Foundations of Biology
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Front cover
American egret, Gainsville, Florida.
Photograph by Samuel Scheiner
Chapter 5
Cells

Living organisms, for all their size and complexity, are all formed of tiny discrete units called cells. These cells are the foundation of life; life itself exists only because it is possible to maintain highly ordered systems against the decay of entropy, and it is the cell which provides the wall between order and disorder. Cells come in a myriad of forms (Figure 5.1). Some of this variety is due to specialization of cells within an organism; for examples, humans contain about 210 different types of cells. Some is due to diversity among organisms; the cells of plants differ from those of animals which differ from those of fungi. The enormous array of forms among single-celled organisms accounts for this diversity as well; there are more than 250,000 species of single-celled Eukaryotes that represent some of the widest array of forms on Earth.

Figure 5.1
A variety of single-celled organisms. A. an archa, Halobacteria, B. a bacteria, Salmonella typhimurium (red), invading cultured human cells, C. a diatom, D. Gerardia, E. Paramecium aurelia. (Photo credits: NASA; Bob Blaylock; NIH; Janice Carr, CDC; Barfooz; Source: Wikipedia)

This chapter will focus primarily on what is common across all of these different types of cells, although the enormous range of cellular variation means that we cannot possibly explore all of its byways. Instead we will focus on what is going on inside the cell, the molecular basis of life. Because all of life on Earth most likely arose from a common ancestor (see Chapter 1), the basic molecular machinery is similar in all cells. Yet there are also important differences. Evolution has led to many variations on the basic theme and new functions have arisen in some lineages. Examining the cellular machinery is a good way of understanding biology’s unity in diversity, how much of life is variation on a central theme.

Scientists who study the biology of cells and molecules have been very successful over the past century in figuring out the pieces that make up a typical cell. This understanding has been driven primarily by improved instrumentation; microscopes have gotten better and better, first using light and then electrons, so that we have been able to observe and study smaller and smaller objects. Following World War II, the development of radioactive chemicals allowed scientists another breakthrough, the ability to trace biochemical pathways. However, this reductionist strategy can take us only so far. We now understand that the functional properties of cells cannot be explained simply by adding up all of the pieces. The cell has emergent properties that come about from how
those pieces are connected to each other, both physically and functionally. The past decade or so has seen the rise of what is now termed systems biology, which is attempting to put the pieces back together to understand the whole. Systems biology has created a renaissance and a new, exciting dynamic in the studies of cells.

**Cells as Foundational Units**

As the foundation of living systems, the cell (Figure 5.2) encompasses life's key attributes: information, variation, complexity, and emergence (Table 5.1). One view of life pertinent to cellular biology is that it consists of a set of controlled chemical reactions. As we will see in this chapter, cells are made up of large, complex molecules, which sustain life because they are able to control chemical reactions that would be impossible outside of a cell. Because of this, the cell exemplifies life as a property that emerges from non-living building blocks.

The theory of cells consists of ten fundamental principles (Table 5.1). The first three principles are about the internal structure and function of cells, the next three are about how cells interact with their external environment and one principle is about energy use and efficiency. The final three are about where cells and their properties come from and provide links with the theories of genetics and evolution (see Chapters 3 and 4).

**Table 5.1 The fundamental principles of the theory of cells**

1. Cells are highly ordered, bounded systems.
2. Cells are composed of heterogeneous parts consisting of subsystems that act to localize resources and processes.
3. Cells are regulated by a network of biochemical and supermolecular interactions.
4. Cells interact with their external environment, including other cells.
5. Cells exchange matter through boundaries consisting of semipermeable membranes.
6. Cells require an external energy source, either chemical or electromagnetic.
7. Cells use energy to create concentration gradients of ions and molecules.
8. New cells are formed from other existing cells.
9. Cells contain all of the information necessary for their own construction, operation and replication.
10. The properties of cells are the result of evolution.

There are two ways that scientists have gained understanding of cell function. One way is studying those functions within a living cell, commonly referred to by the Latin term in vivo. The other way is isolating a function outside of the cell, commonly referred to by the term in vitro, which comes from the Latin word for glass, because these studies are typically carried out in glass test tubes or beakers. Scientists have come to realize that in vitro studies are insufficient for providing understanding of how cells function, one reason being that the chemical reactions that go on in vivo are much more efficient than those same reactions carried out in vitro. This increased efficiency occurs because within the natural environment of the cell, the molecules are in a precise orientation to enhance the reactions, conditions that are difficult or impossible to recreate artificially.

How is it that cells maintain themselves? That question can be answered in several different ways. Much of this chapter will focus on the machinery that makes up a cell, what the parts are in a broad sense, and how they operate. To maintain itself, a cell has to maintain its structure and take in energy and nutrients. Among Earth's many species,
these tasks are accomplish in a wide variety of ways. We can understand this variety by considering a few simple key differences among the many kinds of cells. First, is the cell an entire organism that is fully self-contained, or is it just one unit of a larger organism and not able to exist independently? The latter type live as part of a multicellular organism, while the former type may exist in an aggregation of cells or as a separate individual. Single-celled individuals must be able to accomplish all of a cell’s necessary tasks, while a cell that is part of a multicellular individual may only perform some of those tasks.

The Earth’s species are divided into three broad domains, Bacteria, Archaea and Eukaryota (see Figure 4.2A), a system first proposed by Carl Woese (Box 5A). Bacteria and Archaea have much simpler cells than those of Eukaryotes (Figure 5.2). They are usually described as single-celled organisms, although as discussed in Chapter 6, some species can be considered to be multicellular. Eukaryotes can be either single-celled or multicellular.

![Figure 5.2](image)
Idealized examples of a bacterial cell, a plant cell, and an animal cell. The cells of Eukaryotes have many different types of structures, most notably a nucleus. The cells of Bacteria and Archaea are much simpler. (Created by Mariana Ruiz, Source: Wikipedia)

When we describe cells and their structure and function in this chapter, keep in mind that we are talking about a mythical “average” cell and that no single type of cell does everything. In Chapter 6, when we investigate whole organisms, we will return to many of these same issues of maintenance, but focusing much more on the relationship of the organism with its external world. This chapter looks mostly inward.
Box 5A
Carl Richard Woese

A key component to the science of biology is systematics: the organization of the “tree of life” showing relationships between and the paths of descent of every living creature, from the earliest and simplest single-celled organisms to the most complex variations of life, including humans (see Figure 4.2). Efforts in systematics go back as early as Aristotle (Box 2A), although the modern structure is generally credited to Carolus Linneus, who set the framework that we use today. However, in 1976, it was all turned on its head by a single man: Carl Woese. From the nineteenth century on, the very base of the tree of life was divided into two sections: Prokaryotes, or organisms whose cells do not have nuclei, and Eukaryotes, organisms who do carry nuclei. Woese discovered a third basic classification of life, Archaea.

Born in Syracuse, New York, on July 15, 1928, Woese grew up in the Depression and World War II. After graduating from Amherst College with a degree in physics, he earned a Ph.D. in biophysics (the term first used to describe molecular biology) from Yale University. He stumbled into the microbial world as a post-doctoral scholar at Yale in the 1950s, where he investigated the development of ribosomes, the cell’s protein-synthesis machines. From there, he became interested in the origin of DNA, an interest which would eventually lead to a decades long study of the bacterial genetic code. This study would eventually redefine the way we look at the tiniest and strangest forms of life on Earth.

Because Woese wanted to unravel the complex evolutionary history of DNA and RNA, he needed a comprehensive phylogeny of all organisms to exist on Earth. At the time, however, most microbes were lumped into the broad category of Prokaryotes (most multicellular life, of course, had been studied since ancient Greece and Rome and by then was well-documented). By the 1930s, leading microbiologist C. B. van Niel of Stanford University’s Hopkins Marine Station had cited the classification of Bacteria as the most important unresolved issue in microbiology, but at the time it was impossible to obtain enough information on the characteristics of prokaryotes to determine their relationships. In this instance, as with so many other advances in microbiology, it was the advance of technology that drove the next wave of discovery. Since scientists had, by Woese’s time, spent decades trying unsuccessfully to classify Bacteria by size, shape and metabolism (the same way the huge variety of plants and animals had originally been classified) there was a deep-seated bias against classification of microbes; it was considered an impossible task to phylogenetically order the tiny life forms.

Woese, coming from a background in physics instead of biology, believed that “the world has deep and simple principles, and that if you look at it the right way,” you can find them. He was convinced the then-new molecular science held the key to microbial phylogeny, and used ribosomal RNAs (rRNAs), nucleic acid sequences found in the ribosomes, to attempt to forge relationship ties between Prokaryotes. The advantage of this method was in the fact that rRNA is one of the most conserved elements in all organisms; ribosomes are abundant in cells, and their RNA serves as a comprehensive record of life’s evolutionary history. In order to map out this history, Woese used a tedious, labor-intensive technique known as oligo-nucleotide cataloguing, wherein an rRNA molecule is cut at every guanine (G) residue, and the pieces are then broken into
subfragments with enzymes that sliced at different residues, allowing the original sequence to be reconstructed. These tiny fragments appeared as fuzzy spots on film, and each one had to be physically examined for similarities.

Woese worked this was for a decade, and eventually completed the sequences of 60 types of Bacteria, arranging them by genetic similarity. The work was incredibly tedious, both determining the sequences and comparing them. Today, using modern sequencing technology and computers, the entire process could be accomplished in less than a day. Woese was willing to work alone, staring for hours at strips of film hanging the length of his office.

His work brought him modest $50,000 grants from NASA while he taught molecular biology at the University of Illinois, where he had been hired in 1964. He published phylogenies of chloroplasts and mitochondria, and made the surprising discovery that anaerobic bacteroids (Bacteria that don’t process oxygen the way most life on Earth does) and one group of aerobic Bacteria were closely related. Up until that time, a primary criteria for grouping Bacteria was their form of metabolism, so aerobic and anaerobic Bacteria were placed in completely separate groups.

His biggest breakthrough came in 1976 when Ralph Wolfe, a close colleague of Woese, suggested that he study a strange group of Bacteria that produced methane as a byproduct. At the time, Wolfe was the world expert on these odd Bacteria, known as methanogens. Although these methanogens showed a diverse range of physical forms, they all shared the same metabolism. When he began mapping their genetic sequences, Woese made a startling discovery: genetically, methanogens did not register as Bacteria at all. They bore no relation to either Prokaryotes or Eukaryotes, but stood apart as a third branch of life, which Woese called archaeabacteria – the name was later shortened to simply Archaea. His findings were published in the Proceedings of the National Academy of Sciences (PNAS), with Ralph Wolfe as co-author. This was done to help add weight to a radical discovery; although Woese was considered something of a recluse and eccentric, shunning scientific conferences as places for politicking and social advancement, Wolfe was already a well-regarded figure in his field and a member of the U.S. National Academy of Sciences.

Despite Wolfe’s advocacy of Woese’s findings, most scientists were skeptical. The tiny snippets of rRNA Woese worked with were considered too fragmentary to serve as useful sources of information, especially to overturn a major concept in science like the basic division of life into Prokaryotes and Eukaryotes. For the most part, these doubts were not done in scientific publications, which disheartened Woese. Instead, other scientists spoke directly to Wolfe, telling him that he would ruin his career by associating himself with such a crazy idea. The situation was not helped by the fact that Woese had a retiring nature and a great dislike for professional meetings. As a result, he had few opportunities to try to persuade his colleagues that his hypothesis was correct.

Slowly, however, the tide of scientific opinion began to change. The first major turning point came when an influential microbiologist in Germany, Otto Kandler, supporting Woese’s work with his own studies of the structure of cell walls. His analyses also pointed to basic differences between archaeabacteria and single-celled Prokaryotes and Eukaryotes. By 1980, the American scientific community had begun to follow suit, with other types of Archaea being discovered, such as salt-loving halophiles and the strange and fascinating thermoacidophiles, sulfur-metabolizing methanogens found in the most seemingly life-in hospitable places on Earth. Even so, many resisted his ideas. As late as 1986, Bergey’s Manual, the definitive compendium of microbiology, showed Archaea as a subgroup within the kingdom Prokayotae. Today, however, the notion of three major domains is firmly established and providing new insights into the origins of life and the
rise of Eukaryotes (see main text).

Woese remained bitter over this resistance and the lack of recognition at the time by the leading microbiologists in the United States. Throughout the 1980s, he continued to publish major studies on the aspects of the three domains of life, with his work appearing in leading journals such as Science and PNAS. Eventually, he was recognized with the John D. and Catherine T. MacArthur Award, the Waksman Award from the National Academy of Sciences of the United States, the Crafoord Prize from the Swedish Royal Academy, and in 1990 won the Leeuwenhoek Medal, microbiology’s highest honor. And, remaining true to form, when he received invitations to give lectures at universities and conferences, Woese declined most of them. Although he was familiar with the work by philosophers on the important role of social activities in the process of science, he continued to shun such activities. Woese died on December 30, 2012.
Cells as Bounded Systems

A cell is defined by its boundary, a lipid membrane, which allows a cell to maintain an internal environment that differs from its external environment, concentrating and organizing chemical processes (Figure 1.2). If, again, we regard life as a series of controlled chemical reactions, then that control happens because the chemical reactions are kept together by that boundary (Table 5.1, principle 1).

A membrane sets the stage for two types of feedback systems, those internal to the cell and those between the cell and its exterior. The internal feedback system keeps the chemical reactions in balance. A cell is a dynamic entity, in which parts are continually being assembled, disassembled, and re-assembled for other functions. It is critical that the assembly of new structures keeps pace with the breaking down of old, or the cell will be left without parts necessary for life.

A cell also needs to maintain itself in the face of a changing external environment. Cells do so because their membranes are selectively permeable; they allow some materials in and exclude others. Because of this, the cell is not at equilibrium with its surroundings, and energy is required to continually move molecules into and out of the cell so as to maintain it in that state. If a cell is part of a multicellular organism, the membrane is a critical component of the signal system among the cells. All of these membrane properties will be described in more detail later in this chapter.

Cells as Heterogeneous Systems

Physical structure

Cells are highly structured in ways that increase the efficiency of cellular functions (Table 5.1, principle 2). That structure exists in two senses. First is the physical structure, the ways in which the molecules are arranged. Second is the interaction structure, the ways in which those molecules react with each other. While we can think of these aspects of structure as separate, they are mutually reinforcing. If life is a set of organized chemical reactions, then a central function of cells is to enable those reactions. Chemical reactions consist of the breaking of chemical bonds and the formation of new bonds, a process which requires energy. This is because the chemical bonds of biological molecules are usually stable – the bonds tend to remain in place when they exist and tend not to form spontaneously – and organisms must be able to overcome this stability.

Consider the following example. A molecule of table sugar (sucrose) consists of two subunits, a molecule of glucose and a molecule of fructose (Figure 5.4).

![Figure 5.4](image)

A molecule of sucrose consists of two subunits, glucose and fructose.

It takes 6.6 kilocalories (kcal) of energy to break the chemical bond joining those two subunits. If you dissolve a tablespoon of sucrose in a glass of water, nearly all of it remains as sucrose. Only a few molecules manage to break the bond joining the subunits. Some of the sucrose molecules break down because they have a certain amount of energy from the heat of the solution, that comes about from the molecules always bumping around and creating friction. Those molecules also vary in the amount of energy they have, as some will be moving faster than others.
By chance alone, if some of those molecules are moving fast enough and happen to bump into each other in the right way, the bond on one of them will break. But the odds of this happening are very small. At room temperature, few of the sucrose molecules will break down in this way.

**Enzymes**

All animal species have the capacity to use sucrose, break it down into smaller pieces and use the resulting molecules and energy. To do this, our cells can enhance the chemical reaction that breaks the bond between the component glucose and fructose molecules. That enhancement is done by helper molecules, proteins called enzymes. Enzymes speed up chemical reactions by reducing the amount of energy needed to make or break a chemical bond (Figure 5.5). This happens because of the properties of the enzymes’ structure. Enzymes are usually much larger than the molecules that they are helping and the enzyme has a particular niche or pocket within which the molecule sits. Once in that niche, the enzyme can enhance the chemical reaction in four ways. (1) The molecule might be bent in a precise way, thereby straining its shape and breaking the bond. (2) Two molecules might be brought together in a way that makes bond formation highly likely. (3) The chemical environment immediately around the molecule(s) will be different making bond formation or breakage more likely. (4) The enzyme might provide an alternative chemical pathway for the reaction that requires less energy. For example, the formation of a bond between two molecules might occur by first creating a bond between one of those molecules and the enzyme, then by breaking that bond and using the energy released to form a bond with the other molecule. The enzyme itself is unchanged, thus being available to repeat the reaction many times.

Enzymes are known to enhance over 4000 different chemical reactions, each one due to a different enzyme. They come in many different shapes and sizes since it is the precise three-dimensional structure that gives an enzyme its specificity. An enzyme must be flexible because it is often the bending of the enzyme that makes the chemical reaction happen. Sometimes the enzyme may be made of two or more subunits, separate proteins that are bound together, or it may require other smaller molecules for proper functioning. All of this complexity of enzyme structure allows for many ways that the chemical reactions can be regulated. Finally, the chemical reaction may require additional energy that comes from another molecule acting as an energy carrier. We will discuss both those energy carriers and cellular regulation later in this chapter.

![Figure 5.5](image.png)

**Figure 5.5**

An example of how an enzyme can speed up a chemical reaction. (Created by Tim Vickers, Source: Wikipedia)

**Spatial structures**

Although enzymes enhance chemical reactions, there is still the necessity that all of the pieces of that reaction be assembled in one place. If a chemical bond in a molecule is being broken, the molecule must be brought together with the enzyme in the right way; the same is true when chemical bonds are formed between two separate molecules. If a cell was like a beaker filled with a watery solution, enzymatic reactions would
still be very slow. Even worse, in most cells the number of any one kind of enzyme and the molecules that they are reacting with are usually small, so the chances of them randomly encountering each other are correspondingly small. In addition, a single chemical reaction is almost always insufficient to achieve a meaningful result. Almost all reactions are part of a chain in which the final result is either the creation of a complex structure or the reduction of a complex structure to smaller molecules. Yet, cells manage to carry out these chemical reactions.

The answer to this conundrum is that the cell consists of a complex system of membranes that organize the chemical reactions. The membranes are made of lipids arranged to form sheets, tubes and spheres (Figure 5.3). These lipid membranes are similar in form to those that make up the surface of all cells. Consider the formation of sucrose by the creation of a bond between glucose and fructose. Unlike the breaking of that bond, the creation of the bond happens through a series of six different chemical reactions, and it requires even more energy (21.9 kcal) than to break the bond. The formation of sucrose happens a lot in some species, notably the species of grass called sugar cane, from which we get most of our table sugar. The cells in sugar cane are able to carry out the synthesis of sucrose in an efficient manner because the enzymes involved in this process are lined up on membranes in such a way that the glucose and fructose molecules are passed along so that they have a high probability of being brought together properly, almost like an assembly line in a factory. Unlike a human-built assembly line, which is consciously designed to maximize efficiency, cellular ones are the product of evolution. Because they were not designed at the outset, they can be less efficient than they might be, and inevitably some of the molecules do not make it all of the way through. However, in general these are very efficient processes that create localized concentrations of molecules that greatly enhance the reactions.

All types of cells contain a variety of large molecules, often called macromolecules, to perform many different functions. Even the simpler cells have such molecules arranged as structured systems, but this is even more true of Eukaryotic cells that are highly structured (Figure 5. CC). At first they can seem like a jumble of disparate parts, each with its own name and specialized function, but despite their number, the parts carry out just a few types of functions, and it is really a just single, highly organized system.

Manufacturing processes, for example, involve many different systems. DNA and RNA are made in the nucleus. Proteins are made on ribosomes that typically are attached to a membrane called the endoplasmic reticulum (ER), which gives it a rough appearance (Bacteria and Archaea also have ribosomes, although not ER). Lipids are made on smooth-looking ER. The Golgi apparatus receives molecules made by the ER, and may make further modifications to them as well. Golgi apparatus may also package materials into small membrane spheres, vesicles, that move to the surface of the cell, merge with the surface membrane, and export them from the cell (Figure 5. 6).

The breakdown of molecules in a cell is often isolated into specialized compartments. This occurs for two reasons: first, to ensure that the enzymes performing these functions do not also break down cellular structures, and second because some of the breakdown products are harmful. [One particularly harmful breakdown product is hydrogen peroxide (H2O2) and reactions that create this product are isolated in peroxisomes.] This breakdown occurs in lysosomes in animals and vacuoles in plants (which are also used for storage, especially of water).

In most organisms, energy is processed in two specialized structures. Chloroplasts convert light energy into chemical energy. Mitochondria convert chemical energy in food into other forms that the cell can use. Some Bacteria have neither structure,
Figure 5.6
Linkages among the membrane systems in the Secretory pathway dia-
gram, including nucleus, endoplasmic reticulum and Golgi apparatus.
movement of materials into and out of the cell.
1. Nuclear membrane
2. Nuclear pore
3. Rough endoplasmic reticulum (rER)
4. Smooth endoplasmic reticulum (sER)
5. Ribosome attached to rER
6. Macromolecules
7. Transport vesicles
8. Golgi apparatus
9. Cis face of Golgi apparatus
10. Trans face of Golgi apparatus
11. Cisternae of Golgi apparatus
(Created by Magnus Manske, Source: Wikipedia)

instead using specialized membrane systems for energy metabolism. We discuss both
chloroplasts and mitochondria in detail later in this chapter.

Similar to mammals and their skeletal and muscular systems, cells contain struc-
tures that help provide support and give it form, that allow it to move, and that enhance
communication among cells. The cytoskeleton consists of a meshwork of fine fibers
that extends through the entire cell, providing structural support as well as performing
other functions. These fibers, which can be thick or thin and are composed of globular
and fibrous proteins, provide a place for the other cellular structures to anchor and act
as tracking mechanisms for their movements. Recent research suggests that some fibers
may mechanically transmit signals from the cell surface to its interior. They are responsi-
ble for cell division, particularly guiding the movement of chromosomes (see Figure 3.4).
Cells actively move two ways: crawling and swimming. Crawling is done by building up
fibers in the direction of movement and breaking them down at the opposite end. The
same process is responsible for changes in cell shape.

Swimming is done by the beating of fibers that stick out from the surface of cells.
A cell may have many short fibers, cilia, or just a few or even one long fiber, flagella
(Figure 5.7). Although they differ in length, both have a similar structure, and are found
in Bacteria and Archaea as well as Eukaryotes.

In multicellular organisms, cilia are used for the opposite function, moving materi-
als outside a cell while the cell remains stationary. Some of the cells that line your wind-
pipe have cilia that push out foreign substances that you have inhaled.

The outside of cells can be rigid or flexible, although all cells are surrounded by a
lipid membrane, which itself is flexible. Rigidity is achieved by a cell wall, which is com-
posed of various types of polysaccharides. All plant cells, for example, have walls made
of cellulose (which is what wood is made of). Fungi have cell walls made of chitin, the
same material that makes up the shells of lobsters and insects’ exoskeletons. Bacteria
and Archaea have cell walls made of a variety of types of polysaccharides. Many animal
cells excrete a sticky layer composed of molecules that combine sugars and proteins.
This layer can provide support and protection, and also acts to hold cells together. Cells
may also be held together by specialized junctions that include cytoskeleton fibers that
extend into the cell. In multicellular organisms, adjacent cells may have channels that
allow for the flow of materials and for communication.

The result of all of this is that cells are highly structured. Rather than watery bags
of chemicals, they are viscous solutions, more Jell-o™ than Kool-aid™. The efficient
functioning of a cell is, thus, an emergent property of this viscosity and structure. Al-
though the existence of most of these structures has been known for over a century,
frontiers in biochemistry. Cell biologists are now building conceptual frameworks that take into account how organization and localization of chemical reactions are achieved in the crowded interior of a cell. Doing so will require additional methodologies, particularly the development of new types of microscopes that bridge the gap between light and electron microscopes.

Figure 5.7

scientists are just beginning to understand how they work. Understanding the chemistry of a low-concentration, viscous medium such as the inside of a cell is one of the current

**Cells as Regulated Networks**

The complex physical structures just described exist to support the intricate network of chemical reactions that form the basis for living systems. Inside every cell is a vast network of molecular reactions, each consisting of many steps carried out by a multitude of enzymes (Table 5.1, principle 3). Previously, we described just a single reaction, the linking of fructose and glucose to form sucrose starting with separate sugar molecules, each of which goes through a different chemical reaction before the final linking reaction. An important feature of these networks is that a few highly connected enzymes act as key nodes in the entire network. Scientists are rapidly gaining a lot of knowledge about the structure of the networks that exist in various organisms, mapping out the thousands of connections. However, they are still very poorly understood. The network structure in yeast (Figure 5.8) is probably the best known of any Eukaryote because it is a single-celled organism that is easy to grow in the laboratory. But even for this network, we still know very little about its dynamic properties, how the interaction structure determines how the individual enzymes function together.

In order for life to exist, the component chemical reactions must be controlled. For example, many Bacteria can use different sugars as carbon sources. However, if the only sugar available is glucose, a bacterial cell would waste resources if it also produced the enzymes need to digest fructose. Thus, it is important that the enzymes it creates remain in balance with the molecules available to it as raw materials. Many different types of controls are used to manage this complex dance.

First, control can occur at many different levels. Chemical reactions are controlled by enzymes that are produced through the process of transcription and translation (see Figure 3.14). The amount of enzyme can be controlled by regulating the amount of RNA produced, by regulating how quickly those transcripts are translated into proteins, or by regulating how quickly those enzymes are broken back down into amino acids. Besides regulating enzyme availability, control can also be achieved by regulating the efficiency of the enzyme. Enzymes speed up chemical reactions, but that effect is not necessarily all or nothing. As mentioned previously, enzymes sometimes exist as complexes of several molecules, with others acting in ways to make the enzymes more efficient.
By adding or removing those helper molecules, the rate of the chemical reaction can be varied.

Finally, networks can be controlled by regulating the amount of substrate, or raw material, available. In the same way that a chain is only as strong as its weakest link, a series of chemical reactions that depend on the product of the previous step can proceed only as fast as the slowest step. But what happens to all of the substrate that is piling up behind that rate limiting step, like the shoppers in line at a checkout counter? Often there are negative feedback controls; as the substrate builds up, it acts as a signal to slow down production. This signal can act at any of the control points previously mentioned. In a similar fashion, a substrate can act in a positive fashion. Presenting the bacterium E. coli with glucose triggers the production of the enzymes necessary to break down that molecule.

Just like people in a store finding another counter with a shorter line, chemical reaction networks consist of many divergence points where substrate can be shunted from one series of reactions to another. The tendency of the substrate to be used in one series or another can be controlled through either a push or a pull system; halting or slowing down the movement of a substrate along one pathway will push the remaining substrate to another pathway. Conversely, speeding up the processing of a substrate along a pathway will tend to pull more substrate along. At one of those divergence points, the enzymes responsible for movement towards one or another pathway can be thought of as competing for the substrate. The enzymes may differ in their affinities for the substrates, and that affinity can be regulated by helper molecules as mentioned previously.

The membrane system itself can also be considered part of the interaction network – it is dynamic, with parts continually budding off and merging. For example, the endoplasmic reticulum transfers materials to the Golgi apparatus by creating small membrane spheres. The rate at which that occurs, the rate at which substrate gets moved around inside the cell, or the rate that RNA molecules get moved from the DNA to the ribosomes can also act as network regulators.

**External Interactions**

The network of interactions can also extend beyond the bounds of the cell itself (Table 5.1, principle 4) to other cells (for multicellular organisms) and to the external environment (for all organisms). In some instances those interactions are direct: cells that are next to each other, cells in multicellular organisms that are in direct contact with the environment, or for all single-celled organisms when interacting with their environment. Those same interactions, however, may be indirect as well.
In multicellular organisms a cell may produce a signal which must get passed along, for example through the blood, before it gets acted upon by another cell. Those cell-cell interactions act to regulate processes at the level of the whole organism, in the same way that interactions among components regulate those functions within cells. One outcome of those interactions is the specialization of cells for particular functions. We examine organism function and cell specialization in detail in Chapter 6. Because such signals are often molecules at very low concentrations, understanding their functions and actions required the development of sensitive detection techniques (Box 5B).
Rosalyn Yalow made her career at the cutting edge – as a woman and a nuclear physicist, she carved inroads into early nuclear medicine and served in the vanguard of her gender’s entry into the atomic age. As a female scientist in the middle of the 20th century, she faced blatant discrimination, yet went on to receive the Nobel Prize. Even in her own family she forged an unprecedented path; neither her father, a packing materials wholesaler, nor her mother, a German immigrant and a homemaker, attended high school or college. Her research demonstrates how scientific breakthroughs can come about through the invention of new tools, which often come from someone working across disciplinary boundaries.

Yalow, born on July 19, 1921 in the South Bronx as Rosalyn Sussman, showed an early interest in science. As her parents owned no books, she and her brother Alexander made weekly trips to the public library, and by the age of eight Rosalyn knew she wanted to become a scientist. She gravitated to the logic of science and loved its capacity to explain the natural world.

Yalow was the product of New York City schools, attending Walton High School in the Bronx (one of two Walton graduates to receive the Nobel Prize), where a teacher sparked an interest in chemistry. She went on to attend Hunter College. After reading a biography of Marie Curie and attending Enrico Fermi’s 1939 Columbia University colloquium on nuclear fission, she shifted her studies to nuclear physics. To her, the field seemed to be the most exciting one in the world, with each major experiment garnering a Nobel Prize. At the age of 19 she graduated magna cum laude as Hunter College’s first physics major.

Despite her stellar academic record, Yalow immediately ran into obstacles upon embarking on her graduate studies. She applied for an assistantship at Purdue University in Illinois and was rejected, the University writing to her professor that “She is from New York. She is Jewish. She is a woman. If you can guarantee her a job afterward, we’ll give her an assistantship.” Since a guarantee was not possible, the rejection stood. Yalow ended up having to take a position as a secretary at the College of Physicians and Surgeons at Columbia University. Undeterred despite assertions that a woman would be unable to get into graduate school in physics, she attended classes at Columbia and continued to pursue a graduate education.

Her opportunity came in the form of an offer for a teaching assistantship at the College of Engineering at the University of Illinois at Champaign-Urbana. While at Illinois she met and married Aaron Yalow, a fellow graduate student, eventually having two children, Benjamin and Elanna. The U.S. had entered World War II, and the draft meant that universities were faced with filling their graduate programs with women or shutting them down entirely. Yalow was able to seize this entry into science and academia. She was the first female graduate student in engineering in 24 years, and as the only woman among 400 peers, she faced an incredible amount of pressure to perform. This was compounded by the fact that Hunter’s late adoption of a physics curriculum meant that she was behind her classmates academically; to make up for it, she took two undergraduate courses as well as her three graduate courses. She excelled in her studies, earning
was behind her classmates academically; to make up for it, she took two undergraduate courses as well as her three graduate courses. She excelled in her studies, earning straight A’s – with the exception of the laboratory component of her Optics course, in which she received an A-minus. The chairman of the physics department pointed to her grade as proof that women couldn’t excel in lab work.

Despite the physics chairman’s assertions, Yalow became proficient in both the construction and operation of apparatus for measuring radioactive substances while studying for her Ph.D. under Maurice Goldhaber. She received her doctorate in nuclear physics in 1945 and returned to New York, where she worked as a researcher in the Federal Telecommunications Laboratory – again the only woman among her peers – until the research group left New York the following year. Unable to secure another research position, she ended up teaching physics at Hunter College. Still wanting to pursue a research career, she volunteered to work in Columbia University’s medical laboratory, where she was introduced to the then-brand-new field of radiotherapy. She continued to pursue nuclear medical research over the next three years, first in a part-time position at the Bronx Veterans Administration Hospital, then later becoming a full-time researcher there.

In 1950 she began her 22-year-long collaboration with Dr. Solomon Berson. At the time, Berson was accorded more gravitas than Yalow; due to his medical degree and gender, he had more contacts with scientific journals, professional societies and within academia. Yalow, however, was absolutely single-minded in the pursuit of her research, living in a modest house just a mile from the hospital and eschewing hobbies and leisure travel. At the beginning of their partnership, Yalow and Berson focused on using radioactive isotopes to more accurately estimate blood volume, their first major contribution the development of a technique to measure iodine filtered by the thyroid and kidneys in a set amount of time. From this beginning, they widened their scope to include research into other peptide hormones, in particular insulin. This thrust had personal significance to Yalow, whose husband was diabetic.

Peptide hormones are present in much lower concentrations than other types of hormones, and correspondingly more difficult to track in the body. Although chemical methods of analysis were available for those other hormones, there were no such techniques available for peptide hormones in the 1950’s. Yalow and Berson’s research changed that. Key was the development of a new technique, radioimmunoassay (RIA) that came from Yallow’s training as a nuclear physicist.

Yallow discovered that people who had received insulin injections developed an antibody response to the insulin. This discovery, coming in 1956, challenged the current scientific understanding of insulin – few believed that so small a molecule could trigger an antibody response – but was key to Yallow’s research. She and Berson used a radioactive isotope to tag a known quantity of insulin, then mixed the newly-tagged insulin and its antibody with a blood sample in which the levels of the hormone were unknown. The antibodies would abandon the tagged molecules to attack the naturally-occurring molecules in the blood sample, and by counting the number of tagged molecules without antibodies, they were able to ascertain the concentration of insulin in the blood sample. Radioimmunoassay revolutionized the field of endocrinology, and decades later would garner Yallow a Nobel Prize.

Using RIA, Yallow delved into hormonal research, publishing a series of papers with Berson beginning in 1956 elucidating not only the basic nature of peptide hormones such as insulin, but also the mechanics of diseases caused by hormonal abnormalities. She demonstrated that it was the binding of insulin antibodies leading to abnormal degradation of the hormone that was at the root cause of diabetes, rather than the pancreas
secreting too little insulin as was previously thought. Today we know that such autoim-
munity reactions are the source of more than 80 human illnesses, including type I dia-
tes, rheumatoid arthritis, and lupus.

RIA also offered a life-altering solution to newborn babies afflicted with underac-
tive thyroid. This condition can cause mental retardation, but symptoms only show up at
three months of age after the damage has been done. By allowing a newborn’s thyroid
levels to be checked immediately, the afflicted baby can be treated immediately and the
damage prevented. In addition, they adapted RIA to track vitamins such as B12 as well
as viruses, which allowed donated blood to be tested for hepatitis B.

Despite her achievements, Yalow still faced obstacles. As her work challenged the
current scientific edifice, she faced disbelief and outright rejection in trying to publish
her results. She had to delete her explanation of insulin antibodies before the Journal of
Clinical Investigation would accept her paper on RIA – Yalow saved the rejection letter
and later included it in her Nobel lecture. Despite the huge commercial potential for the
technique, Yalow and Berson refused to patent it, instead making every effort to get RIA
into common use in hospitals and laboratories.

Yalow went on to become the acting chief of the RIA Reference Laboratory at the
Bronx Veterans Administration Hospital in 1968, and then chief from 1969 to 1992.
She was elected to the National Academy of Sciences in 1975 and received the Albert
Lasker Medical Research Award in 1976. The following year she was awarded the Nobel
Prize in Physiology or Medicine, only the second woman to receive the award. In 1982,
when speaking to a group of schoolchildren about the challenges and opportunities of a
life dedicated to science, she said, “Initially, new ideas are rejected. Later they become
dogma, if you’re right. And if you’re really lucky, you can publish your rejections as part
of your Nobel presentation.”

Because they are not awarded posthumously, Berson, who died in 1972, did not
share in the 1977 Nobel Prize. However, at his death Yalow insisted the VA rename the
lab where she and Berson had worked in his honor, so that his name would continue to
appear on her research papers. Yalow died on May 30, 2011, at the time the senior med-
ical investigator emeritus at the Bronx Veterans Administration Hospital and (quite ap-
propriately) the Solomon A. Berson distinguished professor-at-large at the Mount Sinai
School of Medicine.
The cell membrane is the gateway that regulates cellular interactions, that gateway can act in several ways (Figure 5.9). Key to these interactions are the complex structure of the membrane. A cell membrane is not a uniform surface. Rather, it is full of holes, called pores, that are made of specialized proteins embedded in the membrane. The first type of interaction is passive diffusion. Although the pores in the lipid membrane will block the passage of large molecules, single ions can pass through. In passive diffusion the cell does not regulate this movement; instead, the rate is determined by the relative concentrations inside and outside the cell. For example, if the concentration of sodium ions (Na+) is higher inside than outside, on average more ions will be passing through the membrane from the inside out than from the outside in. Although some movement of sodium ions occurs by passive diffusion, much happens through active transport, the second, very important method of regulation of external interactions. For these interactions, the pores actively move ions or molecules from one side of the membrane to another, using energy to do so. Each pore is specialized for the movement of one or a few ions or molecules, which acts as a further regulatory control.

Sometimes what is moved is not material, but information. Again, this information movement is carried out by specialized proteins that extend through the cell membrane. Those proteins act as receptors for specific molecules that provide the signals. When the signal molecule reacts with the protein on the outside of the cell, the protein changes its shape. Depending on how it does this, it will either release another signal molecule on the inside of the cell, or if the protein is an enzyme, the signal molecule may change its activity.

Pores are sufficient to move single molecules, but sometimes a cell must move large amounts of material in or out. Movement of large objects into a cell is how many single-celled eukaryotes eat. For example, an amoeba eats bacteria. It does so by surrounding the bacterial cell with its membrane. That membrane then pinches off, forming a sphere inside the cell (Figure 5.6). Enzymes that are able to break down the bacterial cell are then moved into the bubble. The reverse process occurs in cells of multicellular organisms that are responsible for manufacturing substances used by other cells (Figure 5.6).

The cell membrane is dynamic not only on small scales, but also on very large scales across the entire cell. In animals, when an egg is fertilized by a sperm cell, a change occurs in the membrane that prevents any other sperm from fertilizing that egg. This process occurs in just fractions of a second, spreading outward from the point of fertilization. The cell membranes of both the egg and the sperm perform another important function in this process, containing proteins that bind to each other. Those proteins
are specific to a given species preventing fertilization of an egg by a sperm of a different species. Many people had a hand in fully researching this process, the first of whom was E. E. Just (Box 5C).
Box 5C
Ernest Everett Just

It is a sad reality that social prejudices often thwart the growth and advancement of all subjects, from the sciences to the arts. This is, unfortunately, what happened to Ernest Everett Just, a brilliant biologist and embryologist who published over 70 articles and two very well-received books, and nevertheless was unable to secure a research position in America because of his race. Born on August 14, 1883 in Charleston, South Carolina, Just was African-American, the grandson of a slave who inherited the name Just from his master. His father was an alcoholic and a womanizer, who kept a mistress despite the fact he didn’t make enough money to support his wife and child. He died when E. E. Just was four, and after his father’s death, his mother sold their house in Charleston, and moved to James Island, off the South Carolina coast.

Just’s mother took a job in a phosphate factory, an unusual occupation for a woman, but one that paid much better than traditional “women’s work.” She eventually made enough money to invest in real estate, and founded the first school on the island. She pushed her son to succeed, and at 13 Just enrolled in South Carolina State College (also known as The Colored Normal, Industrial, Agricultural and Mechanical College) where he completed the usual four-year course of work in only three. He then applied for entrance at Kimball Union Academy, a private secondary school in Meriden, New Hampshire, and promptly left on a boat bound for New York without waiting to hear if he had been accepted. He worked aboard the boat to pay for passage, then worked odd jobs in the city until he had made enough money to pay for the rest of the trip to New Hampshire, where he found that he had been accepted and awarded a scholarship reserved for “deserving” students.

At Kimball he studied the classics, and excelled at oratory and journalism, winning an oratory competition and running the student paper. At that point he planned on becoming a classical scholar, and was encouraged by his teachers, who recognized the brilliance of the young Just. After Kimball, he entered Dartmouth in the fall of 1903 at the age of 20 with the intention of continuing to study the classics. While there, he displayed a talent for writing, some of his short stories and poetry being published in various Dartmouth publications. It was here that his interests started gravitating toward biology.

Just was drawn to William Patten, a distinguished paleontologist with a strong effect on Dartmouth’s curriculum, who eventually organized a course on evolution that was required for freshmen. Just was also mentored by J. H. Gerould, who was known for his genetic studies of butterflies.

He graduated in 1907, earning his diploma magna cum laude. It was then that he ran into the first big obstacle of his career: because of his race, he only had two employment opportunities; Howard or Moorehouse College. He went with Howard College, where he was initially assigned to the English department. He was popular with students, and recognized for his teaching skills; he received the Spingarn Medal of the NAACP in 1915.

When he began teaching biology in 1909, his interests again shifted from the classical to the scientific, and he sought Patten’s advice on doing graduate work in zoology. Although Pattern advised him that medicine was a better direction, he nevertheless
recommended Just to Frank R. Lillie, the head of the zoology department at Chicago University. Lillie accepted Just as his assistant at Woods Hole in the summer of 1909, where Just quickly earned a reputation as an excellent scientist, working closely with Lillie, sharing a great mutual respect. Just quickly became an expert collector of sea invertebrates as well as a skilled microscopist, and almost immediately began publishing highly regarded papers, his first article reporting that the first cleavage plane of the _Nereis_ sea worm was determined by where the sperm enters the egg. He was soon sought-after for advice.

At Woods Hole Just soon developed several close friendships; he and A. H. Sturtevant would often eat together, and he spent time with geneticists Donald and Rebecca Lancefield, cytologists Franz Schrader and Sally Hughes (Schrader). With Sally he found an outlet for his literary passions as well as his scientific ones, and the two would often discuss poetry, literature and music, especially the work of D. H. Lawrence, who was considered quite scandalous at the time. Socially, Just was quite popular at Woods Hole; he was handsome, intelligent and personable, with a wide range of interests.

After his first paper, he continued work on _Nereis_, charting the life history, especially the breeding habits, of the worm. He developed a technique to mark the entry point of the sperm into the egg using tiny particles of India ink, and used his experience with _Nereis_ to study the fertilization process of other marine organisms, including _Platyneris_, _Echinarchnus_, and _Arbacia_. All of his work was characterized by careful observations, care taken in the living conditions of the animals, and meticulous attention to experimental details. His _Echinarchnus_ studies verified that eggs become impermeable once a sperm enters; Just mapped two events triggered by its entry - first the nucleus releases a substance making the egg fertilizable, then the sperm enters. In addition to his research work, Just also published articles on techniques of collecting and experimental methods, culminating in a book based on his work at Woods Hole.

In the fall of 1911 he enrolled at the University of Chicago as Lillie’s graduate student, and received his Ph. D. on June 6, 1916. Despite this, and despite his glowing reputation, the only two places he could find employment remained Howard and Moorehouse. Just had by that time proved himself to be a superb technician as well as an extremely careful worker; he set high experimental standards for himself, and was often critical of the methods of others when they fell short of his own expectations. He was open with his criticism and freely disagreed with others when their observations were different from his own. This would prove a serious detriment to his career.

The most notable disagreement took place with Jacque Loeb, who, ironically enough, had recommended Just for the Springarn Award. Just thought Loeb’s work was flawed, and openly said as much. Loeb had argued that the development of an egg was initiated by two steps; cytolysis (which could be induced in the lab by butyric acid), then a quenching with hypertonic seawater. Just showed that the seawater alone was sufficient, and thought that Loeb was simply careless with the details of his experiments. This, along with other criticisms, lead to a major controversy in the scientific community, with embryologists taking sides. Loeb’s public opinion of Just plummeted; unfortunately, Loeb was a liberal deeply interested in social causes, with a special interest in Howard College. When Just was being considered for a position at the Rockefeller Institute for Medical Research, naturally Loeb’s advice was sought. The response Loeb gave probably cost Just his only opportunity for a research position he was likely to encounter as an African American man: “...the man is limited in intelligence, ignorant, incompetent and conceited; in fact his research work is not only bad but a nuisance.” Just was thus forced to remain at Howard.

Although Just continued to spend his summers at Woods Hole and eventually got
a grant to spend half his time at Howard in research, he felt buried under his administrative duties and seemingly endless committee responsibilities. Although he remained productive, publishing around 50 articles by 1930, Howard began having major administration problems, and Just was caught up in them as his relationship with the college’s president deteriorated. Even at Woods Hole, too much of his time was spent helping others rather than working on his own research, and he ran into the ugly spectre of racism when he brought his wife and children up one summer, who quickly left after encountering offensive remarks. After a visit to the Bay of Naples biological station and Europe, Just began to desire a move across the Atlantic.

Sadly, some of his impetus to move stemmed from the racism still rampant in the United States; his opportunities were very limited at home, and moving would afford him the ability to hold a research position. For a man deeply interested in literature and music, the live opera and high-quality chamber music available in Paris and Italy were a strong draw, especially when he met and began an affair with a European woman, Hedwig Schnetzler, whom he eventually married. Unfortunately, his financial situation prevented a move; all his money went to his current wife and children.

This did not deter his interest, however. He became friends with Reinhard Dhorn, director of the Statione Zoologica in Naples, and felt quite at home with European scientists. Dhorn encouraged Just, both in pursuits of science and philosophy, making him his secretary; with long lab hours and concerts in the lobby of the Statione. Just’s natural inclination toward philosophical studies and willingness to speculate was discouraged in America, but nurtured by European scientists like Dhorn, and Just’s later work reflected this encouragement. He was strongly drawn to the Morgan school of genetics, and thought that chromosome theory was a great modern breakthrough, but felt that it fell short in explaining how genetic information translates to development and phenotype. Just turned to cytoplasm, especially ectoplasm (which has more contact with outside agents) for his explanations (although he was always careful to label his speculations as such). In “A single theory for the physiology of development and genetics,” a 1936 paper in which he attempted a synthesis of genetics and embryology, he speculated that the egg starts out with pluripotent cytoplasm, which the chromogosme synthesis then uses to copy itself in cell division. The cytoplasm then has restricted potencies, with somatic cells having more and more restricted set of properties. He later began to speculate that genes are nucleic acid, realizing that chemical studies of nucleoproteins were of greater and greater importance. He hoped to do “…a more exact study of nucleo-protein synthesis to embrace as many different types of eggs as possible” but unfortunately passed away before he could investigate further.

Just later spent time at Kaiser-Wilhelm-Gellschaft in Dahlem in the laboratory of Max Hartmann, where he interacted with Richard Goldschmidt, Otto Mangold, and Johannes Holtfretner. He had earlier become interested in ectoplasm, the outer layer of the cytoplasm in cells, and here he was able to study Amoeba, taking advantage of the creature’s huge cell size. When he began to look in earnest for funding to finance his move to Europe, he immediately ran into problems, with foundations, millionaires, and all other avenues turning him down.

Some of the reluctance to fund Just’s move was concern for the plight of African-Americans – they believed that someone like Just could do more good for the community at Howard. Eventually he received a little funding from the Carnegie Institute, and was given a desk at the Sorbonne (although it was a great honor, it carried no monetary recompense). He managed to get a European divorce in 1939, and married Hedwig; without a family to support, he was able to settle in a small biological station in Roscoff on the French coast overlooking the Channel. The facilities were primitive, but the Channel
waters teemed with biodiversity.

Unfortunately, by 1940 the Germans had invaded Czechoslovakia and the siege of Paris had begun. Just’s colleagues at Woods Hole worried for his safety, and eventually Just decided that he and Hedwig must flee. Problems arose with Just’s passport, and he was interned by the Nazis for a time until his release was negotiated. He was able to book passage out of Spain to New York City, but all his research done at Roscoff was lost in the confusion. Just returned to Howard in failing health, weakened and in pain, and was diagnosed with pancreatic cancer. He died on October 27, 1941, and was commemorated on a United States stamp in 1996.

Just was a very early frontrunner of the field that has come to be known as eco-devo - ecological developmental biology (officially established in 2001 as a subcategory of evolutionary developmental biology). Concerned with studying organisms as a whole, in their natural (as opposed to laboratory) conditions, the field relies on organicism, or materialistic holism, a strong characteristic of Just’s work with cytoplasm and heredity, insisting that lab conditions match closely as possible the natural conditions of an embryo.
Metabolism: Unity and Diversity
The basic chemical reactions
Living systems maintain themselves in an ordered state by using energy (Table 5.1, principle 6; see Chapter 1). The set of co-ordinated chemical reactions that provide organisms with that energy is termed metabolism. Metabolism consists of two linked processes: anabolism, the synthesis of complex substances from simpler ones, and catabolism, the breaking down of those complex substances. Anabolism both creates the structures of living systems and stores energy in organic molecules. Catabolism breaks down structures so that the components can be used for other purposes and uses that stored energy. These twin processes are occurring constantly within each cell. They also occur at a larger scale with some organisms being net creators of organic molecules and stored energy and other organisms being net consumers.

Energy begins in the form of high-energy electrons which are then harnessed for chemical reactions and stored in chemical bonds. The transfer of electrons from one substance to another is called a reduction-oxidation reaction, or redox reaction for short. The gain of an electron is called reduction, and the loss is called oxidation. Cells need to balance the negative electrical charge in the electron (e-) with a positive charge from a proton, i.e., a hydrogen ion (H+) [these reactions can also be thought of as the loss (oxidation) or gain (reduction) of a hydrogen atom].

\[
\text{Reduction} \\
\text{Oxidant} + e^- \rightarrow \text{Product} \\
(Gain of Electrons) \quad (Oxidation Number Decreases)
\]

\[
\text{Oxidation} \\
\text{Reducant} \rightarrow \text{Product} + e^- \\
(Loss of Electrons) \quad (Oxidation Number Increases)
\]

Living systems use a variety of electron donors and electron acceptors as the basis of their energy systems, but all energy systems have that same basic set of paired reactions. All of the energy systems we find today arose in Bacteria and Archaea early in the history of life on Earth, and some components even pre-date life’s origin. Some of those systems are also found in Eukaryotes, where again the systems have a basic similarity across all species while showing diversity in particular aspects.

Organisms can be divided based on their source of energy: whether the energy comes from inorganic sources or from consuming other organisms. Among inorganic sources, light accounts for almost all of the energy fixed by living systems on Earth. Each year approximately 100 terawatts of energy is captured by this process, about seven times more than used by the entire human civilization, converting around 100 billion metric tonnes of carbon into biomass per year.

Light energy is used by nearly all plants, as well as numerous single-celled Eukaryotes and some Bacteria. When light is the energy source, photons are absorbed by specialized molecules that release high-energy electrons. The electron donor is most commonly water (H₂O) and the electron acceptor is carbon dioxide (CO₂) with molecular oxygen (O₂) being released in the process. We look at this process, called photosynthesis, in detail below. Some Bacteria use light energy with other electron donors including hydrogen sulfide (H₂S, which produces elemental sulfur, S) and various organic molecules.

Some Bacteria can also use the chemical energy contained in a variety of inorganic substances. These alternative electron donors include methane (CH₄), hydrogen sulfide (H₂S), ammonia (NH₃), hydrogen (H₂), iron (Fe₂⁺), and manganese (Mn₂⁺) and a
variety of electron acceptors including oxygen (O$_2$), sulfur (S), sulfate (SO$_{4}^2-$), nitrate (NO$_{3}^-$), nitrite (NO$_{2}^-$), and phosphite (HPO$_{3}^2-$). Some of these systems, such as the use of manganese by bacteria living in the deep ocean, were recently discovered and are still not completely characterized. These metabolic processes also play an important role in the environmental cycling of these elements (see Figure 7.1C).

When life originated it used these alternative sources (see Chapter 1). The ability to capture light energy using water and releasing oxygen did not evolve until about 2.5 billion years ago, nearly a billion years after life originated. That event led to the first massive change in the chemistry of the Earth by releasing O$_2$. As we discuss below, that O$_2$ became a critical part of the energy metabolism of most organisms.

Regardless of their energy source, all living organisms on earth require carbon, as it is essential for all organic molecules. Organisms that use CO$_2$ as an electron acceptor use that same source for their carbon. Bacteria that use a different electron acceptor either also fix CO$_2$, or they get their carbon from organic compounds produced by other organisms. All other organisms, including all animals, fungi, and most single-celled Eukaryotes, Bacteria and Archaea get both their carbon and their energy from the same source, the consumption of organic materials.

**Photosynthesis**

Photosynthesis is the process of converting light energy into chemical energy. Chemically, the process can be summarized as: H$_2$O + CO$_2$ = O$_2$ + organic compounds. That summary, however, hides a lot of detail. The entire process can be divided into two segments (Figure 5.11). The first segment is the oxidation step that uses light energy to break H$_2$O into H$^+$ and O$_2$ and captures the energy in two compounds: ATP and NADPH. ATP stands for adenine triphosphate, indicating that it contains three phosphate (PO$_3^+$) units (Figure 5.ATP). The bond between the third phosphate unit and the rest of the molecule contains a lot of energy, but it is also easily broken in a way that can transfer that energy to another chemical bond. This makes ATP one of the primary energy carriers in cells. NADP+, nicotinamide adenine dinucleotide phosphate, is an electron acceptor that can be converted to NADPH, again as a high-energy carrier.

Because this segment uses light energy, it is often referred to as the light reactions. The key molecule in this step is chlorophyll, which is capable of absorbing photons. Those photons change the chemical composition of the chlorophyll, shifting it into an excited state in which it can act as a reducing agent. The energy in that reaction gets passed along through a chain of molecules, in the process of which ATP and NADPH are produced (Figure 5.12). Although it may seem unnecessarily convoluted to have the electron passed along a chain, rather than having the chlorophyll react directly with the ADP and NADP+, the process is necessary to “cool off” the energetic particle.
The light absorbing system is like an antenna that consists of many molecules. Chlorophyll is at the center of the antenna, but other related molecules are part of it, with different molecules best able to absorb different wavelengths of light. Land plants appear green because these molecules absorb light across most of the visible spectrum, and reflect back mostly the green wavelengths. Other groups of photosynthetic Eukaryotes and Bacteria look red, brown, yellow, orange, cyan and even purple because they have other forms of chlorophyll and associated molecules with slightly different absorbance characteristics. All of these photosynthesis systems are based on the same general principle – the capture of light energy as excited electrons – but they carry out that process in many different ways.

The second segment is the reduction step that starts with CO₂ and uses the energy captured in the ATP and NADPH molecules to produce organic compounds, notably glucose. Glucose is the end point of this process because it is much more stable than ATP or NADPH, and thus suitable for both long-term storage of energy and for transportation to other parts of a multicellular organism. Because this segment does not require light energy, it is sometimes referred to as the dark reactions. It is also known as the Calvin cycle or the Calvin-Benson cycle after the people who first described its details (Box 5D). In Eukaryotes, the process of photosynthesis takes place in specialized organelles within the cell called chloroplasts (Figure 5.13). Just as with their other metabolic processes, Bacteria that carry out photosynthesis have membranes that are used to organize the molecules responsible for this process.

Because photosynthesis is the way in which many species get their energy, you might think that those species would always be carrying out photosynthesis as quickly as possible. However, this rarely happens. Just as the amount of food you can consume at any one time is limited, the rate of photosynthesis is limited by many different factors. First, more light energy does not necessarily mean more light captured. A cell contains only so many chloroplasts, which contain only so many chlorophyll molecules. The exciting of the electrons and the passing of that energy to the next molecule in the chain takes a certain amount of time, even if that time can be measured in nanoseconds. The
process also requires $H_2O$ and $CO_2$, and even if both are available in unlimited quantities, it takes time to move them into the cell and into the chloroplasts. Very often light or $H_2O$ are available in limited amounts (a plant in the shade or in a desert), and even the availability of $CO_2$ can be limiting. Those are all short-term limitations; over a longer span of time, there may be limits on the materials needed to build chloroplasts.

Figure 5.13
A. Chloroplasts are specialized organelles in the cells of photosynthetic Eukaryotes where photosynthesis is carried out. (Created by Kelvinsong, Source: Wikipedia)
Box 5D  
Critical Experiment: Describing Photosynthesis

The process of working out the dark reactions of photosynthesis were carried out by a group of scientists at the University of California-Berkeley in the years following World War II. They were led by Melvin Calvin – who was awarded the Nobel Prize in Chemistry in 1961 for this work – and included Andrew Benson and James Bassham. This set of experiments highlights the importance of how the development of new scientific tools can provide new ways to answer questions. In this instance, radioactive isotopes of carbon (14C) became available as a by-product of atomic power and atomic bomb research, at the same time that chemists developed paper partition chromatography, a process which can separate individual compounds from a solution. The researchers utilized these new advances along with autoradiography, a process which can locate radioactive compounds on a paper chromatogram. Although none of these techniques were developed for the problem of describing photosynthesis, as commonly occurs in the sciences, Calvin and his team were able to recognize how those methods could be used to answer their question.

The experiments were carried out with the eukaryotic, one-celled alga Chlorella which had the advantage of growing quickly in solution. They grew them in a flattened flask that was dubbed a “lollipop” because of its shape, one which exposed the alga to as much light as possible, thus maximizing the rate of photosynthesis (Fig. 5D.A). At the start of the experiment, liquid containing 14CO₂ was injected into the lollipop. Then, after a set amount of time, a sample was rapidly placed into boiling ethanol. The boiling ethanol quickly killed the alga, halting photosynthesis.

Critically, the ethanol also extracted the various molecules that were part of the dark reaction. The ethanol, along with the extracted molecules, was then placed on the paper chromatogram. Different molecules would move at different rates along the paper depending on their chemical structure, thereby separating them. The researchers could then use autoradiography to identify those that had incorporated the 14C, and perform further chemical analyses to identify the molecule and even to show which of the carbon atoms were radioactive.

The first thing that they discovered was that the reactions were very fast; after just 30 seconds many different types of molecules contained the radioactive label. Wanting to be as precise as possible – something very important in any scientific experiment – they kept repeating the experiment using shorter and shorter exposure times, until they had it down to just 2 seconds. Even then, a half dozen or more types of molecules were labeled. However one type, 3-phosphoglyceric acid (3PG) (Figure 5D.B), was always the most abundant. From this they concluded that it was the first molecule in the process.

An important clue to what was happening was based on their determination of which of the carbon atoms were radioactive. Most of the labeled atoms were part of the COO group on the end, lending support to the conclusion that this was the newly incorporated 14CO₂ molecule. Sometimes the other atoms were also radioactive, and from this they deduced that the process was cyclical, that is, the 3PG was made by adding
CO₂ to a molecule that was previously derived from 3PG. But what was this molecule? The obvious answer was some sort of two-carbon molecule to which the third was added – however, none of the radioactive molecules that showed up on the paper chromatogram had this structure. When faced with this apparent obstacle, the researchers had to draw on disciplines outside biology itself – in this case, chemistry – to figure out what their results meant. This is a very common occurrence in all scientific fields, not just biology, and this experiment is a prime example of how science rarely happens in isolation, but is extremely interconnected. One molecule that they found was a reduced form of 3PG, a reduction that requires energy, which they hypothesized came from light energy captured in the form of ATP. To prove this, they performed the experiment in the light and in the dark. As predicted, in the dark amounts of 3PG increased and very little of the reduced form were found.

Now that they knew where the 3PG was going to, the next step was to determine where it was coming from. What, exactly, was the unknown precursor molecule – which they called molecule X – and how was it getting turned into 3PG? To figure out the identity of molecule X, the Berkeley group needed another bit of information, which was what would happen if the supply of CO₂ were cut off in the presence of light. In that case, the amount of 3PG should decrease as it gets reduced, but the amount of molecule X should remain the same, or possibly even increase, because there is no CO₂ for the next step of the cycle. When they sifted through the data from their experiments, they found a molecule that fit the bill perfectly, the five-carbon ribulose bisphosphate (RuBP). Instead of a two-carbon precursor, the CO₂ was added to a five-carbon molecule producing an unstable six-carbon molecule that immediately split into two molecules of 3PG.

Once they had worked out these key steps, the rest of the cycle was deduced using similar methods. They discovered that the dark reactions consisted of a number of steps involving four-, five-, six- and seven-carbon molecules. They also discovered the key enzyme in the process, the one responsible for the reaction between RuBP and CO₂, giving it the name ribulose bisphosphate carboxylase (usually called rubisco). Later workers showed that rubisco is found exclusively in the chloroplasts, as are the other molecules and enzymes postulated to be part of the dark reactions, just as would be predicted.

The experiments of Calvin and his team demonstrate one very fruitful way of gaining scientific knowledge. They performed a series of carefully controlled experiments where they would vary one factor at a time, keeping all other factors constant, the sort of experiment advocated by Francis Bacon (see Box 2C). The experiments were guided by a careful logic based on both their broad knowledge of chemistry in general and other similar discoveries. For example, they concluded that the process was cyclical based on their own data and knowledge that other biochemical reaction systems were also cyclical. Finally, they were able to carry out the experiment when they did because of new tools and techniques that others had developed.
**Energy usage**

In many regards, the usage of the energy stored in organic molecules simply reverses the steps that occurred when those molecules were created. Many of the basic features are similar. All energy usage involves redox reactions, just in reverse. Some parts of the process are shared by all species – again pointing to descent from a common ancestor – yet there is much diversity involving the specific details. In Eukaryotes, parts of the process take place in specialized organelles, the **mitochondria**.

![Diagram of metabolic pathways involving glucose](image)

**Figure 5.14**

Glucose, a six-carbon molecule, gets broken down into pyruvate, a three-carbon molecule, releasing energy. The pyruvate may get further oxidized completely into CO₂ if oxygen is available, a process that in Eukaryotes occurs in the mitochondria. If oxygen is unavailable, the pyruvate may be reduced into a variety of three-carbon or two-carbon molecules. (Created by JohnyAbb, Source: Wikipedia)

Because the most common product of photosynthesis is glucose, we will focus on its usage, although the same general principles hold for the breakdown of all organic molecules. One vital, if slightly counterintuitive, aspect of the process is that it takes energy to release energy. Glucose is a six-carbon molecule, and the first steps involve breaking it into two three-carbon molecules that each have a phosphate molecule added. The phosphate comes from ATP, necessitating the use of energy to transfer the phosphate. Those three-carbon molecules are then oxidized to pyruvate, also a three-carbon molecule, in the process producing four molecules of ATP, for a net gain of two ATP, plus two molecules of NADH (similar in structure and function to NADPH). At this point there are a variety of fates for those pyruvate molecules (Figure 5.14).

The first consideration is whether oxygen is available. If it is not, the pyruvate may be involved in a reduction reaction that produces a two-carbon molecule of ethanol plus one molecule of CO₂. This is the process responsible for creating the alcohol in wine and beer. It also uses two molecules of NADH, thus using energy. Although ethanol is a common end-product in these reactions, some organisms produce acetate instead.

Alternatively, the pyruvate may be reduced to a variety of three-carbon molecules, including alanine and lactate, again consuming two NADH molecules. Those molecules may be used to build other structures – alanine, for example, is an amino acid used in proteins – or they may be waste products and eventually expelled. These alternative
fates can take place in a wide variety of organisms, including Bacteria, Archaea, and Eukaryotes that live in places with little or no oxygen. Thus, **anaerobic metabolism** (metabolism in the absence of oxygen) is another example of both the unity and diversity of metabolic systems.

Anaerobic metabolism can also occur in organisms with aerobic metabolisms during short-term periods when oxygen becomes limiting. For example, when you perform extreme physical events like running a marathon, you can exceed the ability of your blood to supply oxygen to your muscles. When that happens, the sugar that your muscles are trying to use gets converted to lactate, and it is the presence of lactic acid that causes your muscles to feel sore.

If oxygen is available, the pyruvate is oxidized to produce three molecules of CO₂ while producing one molecule of ATP, four molecules of NADH and one molecule of FADH₂ (another, similar energy carrier). Most of this happens as part of a cyclical process involving a series of four-, five- and six-carbon intermediates (Figure 5.15). The cycle is variously known as the citric acid cycle, for the first stable intermediate, or the Krebs cycle, for the German-British scientist Hans Krebs, who described much

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**Figure 5.15.** The citric acid cycle (Created by Narayananese, Source: Wikipedia)

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**Figure 5.16**
A. Mitochondria are specialized organelles in the cells of almost all Eukaryotes where glucose is broken down to in the presence of oxygen. (Created by Kelvinsong; Source: Wikipedia) B. Mitochondria from mammalian lung tissue. (Photo by Louisa Howard, Source: Wikipedia)
of the process in the 1930s. In Eukaryotes this process is carried out in the mitochondria, an organelle found in all but a handful of species (Figure 5.16).

This oxygen-requiring process extracts much more energy from the glucose molecule than the first part of the process where glucose was split into two pieces. So, once oxygen-producing photosynthesis evolved and the levels of oxygen in the atmosphere became substantial, organisms could be much more complex. It is probably no coincidence that it is not until after this happens that Eukaryotes evolved because their cells are generally larger much more complex than those of Bacteria and Archaea. A common misconception is that plants do not use oxygen or give off CO₂. Plants, just like other Eukaryotes, have mitochondria and break down glucose. During the day, this process is far outstripped by photosynthesis, so that overall plants are taking in much more CO₂ than they are giving off. At night, however, they are giving off CO₂ just like animals.

Scientists have suggested as part of the Metabolism First theory for life’s origin (see Chapter 1) that a version of the citric acid cycle predated the origin of life. A version of that cycle is found in all species and is linked to the synthesis of most biological molecules. Originally it would have run in the opposite direction as a synthetic cycle, possibly using hydrogen sulfide (H₂S) as the electron donor and iron sulfide (FeS) as the electron acceptor. These chemical reactions do not necessarily require enzymes to happen at rates high enough to create sufficient concentrations of organic molecules, a requirement for pre-living systems. Because the system is cyclic it could form the basis of a self-organizing living system. Only about a billion years later, after cells had evolved and oxygen became plentiful, was the cycle co-opted as part of oxidative metabolism.

**Nutrients**

Because cells are dynamic entities, they require a constant input to maintain themselves. Besides energy, organisms require materials to build their structures and their dynamic nature means that structures are constantly being rebuilt and changed. The building blocks for these structures can be obtained in two ways: a cell can build them from scratch or it can take them in as food. This movement of ions and molecules both into a cell and among the parts of the cell is one of the primary uses of a cell’s energy (Table 5.1, principle 7).

Some organisms can build all of their needed structures beginning with the simplest inorganic molecules: hydrogen and oxygen from H₂O, or from CO₂ or CH₄ which also serve as a source of carbon, nitrogen from N₂, NH₄, HNO₂ or HNO₃, and phosphorus from HPO₄. Such organisms also have to be able to obtain energy from light or chemical sources. Species able to do this include a variety of Bacteria and Archaea, along with plants and other photosynthetic Eukaryotes.

For all other species, these materials are obtained, at least in part, by taking in organic materials built either by the species just mentioned, or from others that have eaten those species. Some material is broken down completely and the basic molecules reused. In other cases, material is broken down just partially, while other material is used as consumed. Consider what happens when you eat a piece of protein, as a burger made either from beef or tofu. The protein is first broken down into its amino acids, many of which may be further broken down into ammonium (NH₄⁺) and carboxylate (HCO₃⁻) ions and then reused to build new amino acids. However, humans are incapable of building the amino acid tryptophan so we must take it in as part of our diet. In this case, both beef and soybeans in the form of tofu can be sources of tryptophan. Because tryptophan must be obtained by consumption, it is called an **essential amino acid**.

The term **vitamin** is used for those molecules that are taken in and used as is without first being broken down, although they may be incorporated into larger
molecules or further modified. For example, vitamin B5 (pantothenic acid) is the coA part of acetyl-coA that participates in the citric acid cycle (Figure 5.CC). Vitamin C (ascorbic acid) is necessary for humans, great apes, bats, and a few other mammals, notably guinea pigs, and some birds. Other mammals and birds are capable of synthesizing this molecule. In some cases, vitamins are needed only under some circumstances. For the synthesis of vitamin D, humans require sunlight which reacts with the pigment melanin in our skin. People living in very northern or southern latitudes which have little sun for large parts of the year must consume vitamin D in their diet.

The network of chemical reactions in a cell (Figure 5.YP) is a linking of the synthesis and breakdown of organic molecules. RNA molecules are assembled as part of the process of transcription (see Chapter 3) and then broken back down into their nucleic acid components to be recycled into new RNA molecules. Often the chemical reactions involved in synthesis and breakdown are very similar, even identical, and in a few cases may even make use of the same enzyme. Depending on which way the reaction is run, it may use energy or it may generate energy. When you eat a bowl of ice cream that is full of sugar, fats and protein, the breakdown of all of those materials provides both energy and material that is then re-used to build new forms of the sugars, fats and proteins to meet the specific needs of your cells.

It is no surprise that the same chemical reactions running forward in plants when synthesizing materials run in the opposite direction in animals when they consume those materials. Most of the biochemical pathways in plants and animals first evolved in the bacterial and archaeal ancestors of Eukaryotes. Natural selection tends to be conservative, re-using and re-purposing functions and structures that may have originally evolved for other purposes (see Chapter 4). Evolution also explains why metabolic pathways sometimes seem overly complex. Evolution always starts with what is already present, then adding or subtracting as mutation and natural selection allow. The result is often a workable solution, rather than the best if it were designed from scratch.

**Cell Replication**

The processes of life exist for and are perpetuated through living organisms maintaining themselves, growing, and reproducing. In chapter 6, we will look at these processes from the perspective of the whole organism. Here, we examine them from the viewpoint of a single cell. We have already looked in detail at the process of maintenance through the intake of matter and energy and the use of those materials for building and regulating cellular structures. If an organism consists of only a single cell, then growth occurs through the intake of matter. At some point, if it has ingested enough material, it will divide into two cells. For multicellular organisms, cell division is the primary way that they grow, although some growth can occur by cell expansion. All cells come from the division of previously existing cells (Table 5.1, principle 8). This process of cell replication is called mitosis. In Chapter 3 we looked at one aspect of this process, the replication of chromosomes (see Figure 3.4). Elaborate cell machinery involving the cytoskeleton exists to ensure that the duplicated chromosomes are correctly sorted into the daughter cells. For the rest of the cellular components, no specific machinery exists. Instead, because all of the parts are spread out across the entire cytoplasm, when cells divide enough material of all types necessary to form the entire machinery of the cell ends up in each of the daughter cells. Mitochondria and chloroplasts go through their own processes of growth, chromosome duplication, and division within a cell, so that they exist in multiple copies. These copies subsequently end up being distributed among the daughter cells.

The information necessary for these processes is contained in the cell's
chromosome(s) (Table 5.1, principle 9), which constitute the mechanism by which information is passed from one generation of cells to the next (Chapter 3). In Bacteria and Archaea there is typically one large circular chromosome, although there may also be additional small circular chromosomes. In Eukaryotes, the nucleus contains one or more large linear chromosomes, while the mitochondria and chloroplasts within the cells contain their own, smaller circular chromosomes. The chromosomal theory of inheritance was first proposed by T. H. Morgan (see Box 3E) in the early twentieth century, which eventually lead to the discovery of the structure of DNA (see Box 3A).

That new cells come from existing cells is one of the two central tenets of cell theory put forward in the 19th century (see Chapter 1), and the promulgation of cell theory was part of the general development of biology as a discipline. The other tenet – that all organisms are composed of cells – is now considered part of the theory of organisms (see Chapter 6).

**The Evolution of Cells**

Cell evolution (Table 5.1, principle 10) has gone through three critical stages: the origin of the first cells, the origin of Eukaryotes, and multicellularity. The first two stages occurred once; all of life on Earth traces to a single common ancestor and all Eukaryotes trace to a single common ancestor. That does not mean that the process happened in a single step; undoubtedly it was a multiphase process. The evolution of multicellular species, however, clearly happened multiple times. The first two stages are similar in that they involved the coming together of independent entities, each with different abilities, to form a new, single cell. The last stage reversed this process to some extent, taking a cell and dividing its abilities among multiple entities. Because evolution includes contingent events (see Table 4.1, principle 7), at least some of the features of cells are due to chance events, although we do not know which ones; for example, scientists debate whether the basic metabolic processes that are shared by all cells were inevitable because they were chemically favored, or if they were just an accident of life’s origin.

**Stage 1: Life’s origin**

The origin of life and the first cell is discussed in detail in Chapter 1. To summarize, if the reconciliation model is correct, then that cell originated when self-replicating nucleic acids and self-catalyzing redox reactions were brought together within a lipid bubble. Each of those components accounted for a different cellular function: information, metabolism, and structure. It was a type of **symbiosis**, an interdependent or mutually beneficial relationship between two or more entities.

Critical to this process is that the various entities develop a way to avoid “cheating,” which is to say, one entity improving its fitness at the expense of its partners. The first cells did this by linking the parts into a shared fate. The information and metabolic components became unable to reproduce on their own. The information contained in the structures of and relationships among the metabolic components became encoded within the information system. Conversely, the information system in moving from RNA to DNA became incapable of independent replication. The linking of all of the pieces of information (nucleic acids) into a single chromosome is another way of creating a shared fate, a strategy found in the single large, circular chromosome of all Bacteria and Archaea. Recently, scientists have tried to answer the question of what comprises the minimum structure and function necessary to be a living cell. In answering this question, they hope to both gain a better understanding of how cells function and insight into what the common ancestor of all life might have looked like, an entity sometimes called the Last Universal Common Ancestor (LUCA). Since that ancestor is now long extinct, its biochemical and genetic make-up has to be deduced by looking at all of the living
species and determining what functions all of them share. Depending on how that calculation is done, the LUCA may have had somewhere between 500 and 1500 genes, about half of which were involved in the maintenance and replication of the information system and the other half involved in cellular metabolism and structure. If this is correct, then clearly a lot of evolution had to have occurred between the time of the origin of the first cell and the ancestor that ultimately gave rise to today’s species. This raises the possibility that life arose multiple times independently and all but one of those origins went extinct. Of course, that is a hypothesis that is impossible to test, as there are no traces of those other possible lineages.

**Stage 2: Eukaryotic cells**

The next stage was the origin of the eukaryotic cell. While much is still unknown about this process, our understanding has improved markedly in the past 40 years since Lynn Margulis popularized the endosymbiotic theory that had been first proposed in 1905 by the Russian botanist Konstantin Mereschkowsk. To understand this theory, consider the mitochondrion, which has several curious features. First, mitochondria replicate through a process of binary fission like Bacteria; they are not built from scratch like other cellular structures. Second, it has not just one membrane but a double membrane. Third, it has a small circular chromosome similar to those in Bacteria that codes for some, but not all, of its machinery. Fourth, the ribosomes in mitochondria are much like those in Bacteria rather than those in the rest of the cell.

Based on this evidence, Margulis and others suggested that the mitochondrion was originally a free-living Bacteria. Typically, Bacteria are consumed by larger single-celled organisms by being engulfed (Figure 5 AE). The hypothesis is that in one instance a bacterium that was particularly good at oxidative metabolism was not consumed, but remained alive inside the cell. The bacterium formed a symbiosis with the surrounding cell: in exchange for pyruvate and other materials, it supplied the cell with energy in the form of ATP, NADH and FADH. Over time, some of the genes on the bacterial chromosome were transferred to the nuclear chromosomes, tying the fate of the mitochondrion to the rest of the cell. The engulfment explains the double membrane; one would have originally been the outer envelope of the independent bacterium, and one formed when the original cell engulfed and attempted to consume the bacterium. It also explains why mitochondria have many features similar to Bacteria. Although this theory was controversial for some time, it is now the accepted explanation. The strongest evidence is based on more recent sequencing of the mitochondrial chromosome showing that its DNA sequence is more like that of some Bacteria than it is like nuclear genes. This process has also identified the group of Bacteria from which mitochondria most likely derived, the Proteobacteria. DNA sequencing has also been able to identify genes now located on nuclear chromosomes that appear to have originated in the mitochondria. As expected, these genes code for functions involved in oxidative metabolism and materials that are transferred into the mitochondria.

What about the rest of the features of eukaryotic cells? Eukaryotes are distinguished from Bacteria and Archaea by having a flexible cell surface, linear chromosomes, a nuclear envelope, a complex membrane system including digestive vesicles, and a cytoskeleton. Some of these features can be explained, while others are still the subject of speculation and research. Based on DNA sequence evidence, Eukaryotes are more closely related to Archaea, particularly the genes that code for proteins involved in information system functions (translation, transcription, replication, and repair). On the other hand, some aspects of eukaryotic cells, such as the cell membrane are more like those of Bacteria. Interestingly, the genes that code for proteins involved with functional and structural aspects of the cell (metabolic enzymes, components of membranes, and
other cellular structures) appear to be more closely related to Bacteria. One possibility is that the original Eukaryote came about through a fusion of an archaeon and a bacterium with the former becoming the nucleus and the latter the cytoplasm. Suggestive of this is that the nuclear membrane, like that of the mitochondria, is also a double membrane. At some point, either before or after this fusion, the organism had to lose its cell wall leaving it with a flexible membrane, and infoldings of that membrane would have produced the complex membrane structure that we see today. The cytoskeleton would have been derived from what was previously strictly external cilia or flagella. What is currently completely unexplained is how chromosomes went from being circular to linear. Even the timing is still very uncertain. There are clear fossil single-celled Eukaryotes 1.6 billion years old, with some possibly as old as 2.1 billion years, and some much sketchier trace evidence as far back as 2.7 billion years.

Once the first Eukaryote appeared, it would have been quickly favored. The complex membrane system provided for greater spatial structuring and more efficient chemistry. Organelles such as mitochondria allow for compartmentalizing of functions, especially those involving chemicals that could harm other parts of the cell. At some point, Eukaryotes evolved meiosis and a regularized system of recombination, greatly increasing the amount of genetic variation (Chapter 3) and the rate of evolution (Chapter 4).

The origin of chloroplasts is similar to that of mitochondria. Like mitochondria, chloroplasts also have their own circular chromosome and a double membrane. This symbiosis, though, occurred at least three different times, the first one about 1.5 billion years ago. The evolution of photosynthesis in single-celled Eukaryotes is quite complex, with evidence of secondary symbiosis: a photosynthetic Eukaryote being engulfed by another Eukaryote. Evidence for this comes from both DNA sequence data and the presence of a triple membrane around the chloroplast.

**Stage 3: Multicellularity**

The third stage in cellular evolution is multicellularity. Like the advent of eukaryotic cells, this development granted an important advantage for organisms that possessed it; the component cells of an organism specialize for different functions. Like the evolution of compartmentalization in eukaryotic cells, specialization increases the efficiency of cell functions. Not only can functions be separated that might interfere with each other, but cells can take on different forms suited to particular tasks. However, separating these functions requires that cells be able to communicate, both during their initial creation and throughout an organism’s lifespan. After all, it would not do for all of your cells to become heart cells, some must become lungs, nerves, skin, and so forth. This means that the communication systems described earlier are critical components; there must be ways to ensure that the cells cooperate. If this communication system breaks down, the results can be disastrous; one way to think about a cancerous cell is as a single cell that is reproducing itself at the expense of the entire individual. We take up the story of multicellularity in more detail in the next chapter.