substance that loses electrons is **oxidized**, while the substance that gains electrons is **reduced**. In reactions involving electron transfer there cannot be an oxidation without a reduction. Note that when an atom or molecule undergoes oxidation or reduction, it may end up with an unequal number of protons and electrons, thereby becoming a charged species called an **ion**.
Like Dissolves Like

Cells are pretty much tiny bags of salty water containing a lot of dissolved molecules and ions. A mixture of water with dissolved substances is called an aqueous solution. The dissolved materials are called the solutes and the water is the solvent.

Some materials clearly don’t dissolve well in water. You’ve undoubtedly noticed that your salad dressing made up of oil-and-vinegar (which is mostly water) contains two distinct layers until you shake it up. The type of particles within a mixture dictates whether they will comingle on a molecular level or form distinct layers. When the particles interact with significant attractive forces, the result is a homogeneous mixture, with all particles comingled randomly on a molecular level to form a solution.

Water is composed of an oxygen atom and two hydrogen atoms. Oxygen has a stronger attraction for the shared pair of electrons than hydrogen, meaning that there is a partial negative charge on the oxygen and a partial positive charge on
the hydrogen. Water is therefore a polar compound, meaning that it has a separation of electric charge. The types of materials that dissolve well in water are other molecules that have charge separation. Chemists summarize this phenomenon with the rule of thumb that “like dissolves like.” That is, because water is a very polar molecule, it dissolves other polar molecules and materials composed of ions, like salt (Figure 2.5). Substances that dissolve well in water are called hydrophilic. On the other hand, molecules such as oil, which do not dissolve well in water, are called hydrophobic. These materials do not dissolve well because there is no separation of charge between the atoms that comprise them.

D. Acids, Bases, and pH

An important type of molecule in biological systems is an acid. Acids produce H⁺ in aqueous solution (chemically identical to a proton). An example is hydrochloric acid, HCl, which splits into its components, H⁺ and Cl⁻, in aqueous solution:

\[ \text{HCl} \rightarrow \text{H}^+ + \text{Cl}^- \]

Acids often react with their chemical opposites, bases, which produce OH⁻ in aqueous solution. An example is sodium hydroxide, NaOH, which splits into its components, Na⁺ and OH⁻, in aqueous solution:

\[ \text{NaOH} \rightarrow \text{Na}^+ + \text{OH}^- \]

Reaction of equal amounts of an acid and a base results in neutralization, or production of water and a salt:

\[ \text{HCl} + \text{NaOH} \rightarrow \text{H}_2\text{O} + \text{NaCl} \]

The pH scale is a way of measuring the amount of acid present in solution. Values for pH typically fall between 0 and 14.0, with low values meaning an acidic solution, high values meaning a basic solution, and 7.0 meaning a neutral solution. The pH is related to the amount of H⁺ in solution as follows:

\[ \text{pH} = -\log [\text{H}^+] \]

Brackets mean that the amount of H⁺ is expressed as the concentration in moles per liter of solution (M).

We can describe a solution as acidic or basic based on the pH as follows:

- **Acidic solutions** have pH < 7.0.
- **Basic solutions** have pH > 7.0

Bodily fluids such as blood have pH values very close to neutral. Because maintaining the correct pH is essential for many of the chemical processes in living organisms, acid-base balance is tightly controlled. Blood pH is normally maintained at 7.4. If the pH rises
or falls by more than about a half-pH unit, serious illness or death may occur. Excessive acidity of the blood results in a condition called metabolic acidosis, which can occur during kidney failure, uncontrolled diabetes, poisoning, and shock. The opposite of acidosis is alkalosis, which results from excess base (alkali) in the body fluids.

Regulation of acid-base balance occurs in the lungs and kidneys by using a buffer system that serves to minimize the effects of added acid or base. Blood buffering is critical, particularly during periods of intense physical activity when lactic acid is produced.

**The Cell**

Organisms are composed of one or more **cells**, the basic units of life. One of the basic principals of biology is that cells only arise from other cells. That is why our bodies contain reserves of **stem cells**, flexible precursor cells that can irreversibly change into many different types of specialized cells. For example, all the different blood cell types (red cells and the various types of white cells) are replaced regularly, arising from a single type of stem cell in the bone marrow. Scientists are actively investigating the potential of stem cells to grow into new tissues to replace those damaged by injury or diseases like Alzheimer's.

There are about 200 different kinds of cells in the human body, and each adult human contains about $10^{13}$ cells all working together. Different types of cells display a wide variety of shapes and sizes. Let's focus on the key features found in a "generic" animal cell (Figure 3). The cell is enclosed by the **plasma membrane**, which forms the boundary that separates the cell from its environment. Only cells of higher organisms, the **eukaryotes**, contain interior compartments called **organelles** that are also enclosed by a membrane.

Key parts of a eukaryotic cell include the following:

- the **nucleus**, where the genetic material containing the information necessary for the synthesis of all cellular molecules is found.
- the **mitochondria**, where fuels are oxidized for energy. On average each cell contains hundreds of mitochondria.
- the **cytosol**, the watery solution of proteins, nutrients, and other molecules in which the organelles are suspended.
Thousands of chemical reactions occur throughout the cell, and careful regulation of all these processes must exist for the good health of the organism. When regulation runs amuck, diseases such as cancer are often the result. In the next sections, we look in detail at the molecules within the cell that are responsible for the tightly coordinated processes that occur there.

**Lipids**

**Overview of Lipids**

Waxes, fats such as lard, and oils belong to the general class of biological molecules called lipids. Although biological lipids are structurally quite diverse, none of them dissolve well in water because they hydrophobic. Lipids play a number of key roles in the cell, representing stored chemical energy, comprising the basic structural units of membranes, and carrying signals between cells.
Energy Storage Lipids: Triglycerides

Most of the energy reserves in humans and other animals are stored in the form of **triglycerides**, lipids that contain a core molecule called *glycerol* bonded to three *fatty acids* (Figure 4). Triglycerides are efficient energy storage molecules for two major reasons. First, they are highly reduced, thereby releasing a lot of energy when they are burned. Second, because they are hydrophobic, the molecules pack closely together without carrying water molecules, reducing the net weight. Carbohydrates, the other principal form of stored chemical energy in living organisms, are highly hydrated, meaning that they are stored with associated water molecules that add to the weight but not to the energy content.

Triglycerides form oily droplets in the watery environment of the cell. Humans and some other animals contain specialized fat cells (*adipocytes*) that are almost entirely filled with triglycerides (Figure 5).

Triglycerides also serve other useful purposes in animals. Polar bears, seals, walruses, and other warm-blooded animals living in extreme climates have a thick layer of fat under the skin to insulate them against the cold. Camels contain a large reserve of triglycerides in their humps. Like all hydrocarbons, combustion of triglycerides produces carbon dioxide and water. Thus, the “ship of the desert” metabolizes its lipid stores to obtain both
water and energy. We will examine how triglycerides are oxidized to release energy when we consider energy production during metabolism.

**Membrane Lipids: Phospholipids**

The boundary between the inside and the outside of a cell (or an organelle) is composed of a double layer of lipids called the membrane (see Figure 3). Biological membranes are comprised largely of phospholipids, similar in structure to the triglycerides except that one of the fatty acids is replaced by a "head group" containing a charged phosphate group (Figure 6).

When placed in water, phospholipids spontaneously assemble into the lipid bilayer that forms the foundation of membranes (Figure 7). Because “like dissolves like”, the charged head groups interact with water on the outside of the structure and the greasy fatty acid tails interact with each other on the inside of the structure. This structure provides a barrier that is relatively impermeable to hydrophilic molecules because of the hydrophobic interior. On the other hand, hydrophobic molecules can effectively "dissolve" in the interior, allowing them penetrate the membrane and get inside the cell.

**Rigid Lipids: Steroids**

Animal membranes also contain cholesterol, a member of the steroid family. All steroids are based on a common structure consisting of a fused-ring system
(Figure 8). This structure is very different from the phospholipids shown above and provides rigidity to the membrane. Up to 25% of the lipids of some membranes can be cholesterol. The single polar group of cholesterol is the -OH, which lines up with the polar head groups of the phospholipids in a membrane. The rest of the molecule inserts itself into the hydrophobic interior of the membrane. Other steroids also play important biological roles, particularly in signaling. Familiar examples include the sex hormones, estradiol and testosterone, which we will talk about more later in the course.
Carbohydrates
Overview of Carbohydrates

Carbohydrates, commonly known as sugars, are quite polar and water-soluble. Carbohydrates are the most abundant biological molecules on Earth and have a variety of cellular functions, including in energy storage and structure.

Monosaccharides

The building blocks of carbohydrates are the monosaccharides. Common monosaccharides include glucose, blood sugar, and fructose, fruit sugar. Monosaccharides can react with other monosaccharides to form disaccharides (containing 2 monosaccharide units; Figure 9), oligosaccharides (3-19 units), and polysaccharides (>20 units).

Polysaccharides

Polysaccharides that contain repeating units of glucose (glucose polymers) are important energy storage and structural molecules in both plants and animals (Table 1). Two important glucose polymers are cellulose and starch, which chemically differ only in how the glucose subunits are linked together (Figure 10). Cellulose has the bonds pointing up, and starch has the bond pointing down. Although this may seem like a minor difference, the two are dramatically distinct. Cellulose, the principal component of wood, is water-insoluble and indigestible (to animals). About a third of all plant matter is cellulose: it provides the scaffolding that holds up most plants, giving rigidity to their cells. On the other hand, starch, which is made by plants to store energy for future use, is an easily digestible compound widely enjoyed in potatoes, pasta, and bread. Humans make a similar molecule for energy storage called glycogen. Cellulose and starch illustrate the principle that structure affects function in biological systems.
Figure 10. Starch and cellulose are both polymers of glucose. They differ only in whether the connecting oxygen atom points down as in starch or up as in cellulose.
Proteins
Overview of Proteins
Proteins have a diverse range of functions in the cell, including nutrient storage, catalysis, immunity, transport, signaling, and structural roles (Table 2). In this section, we first examine the general structures of proteins and then look at some examples in more detail.

<table>
<thead>
<tr>
<th>Protein</th>
<th>Function</th>
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<tbody>
<tr>
<td>Ferritin</td>
<td>Stores iron</td>
</tr>
<tr>
<td>Alcohol dehydrogenase</td>
<td>Oxidizes ethanol</td>
</tr>
<tr>
<td>Gamma globulin</td>
<td>Immune response</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Transports oxygen</td>
</tr>
<tr>
<td>Insulin</td>
<td>Signals sugar uptake</td>
</tr>
<tr>
<td>Keratin</td>
<td>Comprises hair</td>
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Amino Acids and Peptides
Proteins are polymers constructed from twenty different building blocks called amino acids, much as words are constructed from letters. Amino acids all contain an amine and a carboxylic acid group but vary in the identity of the “side chain” (Figure 11). Side chains have different chemical properties (Figure 12), ranging from polar to hydrophobic groups. Amino acids react with other amino acids to form peptides.
Figure 12. The structures of the twenty common amino acids.
An example of a peptide is aspartame, also known as the sugar substitute Nutrasweet® (Figure 13). Other small peptides also have biological activity, including some signaling compounds in the body. The enkephalins, naturally occurring pain relievers made in the brain (endorphins), are pentapeptides, containing five amino acids. Some peptides, such as oxytocin, act as hormones. Oxytocin has powerful biological activity, inducing labor in pregnant women and stimulating the release of milk during nursing.

Figure 13. Some biologically relevant peptides. Aspartame is approximately 200 times sweeter than sugar. Leucine enkephalin is a naturally-occurring pain reliever in the brain. Oxytocin controls contraction of uterine muscle.
Polypeptides

When many amino acids link together, a **polypeptide** is formed. Proteins consist of one or more polypeptide chains. After a polypeptide chain is synthesized in the cell, it folds into a unique three-dimensional shape (Figure 14). Folding is guided by such forces as “like dissolves like” with hydrophobic amino acids typically interacting with other hydrophobic amino acids in the interior and polar amino acids interacting with water on the exterior.

Structure Determines Function

One of the fundamental principles of biochemistry is that the order of amino acids in the polypeptide chain (the **sequence**) determines the three-dimensional shape, or **structure**, of a protein. That is, a particular protein always has the same sequence of amino acids in the same organism and thus the same structure. The key to the action of many proteins in the cell is specific binding to another molecule- this binding is often the result of the two molecules “fitting together” appropriately. Certain amino acids are then poised in exactly the right position to carry out crucial chemical reactions (Figure 15).
Thousands of chemical reactions must occur in a typical cell in order to maintain life. Many of these reactions would occur much too slowly without the aid of protein catalysts called enzymes, which can lead to rate enhancements of up to $10^{17}$. Note that a rate enhancement of $10^{17}$ means that a reaction that takes one second in the presence of an enzyme would take over 3 billion years without the enzyme.

An enzyme is specific for a particular target molecule, called the substrate, much as a key fits only a certain lock. Again, the three-dimensional structure of the protein is crucial for its function. Through a variety of chemical strategies,
enzymes induce their substrate to undergo a particular chemical reaction, much as a key opens a lock. Like the key, the enzyme remains unaltered by the reaction.

Many poisons and pharmaceuticals act by inhibiting enzymes. One example is the nonsteroidal anti-inflammatory drugs (NSAIDS), which include many compounds in the athlete’s medicine cabinet (such as ibuprofen, acetominophen, and aspirin). These compounds inhibit a specific enzyme involved in the production of prostaglandins (Figure 16). Prostaglandins are hormones that act locally to produce diverse effects in the body, including transmission of pain information to the brain, modulation of the thermostat in the hypothalamus, and inflammation. Blocking the production of these messengers means that the NSAIDs have many beneficial effects in the body, including reduction of pain, fever, and inflammation.

![Arachidonic Acid][1]

![Prostaglandin][2]

**Fig 16** Aspirin and other NSAIDs inhibit the enzyme cyclooxygenase (COX), which is required for the synthesis of prostaglandins, regulators of pain, fever, inflammation, blood clotting, and other cellular processes. Thus prostaglandin inhibitors reduce pain, fever, and inflammation and thin the blood.
Antibodies

The action of the immune system is mediated by another class of proteins called antibodies. Antibodies are composed of four polypeptide chains, two “heavy” chains and two “light” chains, which interact to form a Y-shaped structure (Figure 17). Antibodies bind to specific molecules called antigens, which are often part of disease-causing microorganisms. Specificity arises from the amino acids at the tips of the Y, which differ between antibodies and are therefore called the “variable” regions. Rather than inducing their antigens to undergo chemical reactions like enzymes, antibody binding triggers a massive immune response that results in annihilation of the invader.

**Figure 17** General structure of an antibody, which binds specifically to its target antigen. Using this binding mechanism, an antibody tags a foreign invader, like a microbe, for attack by other parts of the immune system. Antibodies are produced by white blood cells.
Antibody responses are vital to help us fight infectious disease but can have disastrous consequences, as in the case of the rejection of blood of the wrong type. Specific carbohydrates on the surface of red cells determine blood type. These carbohydrates also act as antigens for specific antibodies found in people with other blood types. For example, people with type A blood have the A antigen on the surface of their red cells and antibodies in their bloodstream against the type B antigen. If type B blood is injected into a person with type A blood, these antibodies will perceive the type B blood cells as invaders and target them for destruction by the immune system. Additionally, antibody binding to the B-antigens triggers clumping of the foreign cells into an insoluble mass, a process called agglutination (Figure 18). Serious consequences may result for the patient, including shock, kidney failure, and death.

Before blood types were discovered in 1900, doctors experimented with blood transfusions in patients dying from severe blood loss, often transferring blood directly from a healthy donor. Sometimes these treatments saved lives and other times they hastened death when the blood was of the wrong type. Discovery of
ABO blood types was a key step in the ability to use transfusions routinely in medical procedures.

The agglutination reaction is now used to determine blood type. Specific antibodies are added to a sample of blood. The antibody that clumps the cells together to form a solid that falls out of solution (a precipitate) reveals the blood type. Before receiving a transfusion today, a patient’s blood is routinely typed to avoid problems with blood incompatibility.

**Structural Proteins**

Proteins also play a variety of structural roles. Muscle, hair, skin, and connective tissue are largely comprised of proteins with three-dimensional structures well suited for their functions. Amazingly, the same protein, keratin, comprises not only hair and skin but also wool, nails, claws, quills, horns, and hoofs. The degree of hardness of the resulting material is dependent on the number of covalent linkages involving the amino acid cysteine. Two cysteines form an S-S covalent bond (a disulfide linkage) that links keratin strands together to form multi-stranded fibers. In the toughest keratin filaments, such as those comprising rhinoceros horn, almost one in five amino acids is a cysteine involved in a disulfide linkage.

**Abnormal Protein Structures**

A recurring biochemical theme is that protein structure determines function. Occasionally, there is an error, or a mutation, in a crucial amino acid of a protein. Mutations can be a recipe for disaster. An example is hemoglobin S, in which the nonpolar amino acid valine replaces the polar amino acid glutamate on the protein surface, resulting in an unfavorable interaction with water (Figure 19). Instead, a new interaction with another hemoglobin molecule results. The net result is an aggregation of hemoglobin molecules to insoluble fibers that cause red blood cells to “sickle” and then burst under certain conditions.

Individuals who inherit hemoglobin S from both parents can suffer greatly from this disorder, called sickle cell disease, which can even result in death. Ironically, possession of one copy of this type of hemoglobin is an advantage to those who live in regions plagued by malaria, such as Africa and the Mediterranean, because the malarial parasite cannot survive in red blood cells that contain hemoglobin S.

Many other genetic diseases are the result of a protein that contains a single “wrong” amino acid, leading to the loss of functional protein. How does the structure of a protein go wrong? Typically, it is an error in the gene that codes for that protein, leading us to the last type of biological building block, the nucleic acids.
**Figure 19.** Left: The presence of a single hydrophobic amino acid on the surface of hemoglobin (top) results in individual molecules clumping together (middle), eventually forming long, insoluble fibers (bottom). Right: The result is “sickling” of red cells to an elongated shape that can lead to painful “log jams” in blood vessels.
Nucleic Acids

Overview of Nucleic Acids

The instructions to assemble each protein in the cell can be found in the genetic material, comprised of the nucleic acids, DNA and RNA. Deoxyribonucleic acid (DNA) is the carrier of genetic information, while ribonucleic acid (RNA) plays a role in using the information contained within the DNA to make new molecules in the cell. Some viruses use RNA as their genetic material instead of DNA.

DNA and RNA are both polymers of nucleotide subunits (Figure 20) linked by phosphate groups to form long chains. Inside the nucleus, DNA interacts with proteins for tight packaging so that the 3-meter long chains can fit inside such a small space (Figure 21). With few exceptions, each cell in the human body contains 3 billion nucleotide units assembled into nuclear DNA. Mitochondria also contain their own DNA, which is present as a circular molecule of about 17,000 nucleotide units.

Fig 20 The fundamental building block of DNA and RNA is the nucleotide, which contains an acidic phosphate group, (green), a five-membered sugar ring (blue), and one of five possible purine or pyrimidine bases (right), attached to the sugar (ribose) at the purple nitrogen atoms. Both DNA and RNA have adenine, guanine, and cytosine. The fourth base is uracil in RNA and thymine in DNA.
Structure of the Gene

Two chains of DNA form a **double helix** in which the chains run in opposite directions with the sugar-phosphate “backbone” on the outside and the bases on the inside. Relatively weak interactions, called hydrogen bonds, between adenine and thymine and between guanine and cytosine act as “glue” to hold the structure together. The charged phosphates on the outside of the structure interact favorably with the polar water of the cell.

While people have long noticed that certain characteristics are passed on from generation to generation, it was not until the early twentieth century that scientists realized that certain diseases can also be hereditary. This observation was made by Sir Archibald Garrod (1857-1936), an astute English physician studying the disease **alkaptonuria**, one symptom of which is production of black urine. Garrod demonstrated unequivocally that alkaptonuria is inherited and proposed the novel idea that it results from a defective enzyme leading to improper metabolism of the black compound. Normal individuals break down this compound so that it does not appear in the urine.

Garrod's work implied a link between DNA, the molecule of inheritance, and enzymes, the cell’s catalysts. In the 1940’s, it was proposed that a single region of DNA called a **gene** codes for a single enzyme (the “one gene-one enzyme” hypothesis). This proposal has been modified only slightly in the last sixty years. The next step was to determine how DNA codes for a biological product.
Cracking the Code

The mechanism by which a DNA sequence is interpreted in the cell is extremely complex, involving a number of biological molecules working cooperatively. There are two major steps in the process: transcription, in which an intermediary molecule called a messenger RNA (mRNA) is created from the DNA template, and translation, in which the instructions carried by the mRNA are used to create the corresponding protein product (Figure 22). We will not discuss the details of this process, but it’s important to know that the sequence of the nucleotides determines the sequence of the protein that’s made.

Figure 22. In the process of transcription, the sequence of one of the DNA strands (the gene) is "read" by the cellular machinery to create a new messenger RNA (mRNA) molecule. The mRNA is “complementary” to the DNA in the same way that the two DNA strands are complementary to each other. For example, if the coding strand has a G, then the mRNA has a C. Because RNA uses U instead of T, an A in the DNA becomes a U in the mRNA. In the process of translation, the sequence of the mRNA is interpreted by the ribosome in three base units as a specific amino acid. The ribosome links each successive amino acid to the growing chain.