The Machinery of Life

Second Edition

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The Immune System Piercing a Bacterial Cell Wall Our blood contains proteins that recognize and destroy invading cells and viruses. This illustration shows a cross section through a bacterial cell (lower half, in greens, blues and purples) being attacked by proteins in the blood serum (at the top, in yellows and oranges). Y-shaped antibodies begin the process by binding to the surface of the cell, and are in turn recognized by the six-armed protein at upper center. This begins a cascade of actions that ultimately lead to the formation of a membrane attack complex, shown here piercing the cell wall of the bacterium (1,000,000 X)

Preface

Imagine that we had some way to look directly at the molecules in a living organism. An x-ray microscope would do the trick, or since we're dreaming, perhaps an Asimov-style nanosubmarine (unfortunately, neither is currently feasible). Think of the wonders we could witness firsthand: antibodies attacking a virus, electrical signals racing down nerve fibers, proteins building new strands of DNA. Many of the questions puzzling the current cadre of scientists would be answered at a glance. But the nanoscale world of molecules is separated from our everyday world of experience by a daunting million-fold difference in size, so the world of molecules is completely invisible.

I created the illustrations in this book to help bridge this gulf and allow us to see the molecular structure of cells, if not directly, then in an artistic rendition. I have included two types of illustrations with this goal in mind: watercolor paintings which magnify a small portion of a living cell by one million times, showing the arrangement of molecules inside, and computer-generated pictures, which show the atomic details of individual molecules. In this second edition of *The Machinery of Life*, these illustrations are presented in full color, and they incorporate many of the exciting scientific advances of the 15 years since the first edition.

As with the first edition, I have used several themes to tie the pictures together. One is that of scale. Most of us do not have a good concept of the relative sizes of water molecules, proteins, ribosomes, bacteria, and people. To assist with this understanding, I have drawn the illustrations at a few consistent magnifications. The views showing the interiors of living cells, as in the Frontispiece and scattered through the last half of the book, are all drawn at one million times magnification. Because of this consistent scale, you can flip between pages in these chapters and compare the sizes of DNA, lipid membranes, nuclear pores, and all of the other molecular machinery of living cells. The computer-generated figures of individual molecules are also drawn at a few consistent scales to allow easy comparison.

I have also drawn the illustrations using a consistent style, again to allow easy comparison. A space-filling representation that shows each atom as a sphere is used for all the illustrations of molecules. The shapes of the molecules in the cellular pictures are simplified versions of these space-filling pictures, capturing the overall form of the molecule without showing the location of every atom. The colors, of course, are completely arbitrary since most of these molecules are colorless. I have chosen them to highlight the functional features of the molecules and cellular environments.

In the drawings of cellular interiors, I have made every effort to include the proper number of molecules, in the proper place, and having the proper size and shape. In the 15 years since publication of the first edition, a remarkable variety of new data have become available to support these pictures, but the published data on the distribution and concentration of the molecules are still far from complete. As a result, the cellular pictures are subject to some personal interpretation, especially the illustrations of human cells in Chapters 5 and 6.

As in the first edition, I have written the text with the nonscientist reader in mind, and I have drawn the illustrations at a level of scientific rigor meant to satisfy readers who are scientists. For the lay reader, this book is an introduction to molecular biology—a pictorial overview of the molecules that orchestrate the processes of life. The new edition includes many new results from the study of molecular biology, and includes a new chapter on life, aging and death.

Please note, however, that this book is not meant to be comprehensive—I have chosen a series of subjects that capture the aspects of molecular biology that I find most salient, and most fascinating. The reader is referred to the excellent textbooks listed at the end of the book for more detailed and comprehensive information. In particular, *Molecular Biology of the Cell* will point the way to further study of nearly any subject in cell or molecular biology. For the scientist, it is my hope that this book will continue to provide a touchstone for intuition. Please use the illustrations, as I have, to help imagine biological molecules in their proper context: packed into living cells.

I thank the people who have been instrumental in seeing this project from concept to conclusion. Arthur Olson has continued to provide useful comments at every stage, as well as providing an amazing working environment in the Molecular Graphics Laboratory at the Scripps Research Institute in La Jolla. Much of the material from this book draws on my Molecule of the Month series at the RCSB Protein Data Bank, which has kindly supported my illustration and writing for the past 8 years. I also thank the Fondation Scientifique Fourmentin-Guilbert for their kind support of this project. The computer-generated illustrations were produced with methods that I developed under the auspices of the Daymon Runyon-Walter Winchell Cancer Research Fund, the National Institutes of Health, and the National Science Foundation. Finally, I would like to thank Bill Grimm for his support and confidence.

La Jolla, CA D.S. Goodsell

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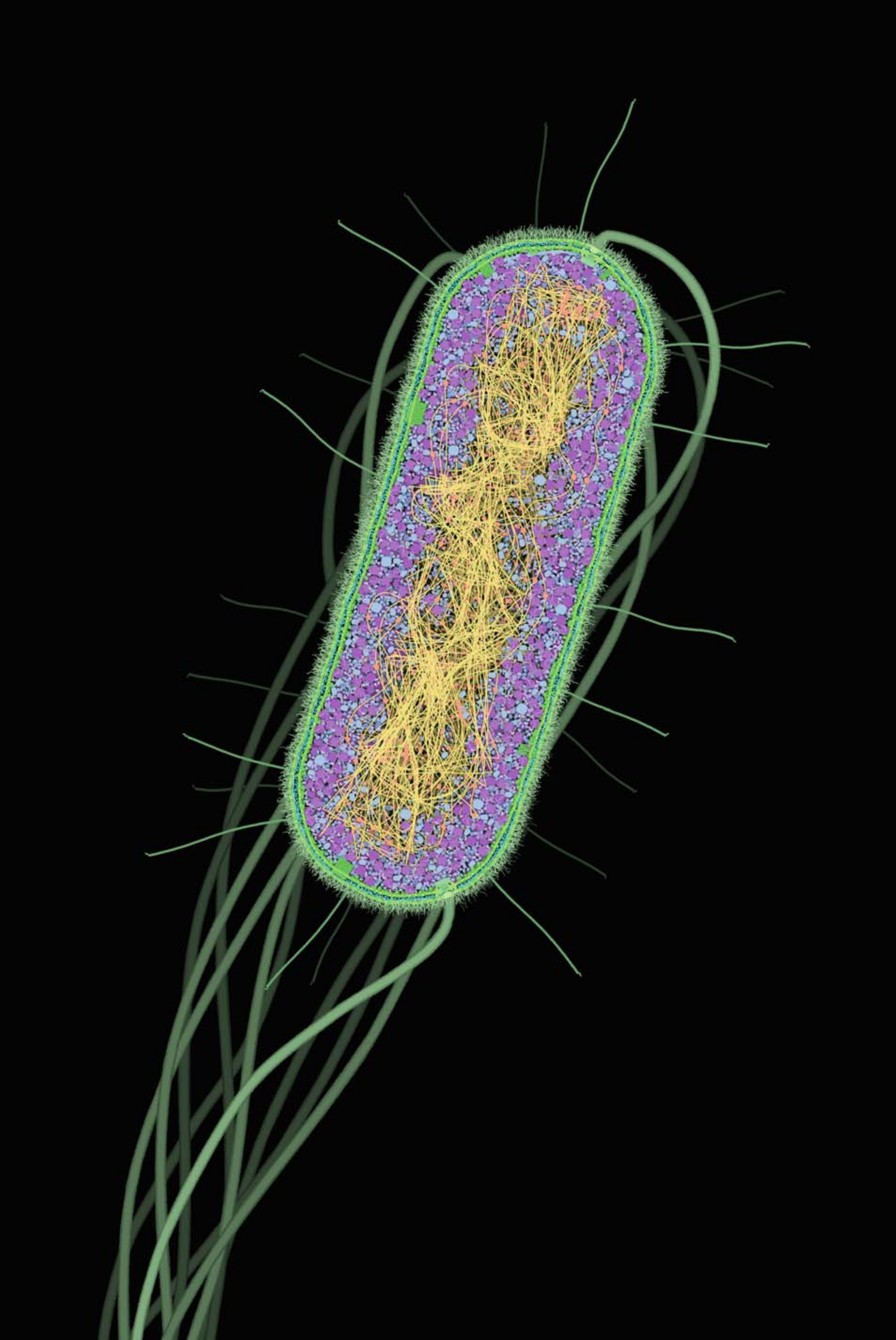

Chapter 1
Introduction

Our world is overflowing with the diversity of life. Imagine that you are taking a leisurely walk through a wooded park. Oak and maple trees cast dancing shadows under the noonday sun. Birds and butterflies dart through the air and a squirrel scampers noisily up a tree trunk. In a typical woodland area, you will be surrounded by dozens of types of trees and plants, filled with even more types of birds. Insects will be crawling on the ground, climbing in the foliage, and flying through the air. Even in the middle of the city, you can find a huge selection of different plants—some carefully tended and some stealthily avoiding the gardener—filled with a variety of birds and insects, all scraping out a living between the houses and concrete.

Next time you are wandering through a park or hiking in the woods, anywhere there are plants and animals, take a moment to examine your surroundings with the eye of a biologist. At its best, science reveals the many wonders hiding behind our familiar experience of the world . . .and this woodland scene carries the evidence of something truly remarkable. By examining the plants, birds, and animals that surround us, scientists have discovered that you and I are directly related to every other living thing on the Earth. With a little bit of critical observation, you can discover this relationship yourself.

Fig. 1.1 The Machinery of Life All life on the Earth is composed of cells, which are themselves composed of molecules. A cross section through a single bacterial cell is shown here. It is surrounded by a multi-layered cell wall, colored green. The long corkscrew-shaped flagella are turned by motors in the cell wall, propelling the cell through its environment. The interior of the cell is filled with molecular machines for building and repairing molecules, for harnessing different sources of energy, and for sensing and protecting against environmental dangers (70,000 X)

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A casual look is enough to show that you are closely related to your mother and father, to your brothers and sisters, and even to the other men and women who might be hiking past you on a wooded trail or crowded boulevard. We are all negligibly different, varying only in nuances of proportion and subtleties of shade. We share the same senses, we walk and talk using the same combination of muscles and bones, we are all born the same way, and we all die as our bodies wear out after a similar amount of time. You do not need to trace family trees to prove that all human beings are related: you can tell just by looking.

The relationship to our biological next of kin, however, requires a bit more observation to discover. A trip to the zoo will reveal our close kinship with familiar animals. Birds and mammals, reptiles, amphibians, and fish are all cousins many times removed. A short study of anatomy is needed to show the family resemblance. We all share similar digestive and nervous systems and a system of bones and muscles built around a head, torso, and four limbs. The differences between us and elephants or lizards are trifles of magnitude: longer legs, denser fur, or sharper teeth.

Things get really interesting when you start looking at our extended biological family. This includes all living things: plants, sponges, insects, flatworms, and all sorts of exotic distant relatives. You need to use many of the tools of biology to see our relationship with these family members. A study of anatomy does not help much—you are so different from a tree that it is difficult to make meaningful analogies between, for instance, your stomach and tree roots, both of which are used to gather food. But when you look in the microscope, you will find that all living organisms are composed of cells, and that the cells in a tree look amazingly similar to the cells in your own hand.

Perhaps the most remarkable observation from biology is that even bacteria share this family history with us. Bacteria are composed of a single cell (Fig. 1.1) instead of the trillions of cells that make up your own body, but that single cell uses much the same machinery as your own cells. If you look very closely at the molecules that orchestrate the processes of life, the resemblance is apparent (Fig. 1.2). Every living thing on Earth uses a similar set of molecules to eat, to breathe, to move, and to reproduce. Because of this, trees and frogs and botulism bacteria all require water and food, they all will die if they get too hot or too cold, and they can reproduce and make new trees and frogs and botulism bacteria if the conditions are just right.

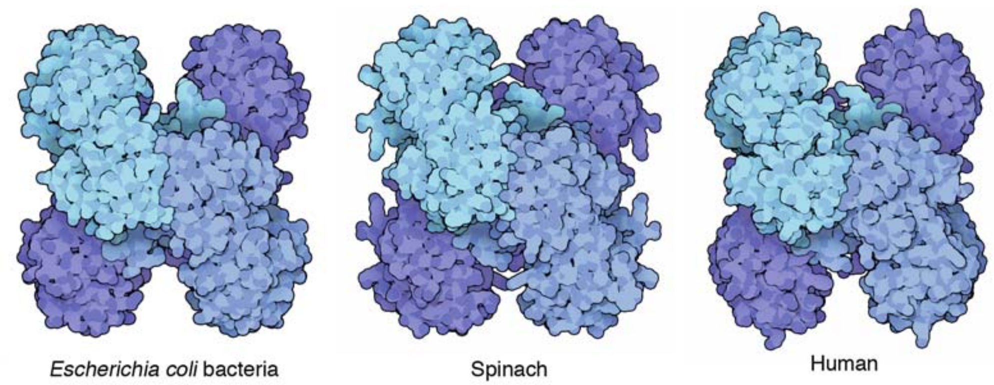

Fig. 1.2 Molecular Machinery Many molecular machines are virtually identical in all living cells. This is particularly true for molecules that play an essential role in the processes of life, such as the enzyme glyceraldehyde-3-phosphate dehydrogenase, which is vital for the metabolism of sugar in all three organisms. This illustration shows the similar form of the enzyme from a bacterial cell (left), a plant cell (center), and human cells (right) (5,000,000 X)

In this book we will explore this common birthright of molecular machines. We will start with a look at the machines themselves and the unusual molecular world in which they operate. Then, we will explore how they are combined in living cells. Finally, we will look at a few special topics related to our own molecules and cells.

A Matter of Scale

Almost everything that we will discuss in this book is too small to see. Cells are small but not unimaginably small, and molecules are really, really small. Cells are about 1000 times smaller in length than objects in our everyday world. The largest cells, such as protozoa, can be seen with a magnifying glass, but a microscope is needed to see most of the cells in your body. Typical human cells are about 10 μm in length. This is roughly 1000 times smaller than the last joint in your finger. A 1000-fold difference in size is not difficult to visualize: a grain of rice is about 1000 times smaller in length than the room you are sitting in. Imagine your room filled with grains of rice. That will give you an idea of the billion or so cells that make up your fingertip.

Another 1000 times reduction takes us to the world of molecules. Molecules are so small that they are smaller than the wavelength of

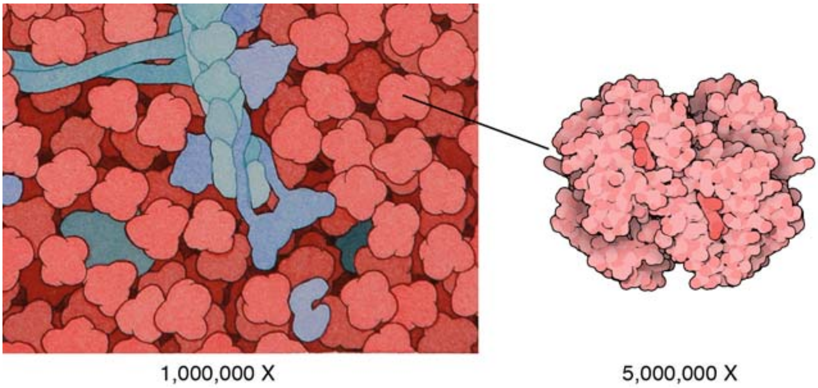

Fig. 1.3 Molecular Illustrations Two types of pictures are used for most of the illustrations in this book. To create pictures of individual molecules, such as the hemoglobin molecule shown on the right here, a computer program draws a sphere for each atom in the molecule, centered on the nucleus of the atom and approximately the size of the cloud of electrons that surrounds the nucleus. In these illustrations, you can easily see individual atoms—this one is drawn at 5,000,000 X magnification. In the hand-drawn illustrations that show molecules inside cells, such as the portion of a red blood cell shown on the left, the shapes of these molecules are simplified, and individual atoms are too small to be seen (they would be about the size of a grain of salt at this magnification). The hand-drawn illustrations are presented at a consistent magnification of 1,000,000 X

light, so there is no way to "see" them directly with a light microscope. Instead, we use methods like x-ray crystallography, NMR spectroscopy, electron microscopy, or atomic force microscopy to discover the arrangement of atoms in the molecule, and then we create artificial pictures of them (Fig. 1.3). An average protein, taken from any cell, contains about 5000 atoms and is about one-thousandth the length of a typical cell, or about one-millionth the width of your fingertip. Again, to get an idea of these sizes, think of a room filled with rice grains. This will give an idea of the size of the proteins that are packed into each of your cells.

The Molecular World

The molecules in our cells perform their jobs in a strange, unfamiliar world, so we have to be careful. When trying to understand a molecular process, our intuition may lead us astray. The principles that guide objects in our everyday world—gravity, friction, temperature—

are different at the molecular scale and often have surprisingly different effects.

One basic thing remains the same at our size and at molecular size: the solidity of matter. At the scale of molecules, we do not need to worry too much about the odd things that happen with quantum mechanics: to a first approximation, molecules have a definite size and shape, and it is perfectly fine to imagine them bumping into each other and fitting together if the shapes match. If we look closely, their edges may be a bit fuzzy, but for most purposes, we can think of them as physical objects like tables and chairs.

Other properties, however, are very different when we enter the molecular world. For instance, molecules are so small that gravity is completely negligible. The motions and the interactions of biological molecules are completely dominated by the surrounding water molecules. At room temperature, a medium-sized protein travels at a rate of about 5 m/s (the speed of a fast runner). If placed alone in space, this protein would travel its own length in about a nanosecond (a billionth of a second). Inside the cell, however, this protein is battered from all sides by water molecules. It bounces back and forth, always at great speed, but takes a long time to get anywhere (Fig. 1.4). When

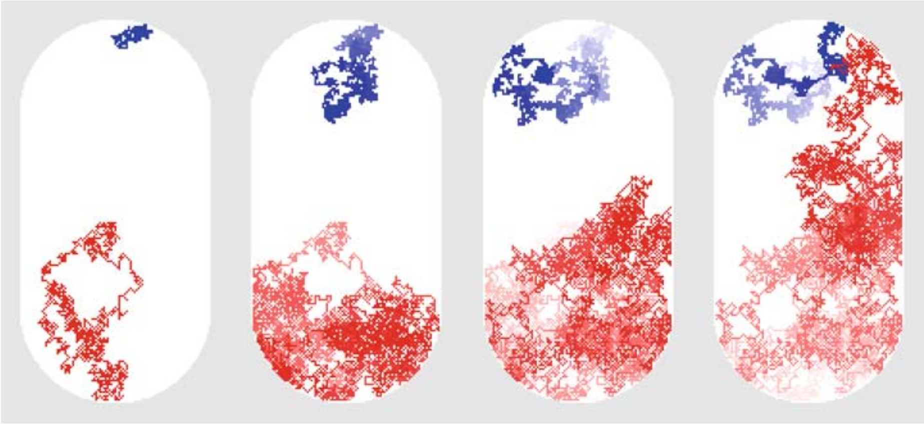

Fig. 1.4 Molecular Diffusion Molecules constantly diffuse within the interior of cells, randomly bumping from place to place. This illustration shows several snapshots from a computer simulation of a protein and a sugar molecule diffusing inside a bacterial cell. The path of the protein is shown in blue and the path of sugar is shown in red. They start at opposite ends and explore much of the space inside before they reach each other

surrounded by water, this typical protein now requires almost a thousand times longer to move a protein-sized distance.

Imagine a similar situation in our world. You enter an airline terminal and want to reach a ticket window on the far side of the room. The distance is several meters—a distance comparable to your own size. If the room is empty, you dash across in a matter of seconds. But imagine instead that the room is crowded full of other people trying to get to their respective windows. With all the pushing and shoving, it now takes you 15 minutes to cross the room! In this time, you may be pushed all over the room, perhaps even back to your starting point a few times. This is similar (although molecules do not have a goal in mind) to the contorted path molecules take in the cell.

You might ask how anything ever gets done in this chaotic world. It is true that the motion is random, but it is also true that the motion is very fast compared to the motion in our familiar world. Random, diffusive motion is fast enough to perform most of the tasks in the cell. Each molecule simply bumps around until it finds the right place.

To get an idea of how fast this motion is, imagine a typical bacterial cell like the one in Fig. 1.1, and place an enzyme at one end and a sugar molecule at the other. They will bump around and wander through the whole cell, encountering many molecules along the way. On average, though, it will only take about a second for those two molecules to bump into each other at least once. This is truly remarkable: this means that any molecule in a typical bacterial cell, during its chaotic journey through the cell, will encounter almost every other molecule in a matter of seconds. So as you are looking at the illustrations in this book, remember that static images give only a single snapshot of this teeming molecular world.