1 Introduction to the cell

The number of cells in the human body is literally astronomical, about three orders of magnitude more than the number of stars in the Milky Way. Yet, for their immense number, the variety of cells is much smaller: only about 200 different cell types are represented in the collection of about 10^{14} cells that make up our bodies. These cells have diverse capabilities and, superficially, have remarkably different shapes, as illustrated in Fig. 1.1. Some cells, like certain varieties of bacteria, are not much more than inflated bags, shaped like the hot-air or gas balloons invented more than two centuries ago. Others, such as nerve cells, may have branched structures at each end connected by an arm that is more than a thousand times long as it is wide. The basic structural elements of most cells, however, are the same: fluid sheets, sometimes augmented by shear-resistant walls, enclose the cell and its compartments, while networks of filaments maintain the cell's shape and help organize its contents. Further, the chemical composition of these structural elements bears a strong family resemblance from one cell to another, perhaps reflecting the evolution of cells from a common ancestor; for example, the protein actin, which forms one of the cell's principal filaments, is found in organisms ranging from yeasts to humans.

The many chemical and structural similarities of cells tempt us to search for systematics in their architecture and components. We find that the structural elements of the cell are *soft*, in contrast to the hard concrete and steel of buildings and bridges. This is not a trivial observation: the mechanical properties of soft materials may be quite different from their hard, conventional counterparts and may reflect different microscopic origins. For instance, the fact that soft rubber becomes more resistant to stretching when heated, compared with the tendency of most materials to become more compliant, reflects the genesis of rubber elasticity in the variety of a polymer's molecular configurations. The theoretical framework for understanding soft materials, particularly flexible networks and membranes, has been assembled only in the last few decades, even though our experimental knowledge of soft materials goes back two centuries to the investigation of natural rubber by John Gough in 1805.

The functions performed by a cell can be looked upon from a variety of perspectives. Some functions are chemical, such as the manufacture of proteins, while others could be regarded as information processing, such

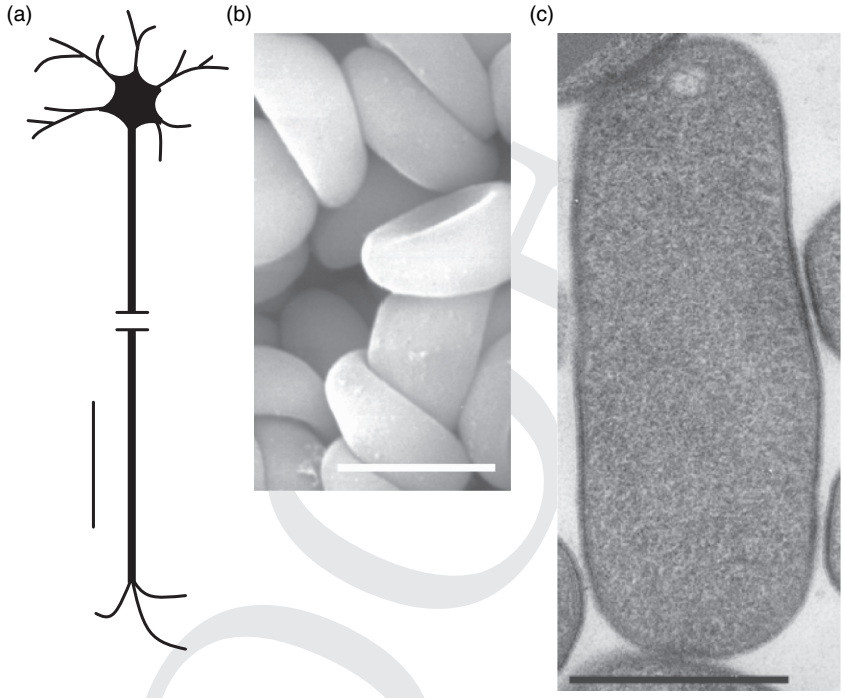


Fig. 1.1 Examples of cell shapes. (a) A neuron is a highly elongated cell usually with extensive branching where it receives sensory input or dispatches signals; indicated by the scale bar, its length may be hundreds of millimeters. (b) Mammalian red blood cells adopt a biconcave shape once they lose their nucleus and enter the circulatory system (bar is 4 μm; courtesy of Dr. Elaine Humphrey, University of British Columbia). (c) Cylindrically shaped, the bacterium *Escherichia coli* has a complex boundary but little internal structure (bar is 0.9 μm; courtesy of Dr. Terry Beveridge, University of Guelph). The image scale changes by two orders of magnitude from (a) to (c).

as how a cell recognizes another cell as friend or foe. In this text, we concentrate on the *physical* attributes of cells, addressing such questions as the following.

- How does a cell maintain or change its shape? Some cells, such as the red blood cell, must be flexible enough to permit very large deformations, while others, such as plant cells, act cooperatively to produce a mildly stiff multicellular structure. What are the properties of the cell's components that are responsible for its strength and elasticity?
- How do cells move? Most cells are more than just inert bags, and some can actively change shape, permitting them to jostle past other cells in a tissue or locomote on their own. What internal structures of a cell are responsible for its movement?
- How do cells transport material internally? For most cells, especially meter-long nerve cells, diffusion is a slow and inefficient means of

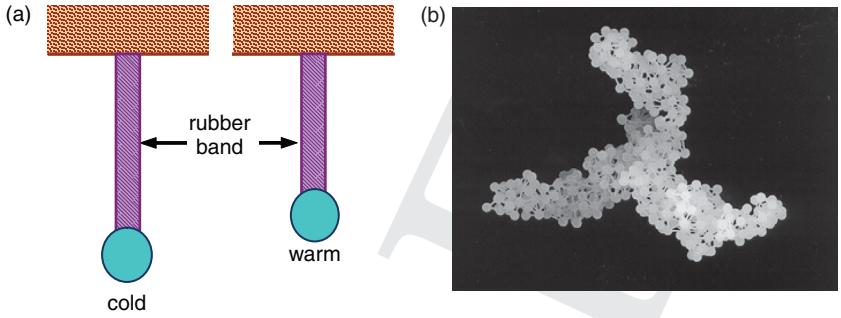


Fig. 1.2 (a) When natural rubber is heated, it becomes more resistant to stretching, an effect which can be demonstrated by hanging an object from an elastic band. When heated, the elastic band contracts, causing the object to rise. (b) A fluid membrane extends arms and fingers at large length scales, although it is smooth at short length scales (simulation from Boal and Rao, 1992a).

transporting proteins from their production site to their working site. What mechanisms, generating what forces, does a cell use for efficient transportation?

- How do cells stick together, as a multicellular organism such as ourselves, or how do they avoid adhering when it is unwanted? Do the thermal fluctuations of the cell's flexible membranes affect adhesion, or is it strictly a chemical process?
- What are the stability limits of the cell's components? A biological filament may buckle, or a membrane may tear, if subjected to strong enough forces. Are there upper and lower limits to the sizes of functioning cells?

To appreciate the mechanical operation of a whole cell, we must understand how its components behave both in isolation and as a composite structure. In the first two sections of this text, we treat the components individually, describing filaments and networks in Part I, followed by fluid and polymerized membranes in Part II. These two sections provide an experimental picture of the cell's structural elements and develop theoretical techniques to interpret and predict their mechanical characteristics. We demonstrate that many properties of soft materials are novel to the point of being counterintuitive; as illustrated in Fig. 1.2, some networks may shrink or stiffen when heated, while fluid sheets form erratic arms and fingers over long distances. Both of these effects are driven by entropy, as we will establish below.

Although it is important to understand the individual behavior of the cell's components, it is equally important to assemble the components and observe how the cell functions as a whole. Often, a given structural element plays more than one role in a cell, and may act cooperatively with other elements to produce a desired result. In Part III, we examine several aspects of multicomponent systems, including cell mobility, adhesion and deformation. The growth and division processes of the cell are of

particular importance to its propagation, and these are the topics of the final two chapters of the text.

1.1 Designs for a cell

Although his own plans for Chicago skyscrapers were not devoid of decoration, architect Louis Sullivan (1856–1924) argued that functionally unnecessary embellishments detracted from a building's appeal. His celebrated dictum, "Form follows function", has found application in many areas beyond architecture and engineering, and is particularly obvious in the designs that evolution has selected for the cell.

Let's begin our discussion of the cell, then, by reviewing some strategies used in our own architectural endeavors, particularly in situations where functionality is demanded of minimal materials. Viewing the cell as a self-contained system, we look to the construction of boats, balloons and old cities for common design themes, although we recognize that none of these products of human engineering mimics a complete cell.

1.1.1 Thin membranes for isolating a cell's contents

Sailing ships, particularly older ships built when materials were scarce and landfalls for provisioning infrequent, face many of the same design challenges as cells. For example, both require that the internal workings of the system, including the crew and cargo in the case of a boat, be isolated in a controlled way from the system's environment. As illustrated by the merchant ship of Fig. 1.3(a), the naval architects of the fifteenth century opted for complex, multicomponent structures in their designs. The boundary of the boat is provided by a wooden "membrane" which need not be especially thick to be largely impermeable. However, thin hulls have little structural strength to maintain the boat's shape or integrity. Rather than make the planks uniformly thicker to increase the strength of the hull, naval architects developed a more efficient solution by reinforcing the hull at regular intervals. The reinforcing elements in Fig. 1.3(a) are linear, linked together to form a tension-resistant scaffolding around the hull. In the design of all but the simplest cells, evolution has similarly selected a cytoskeleton or cell wall composed of molecular filaments to reinforce the thin plasma membrane of the cell boundary.

1.1.2 Networks for tensile strength

The rigging of the sailing ship of Fig. 1.3(a) illustrates another design adopted by the cell. Rather than use stout poles placed on either side of the

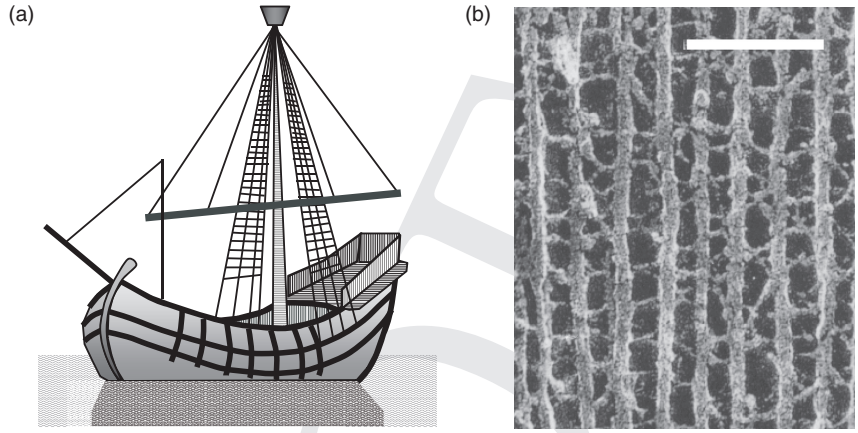
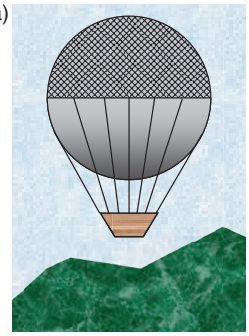


Fig. 1.3 (a) An early fifteenth-century merchant ship displays the efficient use of materials in the design of the reinforced hull and rigging (original illustration by fifteenth-century engraver Israel von Mekenem; redrawn by Gordon Grant in Culver, 1992; ©1994 by Dover Publications). (b) Cross-linked filaments inside a nerve cell from a frog. Neurofilaments (running vertically) are 11 nm in diameter, compared with the cross-links with diameters of 4–6 nm (bar is 0.1 μm; reprinted with permission from Hirokawa, 1982; ©1982 by the Rockefeller University Press).

mast to *push* it into position, a boat uses ropes on either side of the mast to *pull* it into position. By pulling, rather than pushing, the structural elements need only have good tension resistance, rather than the more demanding compression or buckling resistance of poles. Employing strings and ropes with good tensile strength but little resistance to buckling, rigging provides the required functionality with minimal materials. Because the tensile strength of a rope is needed just along one direction, between the top of the mast and the attachment point on the hull, rigging uses only weak lateral links between the strong ropes connected to the mast. This is a design observed in the cross-linking of filaments in nerve cells, as seen in Fig. 1.3(b), and in the cell walls of cylindrical bacteria, which is composed of stiff filaments oriented in the direction bearing the largest stress, linked together transversely by floppy molecular chains.

The relationship between the mast and rigging of a boat exhibits an intriguing balance of tension and compression: the mast has a strong resistance to compression and bending but is held in place by rigging with little resistance to bending. The cytoskeleton of the cell also contains a mix of filaments with strong and weak bending resistance, although these filaments span a more modest range of stiffness than ropes and masts. From Newton's Third Law of mechanics, tension/compression couplets may exist throughout the cell, and there are many examples of thin biofilaments bearing tension while thick ones carry compression without buckling.

(a)



(b)

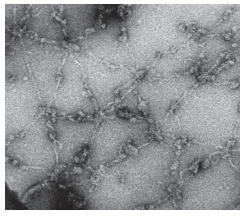


Fig. 1.4

(a) In a hot-air balloon or gas balloon, a thin membrane confines the gas within the balloon, and an external network provides mechanical attachment points and may aid in maintaining the balloon's shape. (b) A two-dimensional network of the protein spectrin is attached to the inside of the red blood cell membrane to provide shear resistance. Shown partially expanded in this image, the separation between the six-fold junctions of the network reaches 200 nm when fully stretched (courtesy of A. McGough and R. Josephs, University of Chicago; see McGough and Josephs, 1990).

1.1.3 Composite structures for materials efficiency

The forces on a boat are not quite the same as the forces experienced by a cell. An important difference is that the external pressure on the hull from the surrounding water is greater than the interior pressure, so that the internal structure of the boat must contain bracing with good compression resistance to prevent the hull from collapsing. In contrast, the interior pressure of some cells, such as many varieties of bacteria, may be much higher than their surroundings. Thus, the engineering problem facing a bacterium is one of explosion rather than collapse, and such cells have a mechanical structure which more closely resembles the hot-air balloon illustrated in Fig. 1.4(a). Balloons have a thin, impermeable membrane to confine the low-density gas that gives the balloon its buoyancy. Outside of the balloon is a network to provide extra mechanical strength to the membrane and to provide attachment sites for structures such as the passenger gondola. By placing the network on the outside of the membrane and allowing the interior pressure to force physical contact between the network and the membrane, the attachment points between the two structural components need not be reinforced to prevent tearing. Again, the network is under tension, so its mechanical strength can be obtained from light-weight ropes rather than heavy poles. Plant cells and most bacteria make use of external walls to reinforce their boundary membrane and balance the pressure difference across it. In a red blood cell, the two-dimensional network illustrated in Fig. 1.4(b) is attached to the membrane's *interior* surface to help the cell recover its rest shape after deformation in the circulatory system.

1.1.4 Internal organization for efficient operation

Advanced cells have a complex internal structure wherein specialized tasks, such as energy production or protein synthesis and sorting, are carried out by specific compartments collectively referred to as organelles. An equivalent system of human design might be a city, in which conflicting activities tend to be geographically isolated. Residential areas might be localized in one part of the city, food distribution in another, manufacturing in yet a third. How can these activities best be organized for the efficient transport of people and material within the city? Consider the plan of the walled city illustrated in Fig. 1.5(a). At this stage in its development, this city still enjoyed fields and open space (green) within its walls, separated from its residential and commercial buildings (magenta). The boundary is defined by the town wall, designed less to confine the inhabitants of the city than to keep hostile forces from entering it. Like the proteins of the cell's plasma membrane, strong gates (pink ovals in the diagram) control much of the

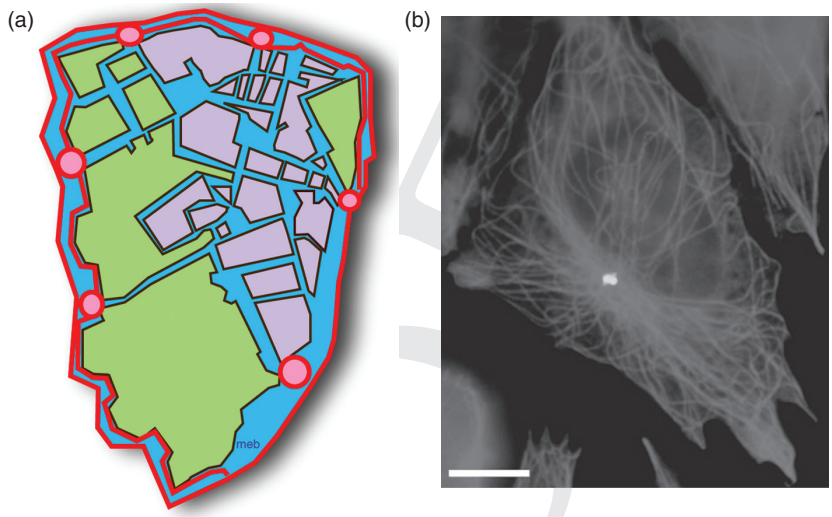


Fig. 1.5 (a) Plan of Quebec in the eighteenth century. Streets within the city walls (red) form an irregular web, with entry points indicated by red disks. (b) The array of microtubules in a cultured fibroblast helps organize the cell's organelles and provides transportation corridors (bar is 10 μm; reprinted with permission from Rodionov *et al.*, 1999; ©1999 by the National Academy of Sciences (USA)).

access to the town's interior. The walls of old cities also reflect the optimal deployment of limited resources, such as the stones used in their construction and the skilled labor needed to assemble them. The minimal town wall needed to enclose a given land area is a circle, just as the minimal cell boundary to enclose a given protein-rich volume is a spherical shell. Of course, other factors, such as their function or mechanisms for growth and division, also influence the design and shape of towns and cells alike. Thus, the design in Fig. 1.5(a) takes advantage of the cliffs and river along the eastern flank of the city so as to concentrate its fortifications along the western side.

An effective transportation system to direct the flow of people and materials is mandatory in an urban setting; for instance, it would be chaotic if visitors arriving at the gates to the city were forced to randomly diffuse through a jumble of houses in search of their destination. Such diffusive processes are very slow: the displacement from the start of a path, as the proverbial crow flies, increases only as the square root of the total path length walked by the visitor. To overcome this problem, cities use dedicated rights-of-way, including roads and railways, to guide traffic between specific locations. Depending on its layout, the most efficient street pattern may be an irregular web, rather than a grid, although the latter has become commonplace in modern times because it simplifies the layout of lots for building construction. In the design of cells, stiff filaments may

provide pathways along which specialized molecules can carry their cargo; for instance, microtubules crowd the transportation corridor of the long section of the nerve cell of Fig. 1.1(a) and their layout also can be seen in the fibroblast of Fig. 1.5(b).

1.1.5 Materials to match the expected usage

Lastly, what about the choice of construction materials? Buildings and bridges are subject to a variety of forces that degrade a structure over time and may ultimately cause it to fail. Thus, the engineering specifications for structural materials will depend not only on their cost and availability, but also upon the building's environment and the nature of the forces to which it is subjected. As far as mechanical failure is concerned, each material has its own Achilles' heel, which may limit its applicability to certain structures. For instance, steel provides the flexibility needed to accommodate vibrations from the traffic on a suspension bridge, but has a lifetime imposed by its resistance to corrosion and fatigue. Further, the longevity we expect for our buildings and bridges is influenced by anticipated usage, public taste, and technological change, to name a few criteria. It is senseless, therefore, to overdesign a building that is likely to be torn down long before the mechanical strength of its components is in doubt. Similarly, the choice of materials for the construction of a cell is influenced by many competing requirements or limitations. For instance, some molecules that are candidates for use in a cell wall may produce a wall that is strong, but not easily repairable or amenable to the process of cell division. Further, the availability of materials and their ease of manufacture by the cell are also important considerations in selecting molecular building blocks and in designing the cellular structure. Lastly, all of these conflicting interests must be resolved so that the organism is sufficiently robust and long-lived to compete in its environment.

What we have done in this section is search for common architectural themes in the designs of boats and balloons, and the plans of towns and cities. We find that designs making effective use of available materials often employ specialized structural elements that must act cooperatively in order to function: thin membranes for boundaries, ropes for tensile strength, and walls to balance internal pressure. The choice of construction materials for a given structural element is determined by many factors, such as availability or ease of assembly and repair, with the overall aim of producing a structure with an acceptable lifetime. As we will see in the following sections, evolution has selected many of the same effective design principles as human engineering to produce cells that are adaptable, repairable and functional in a wide range of environments. As we better understand Nature's building code, we will discover subtle features that may have application beyond the cellular world.

1.2 Cell shapes, sizes and structures

Despite their immense variety of shapes and sizes, cells display common architectural themes reflecting the similarity of their basic functions. For instance, all cells have a semi-permeable boundary that selectively segregates the cell's contents from its environment. Frequently, cells adopt similar strategies to cope with mechanical stress, such as the reinforced membrane strategy of boats and balloons discussed in Section 1.1. Further, the chemical similarities among the structural elements of different cells are remarkably strong. In this section, we first review some of the basic mechanical necessities of all cells and then provide a general overview of the construction of several representative cells, namely simple cells such as bacteria, as well as complex plant or animal cells. A longer introduction to cell structure can be found in Appendix A or textbooks such as Alberts *et al*. (2008) or Prescott *et al*. (2004).

As described in Section 1.1, the outer boundaries of boats and balloons are fairly thin compared with the linear size of the vessels themselves. Modern skyscrapers also display this design: the weight of the building is carried by an interior steel skeleton, and the exterior wall is often just glass cladding. A cell follows this strategy as well, by using for its boundary a thin membrane whose tensile strength is less important than its impermeability to water and its capability for self-assembly and repair. By using thin, flexible membranes, the cell can easily adjust its shape as it responds to its changing environment or reproduces through division.

Whether this membrane needs reinforcement depends upon the stresses it must bear. Some proteins embedded in the membrane function as mechanical pumps, allowing the cell to accumulate ions and molecules in its interior. If the ion concentrations differ across its membrane, the cell may operate at an elevated osmotic pressure, which may be an order of magnitude larger than atmospheric pressure in some bacteria (bicycle tires are commonly inflated to about double atmospheric pressure). The cell may accommodate such pressure by reinforcing its membrane with a network of strings and ropes or by building a rigid wall. Even if the membrane bears little tension, networks may be present to help maintain a cell's shape.

What other mechanical attributes does a cell have? Some cells can locomote or actively change shape, permitting them to pursue foes. For example, our bodies have specialized cells that can remove dead cells or force their way through tissues to attack foreign invaders. One way for a cell to change its shape is to possess a network of stiff internal poles that push the cell's surface in the desired manner. Consequently, several types of structural filament, each with differing stiffness, are present in the cell: some filaments are part of reinforcing networks while others are associated

with locomotion or internal transportation. Of course, conservation of momentum tells us that there is more to cell motion than pushing on its boundary: to generate relative motion, the cell must adhere to a substratum or otherwise take advantage of the inertial properties of its environment.

The operative length scale for cells is the micron or micrometer (μm), a millionth of a meter. The smallest cells are a third of a micron in diameter, while the largest ones may be more than a hundred microns across. Nerve cells have particularly long sections called axons running up to a meter from end to end, although the diameter of an axon is in the micron range. Structural elements of a cell, such as its filaments and sheets, generally have a transverse dimension within a factor of two of 10^{-2} μm, which is equal to 10 nm (a nanometer is 10^{-9} m); that is, they are very thin in at least one direction. For comparison, a human hair has a diameter of order 10^{2} μm.

Let's now examine a few representative cells to see how membranes, networks and filaments appear in their construction. The two principal categories of cells are prokaryotes (without a nucleus) such as mycoplasmas and bacteria, and eukaryotes (with a nucleus) such as plant and animal cells. Having few internal mechanical elements, some of today's prokaryotic cells are structural cousins of the earliest cells, which emerged more than 3.5 billion years ago. Later in the Earth's history, eukaryotes adopted internal membranes to further segregate their contents and provide additional active surface area within the cell. We begin by discussing generic designs of prokaryotic cells.

1.2.1 Mycoplasmas and bacteria

Mycoplasmas are among the smallest known cells and have diameters of perhaps a third of a micron. As displayed in Fig. 1.6, the cell is bounded by a plasma membrane, which is a two-dimensional fluid sheet composed primarily of lipid molecules. Described further in Appendix B, the principal lipids of the membrane have a polar or charged head group, to which are attached two hydrocarbon chains. The head groups are said to be hydrophilic, reflecting their affinity for polar molecules such as water, whereas the non-polar hydrocarbon chains are hydrophobic, and tend to shun contact with water. In an aqueous environment, some types of lipids can self-assemble into a fluid sheet consisting of two layers, referred to as a lipid bilayer, with a combined thickness of 4–5 nm. Like slices of bread in a sandwich, the polar head groups of the lipids form the two surfaces of the bilayer, while the hydrocarbon chains are tucked inside. The bilayer is a two-dimensional fluid and does not have the same elastic properties as a piece of cloth or paper. For instance, if you wrap an apple with a flat sheet of paper, the paper develops folds to accommodate the shape of the apple;

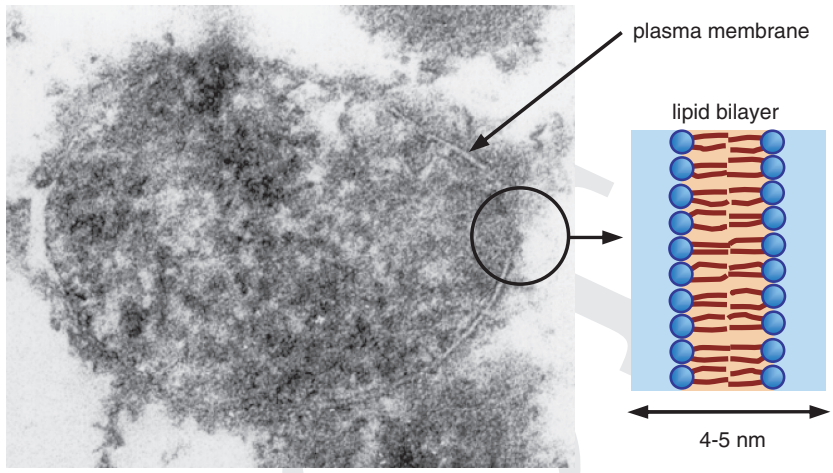


Fig. 1.6 Thin section of *Mycoplasma hominis*, illustrating the plasma membrane isolating the contents of the cell from its surroundings. As shown in the cartoon enlargement, the plasma membrane contains a bilayer of dual-chain lipid molecules, about 4–5 nm thick in its pure form, and somewhat thicker in the presence of other membrane components. Proteins are found in both the plasma membrane and the cell's interior (the fuzzy patches are protein-manufacturing sites called ribosomes). Typical diameter of a mycoplasma is a third of a micron, although the one shown here is 0.6 μm across. Adhering to the external surface of this cell is a precipitate from the animal blood serum in which the cell was grown (courtesy of Dr. Terry Beveridge, University of Guelph).

however, if you dip the apple in thick syrup, the syrup flows and forms a smooth, two-dimensional fluid coating on the apple's surface.

The interior of a mycoplasma contains, among other things, the cell's genetic blueprint, DNA, as well as large numbers of proteins, which also may be embedded in the plasma membrane itself. Although the beautiful world of biochemistry is not the focus of this text, we pause briefly to mention the size and structure of proteins and DNA (more details are provided in Appendix B). Ranging in mass upwards of 10^5 daltons (one dalton, or D, is one-twelfth the mass of a carbon-12 atom), proteins are linear polymers of amino acids containing an amino group ($-NH_3^+$) and an organic acid group ($-COO^-$). Many proteins fold up into compact structures with diameters ranging from a few to tens of nanometers, depending upon the mass of the protein, and some varieties of these globular proteins, in turn, are monomers in still larger structures such as cytoskeletal filaments with diameters ranging up to 25 nm. Like proteins, DNA (deoxyribonucleic acid) and RNA (ribonucleic acid) are polymers with a backbone consisting of a sugar/phosphate repeat unit, to each of which is attached one member of a small set of organic bases, generating the linear pattern of the genetic code. In the form of a double helix, DNA is 2.0 nm in diameter.

Most bacteria both are larger and have a more complex boundary than the simple plasma membrane of the mycoplasma. For instance, the bacterium *Escherichia coli*, an inhabitant of the intestinal tract, has the shape of a cylinder about 1 μm in diameter, and several microns in length, capped by hemispheres at each end. The interior of a bacterium may be under considerable pressure but the presence of a cell wall prevents rupture of its plasma membrane. Except in archaebacteria, the cell wall is composed of layers of a sugar/amino-acid network called peptidoglycan: Gram-positive bacteria have a thick layer of peptidoglycan encapsulating a single plasma membrane (Fig. 1.7(b)), whereas Gram-negative bacteria have just a thin layer of peptidoglycan sandwiched between two lipid bilayers [Fig. 1.7(a)], the inner one of which is the plasma membrane. Parenthetically, this classification reflects the ability of a bacterium to retain Gram's stain. As shown in Fig. 1.7(c), the peptidoglycan network is anisotropic (i.e. does not have the same structure in all directions), with its sugar chains oriented around the girth of the bacterium, the direction which bears the greatest surface stress. The sugar chains are linked transversely with loose strings of amino acids, the latter bearing only half the surface stress that the sugar chains bear. In analogy with a ship's rigging, the sugar chains are like the strong ropes attached to the mast, while the amino-acid strings are weaker cords that link the ropes into a network.

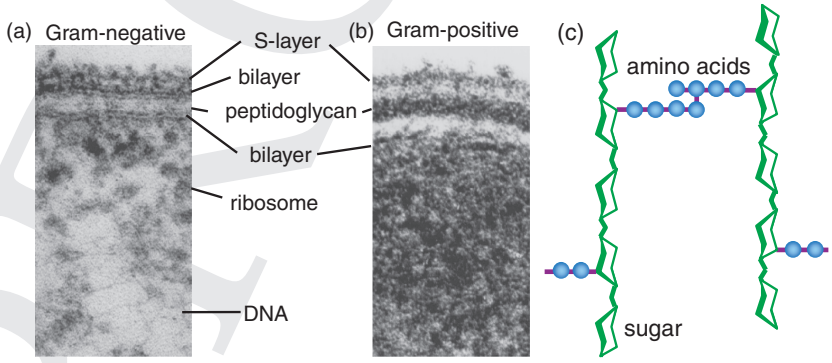


Fig. 1.7 Boundary structure of bacteria. (a) A Gram-negative bacterium, such as *Aermonas salmonicida*, has a very thin layer of peptidoglycan sandwiched between two membranes. Thin strings visible in the cell's cytoplasm are DNA. (b) In Gram-positive bacteria, such as *Bacillus stearothermophilus*, only one bilayer is present, and the peptidoglycan blanket is much thicker. These bacteria have an additional layer of proteinaceous subunits on their surface (S-layer), which is not always present in other bacteria (courtesy of Dr. Terry Beveridge, University of Guelph). (c) The molecular structure of peptidoglycan displays stiff chains of sugar rings, oriented around the girth of the bacterium, cross-linked by floppy strings of amino acids oriented along its axis.

1.2.2 Plant and animal cells

The general layout of a plant cell is displayed in Fig. 1.8(b). Exterior to their plasma membrane, plant cells are bounded by a cell wall, permitting them to withstand higher internal pressures than a wall-less animal cell can support. However, both the thickness and the chemical composition of the wall of a plant cell are different from those of a bacterium. The thickness of the plant cell wall is in the range of 0.1 to 10 μm, which may be larger than the total length of some bacteria, and the plant cell wall is composed of cellulose, rather than the peptidoglycan of bacteria. Also in contrast to bacteria, both plant and animal cells contain many internal membrane-bounded compartments called organelles. Plant cells share most organelles with animal cells, although plant cells alone contain chloroplasts; liquid-filled vacuoles are particularly large in plant cells and may occupy a large fraction of the cell volume.

As illustrated in Fig. 1.8(a), animal cells share a number of common features with plant cells, but their lack of space-filling vacuoles means that animal cells tend to be smaller in linear dimension. Neither do they have a cell wall, relying instead upon the cytoskeleton for much of their mechanical rigidity, although the cytoskeleton does not provide the strength that would allow an animal cell to support a significant internal pressure. Some components of the cytoskeleton meet at the centriole, a cylindrical organelle about 0.4 μm long. The most important organelles of plant and animal cells are the following.

- The nucleus, with a diameter in the range 3 to 10 μm, contains almost all of the cell's DNA and is bounded by a pair of membranes, attached to

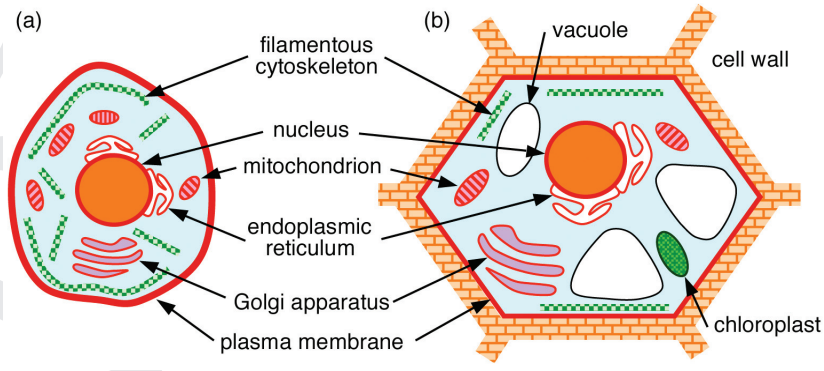


Fig. 1.8 Schematic sections through generic animal (a) and plant (b) cells showing the layout of the organelles and other structural components. Having a more complex internal structure than bacteria, these cells are correspondingly larger, typically 10–100 μm for plants and 10–30 μm for animals.

each other at pores to allow the passage of material across the nuclear envelope.

- The endoplasmic reticulum surrounds the nucleus and is continuous with its outer membrane. As a series of folded sheets, the rough endoplasmic reticulum has a small volume compared to its surface, on which proteins are synthesized by strings of ribosomes, like beads on a necklace.
- The membrane-bounded Golgi apparatus is the site of protein sorting, and has the appearance of layers of flattened disks with diameters of a few microns. Small vesicles, with diameters in the range 0.2 to 0.5 μm, pinch off from the Golgi and transport proteins and other material to various regions of the cell.
- Mitochondria and chloroplasts, the latter present only in plant cells, produce the cell's energy currency, ATP (adenosine triphosphate). Shaped roughly like a cylinder with rounded ends (often 0.5 μm in diameter), a mitochondrion is bounded by a double membrane. Also bounded by a double membrane, but containing internal compartments as well, chloroplasts are about 5 μm long and are the site of photosynthesis.

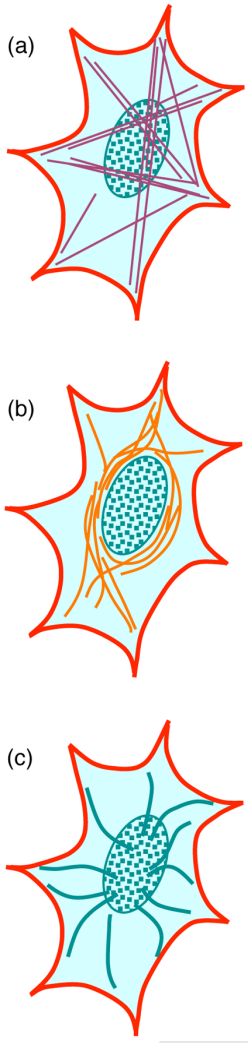


Fig. 1.9

Schematic organization of cytoskeletal filaments in a fibroblast: actin (a), intermediate filaments (b), and microtubules (c).

All of the material within the cell, with the exclusion of its nucleus, is defined as the cytoplasm, which contains organelles as well as the cytosol. The cytoplasm is rich with macromolecules, including DNA and various proteins, both globular and filamentous. For example, the protein content (percent by weight, where 1% = 10 mg/ml) is 20%–32% in bacteria but 35% in red blood cells, neither of which contains organelles. Conversely, the water content of the cytoplasm is just 70%–80% by weight. It's no surprise that the aqueous component of the cytoplasm is well below 90%, for it would be inefficient from the chemical reaction standpoint for reactants to diffuse through a low concentration environment searching out a reaction partner. However, the substantial concentration of proteins increases the viscosity of the cytoplasm and hence reduces the diffusion rates: the effective viscosity of the cytoplasm for diffusion of typical proteins is about three times the viscosity of pure water. Further, the presence of filaments in the cytoplasm may create a meshwork that hinders the motion of large proteins or other objects, further increasing the effective viscosity that they experience (drag forces in viscous environments are treated in Chapter 2).

Permeating the cytosol in some cells, or simply attached to the plasma membrane in others, is the cytoskeleton, a network of filaments of varying size and rigidity. The various filament types of the cytoskeleton may be organized into separate networks with different mechanical properties. In the schematic cell shown in Fig. 1.9, slender filaments of actin are associated with the plasma membrane, while thicker intermediate filaments are connected to cell attachments sites, and stiff microtubules radiate from the microtubule organizing center. In addition to providing the cell with

mechanical strength, elements of the cytoskeleton may function as pathways for the transportation of material, much like the roads of a city.

The above survey of cell structure demonstrates several things. First, membranes are ubiquitous components of the cell, providing boundaries for the cell itself and for the cell's organelles and other compartments. Membranes contain both proteins and dual-chain lipids, the latter capable of self-assembly into bilayers under the appropriate conditions, as we will establish in Chapter 5. Being only 4–5 nm thick, bilayers are very flexible and can adapt to the changing shape of the cell as needed. Second, filaments are present in the cell in a variety of forms, sometimes as isolated molecules like DNA or RNA, sometimes as part of a network like the cytoskeleton or cell wall. The filaments range up to 25 nm in diameter; the thickest filaments appear stiff on the length scale of the cell, while the thinnest filaments appear to be highly convoluted. Most individual filaments, networks and membranes of cells are then *soft*, in that they may be easily deformed by forces commonly present in a cell. We now discuss in more detail what is meant by "soft", and describe the thermal fluctuations in the size and shape of filaments and membranes.

1.3 Biomaterials: soft strings and sheets

In a cell, most filaments are not straight like the beams of a skyscraper nor are the membranes flat like the steel sheets in the hull of a boat. For instance, Fig. 1.10(a) is an image of DNA immobilized on a substrate, looking much like long pieces of thread thrown casually onto a table. Similarly, Fig. 1.10(b) demonstrates how membranes, in this case isolated membranes from *Escherichia coli*, can sustain regions of very high curvature. These images hint that the strings and sheets in cells are soft, a hypothesis that is confirmed by observing the ease with which they are deformed by ambient forces within the cell and by those applied externally.

Words like *hard* and *soft* are used in at least two contexts when describing the elastic characteristics of a material. Sometimes the terms are used in a comparative sense to reflect the property of one material relative to another; for example, Moh's scale is a well-known logarithmic measure of hardness (talc has a hardness of 1 on this scale, while diamond has a hardness of 10). In another usage, softness indicates the response of an object to forces routinely present in its environment. In thermal equilibrium, an object can acquire energy from its surroundings, permitting or forcing it to change shape even if energy is needed to do so. The amplitude of these thermal fluctuations in shape depends, of course, on the softness of the material. While rigid objects may not even modestly change shape

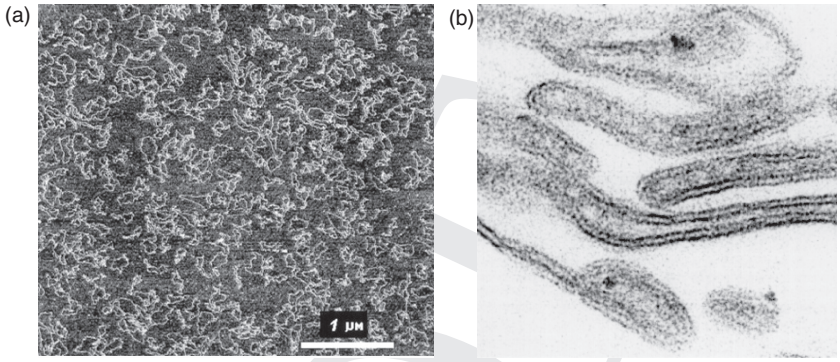


Fig. 1.10

(a) Atomic force microscope image of DNA on a mica substrate (bar is 1 μm; reprinted with permission from Shlyakhtenko *et al.*, 1999; ©1999 by the Biophysical Society). (b) Thin section of outer membranes extracted from *E. coli* after staining with osmium tetroxide and uranyl acetate. The bilayer, clearly visible as parallel black lines, is 7.5 nm thick (courtesy of Dr. Terry Beveridge, University of Guelph).

in response to thermal fluctuations in their energy, flexible filaments may bend from side to side and membranes may undulate at room temperature. We now describe the rigidity and thermally driven shape changes of biological filaments and sheets on cellular length scales; the elastic behavior of macroscopic objects like leaves and feathers can be found in Vogel's very readable book on the subject (Vogel, 1998).

1.3.1 Soft filaments

The resistance that any filament offers to bending depends upon its size and material composition: thick ropes are stiffer than thin strings and steel is more rigid than cooked pasta. To qualitatively understand their bending behavior, consider what happens when a force is applied to the free end of a thin filament, while the other end is fixed, as indicated in Fig. 1.11. The energy required to gently bend a rod into the shape of an arc depends on three factors:

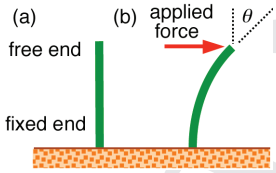


Fig. 1.11

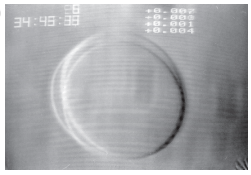
The energy required to gently bend a straight rod (a) is proportional to the square of the bending angle θ, defined in (b).

- the bending angle, θ in Fig. 1.11; the deformation energy increases like the square of the angle, just as the potential energy of a simple spring increases like the square of its displacement from equilibrium.
- the material composition of the rod; for instance, it takes about one hundred times more energy to bend a metallic filament (like copper) than an otherwise identical biofilament, through the same bending angle.
- the diameter (and cross sectional shape) of the filament; for example, the rigidity of a thin, cylindrical rod increases like the fourth power of its diameter.

This last factor means that thick cellular filaments such as microtubules, with diameters of 25 nm, have a bending resistance about two orders of magnitude larger than thin actin filaments, of diameter 8 nm: the fourth power of their diameters has the ratio $(25/8)^4 = 95$. Thus, the cell has at its disposal a selection of filaments spanning a large range of bending rigidity, from floppy threads to stiff molecular ropes, and these filaments bend much more easily than if they were made of metal or similar materials.

What about the thermal motion of a filament as it waves back and forth, exchanging energy with its environment? Very stiff filaments hardly move from their equilibium positions; for them, the value of θ in Fig. 1.11 is usually close to zero. In contrast, highly flexible filaments may sample a bewildering variety of shapes. For instance, at room temperature, an otherwise straight microtubule 10 μm long would be displaced, on average, by about a tenth of a radian (or 6 degrees of arc) because of thermal motion. Were the microtubule made of steel, its mean angular displacement would be less than one degree of arc. In comparison, a 10 μm length of the filamentous protein spectrin, which is much thinner and more flexible than actin, would look like a ball of thread.

(a)



(b)

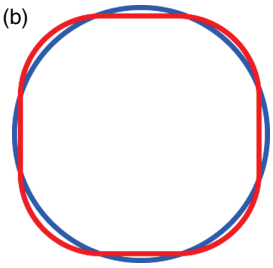


Fig. 1.12

(a) Pure lipid vesicles, whose surface area is slightly more than the minimum needed to contain its aqueous contents, display thermal undulations like those shown in these superimposed video images. (b) Schematic representation of some surface oscillations of a vesicle; a circle representing the mean position of the surface is drawn in grey for comparison (reprinted with permission from Yeung and Evans, 1995; courtesy of Dr. Evan Evans, University of British Columbia, ©1995 by Les Editions de Physique).

1.3.2 Soft sheets

In analogy to flexible filaments, membranes possess a bending resistance that depends on their geometry and material composition. For the membranes of the cell, this resistance covers a much smaller range – perhaps only a factor of ten – than the many orders of magnitude spanned by the bending resistance of cellular filaments. The reason for modest range in bending rigidity is mainly geometrical: reflecting their rather generic lipid composition, viable cell membranes tend to have a thickness of about 4–5 nm, insufficient to take advantage of the power-law dependence of the bending rigidity on membrane thickness. However, these biological membranes do exhibit about two orders of magnitude less resistance to bending than would an otherwise identical membrane made from copper or steel.

The energy required to bend an initially flat bilayer into a closed spherical shape like a cell is neither trivial nor insurmountable, as is demonstrated in Chapter 7. However, gentle undulations of membranes, such as those illustrated in Fig. 1.12(a), can be generated by thermal fluctuations alone. The figure displays images of a pure lipid vesicle, which has a mechanical structure like a water-filled balloon, except that the boundary is a fluid membrane. The images in Fig. 1.12(a) are separated by an elapsed time of 1 s, and have been superimposed to show the amplitude of the undulations. The types of motion executed by the surface are shown schematically in Fig. 1.12(b), where the circle indicates the mean position of the membrane. Clearly, the membrane is sufficiently stiff that the wavelength of the undulations is similar to the size of the vesicle, and not dramatically smaller.

1.3.3 Soft vs. hard: entropy vs. energy

The deformation resistance of a material is quantitatively characterized by its elastic moduli; for instance, a solid has a higher compression modulus than does a gas. Does this mean that the elastic behavior of gases has a different origin or receives different contributions than that of hard solids? The deformation resistance of a solid is primarily energetic: the equilibrium arrangement of the atoms or molecules in a solid at moderate temperatures is determined by energy minimization. Hence, there is an energy cost for displacing these atoms or molecules from their preferred locations when the material is strained.

The situation is different for a gas. J. J. Waterston, a pioneer in the theory of gases, invoked a cloud of flying insects as a metaphor for a gas and we can imagine the effort needed to force a swarm of wasps into a tiny volume (see Section 2–1 of Kauzmann, 1966). During the compression of a dilute gas, there is little change to the interaction energy between its atomic or molecular constituents because they are simply not close to each other, compared to the separation between the constituents of a solid. What changes, then, is not the interaction energy but rather the entropy of the gas. As reviewed in Appendix C, entropy is a measure of the number of configurations that a system can adopt, including spatial configurations as well as molecular shapes. By compressing the volume, the physical space that the system can explore is reduced, and hence its entropy is reduced. According to the second law of thermodynamics, a reduction in entropy cannot occur spontaneously – energy must be added to the system (through work, for example) to decrease its entropy.

The elasticity of soft materials often has both energetic and entropic contributions, depending on its state of strain. Entropic contributions tend to be relatively larger when the system is only modestly deformed, whereas energetic contributions may become important at high deformation. Consider the behavior of a flexible chain in one spatial dimension as a specific example. Suppose the links on the chain are completely flexible so that it takes no energy to introduce a kink by reversing the direction of the chain. The configurations available to such a chain with four links of equal segment length is shown in Fig. 1.13, where the left-hand end of the chain is held fixed and the right-hand end can be pulled by a horizontal force. We assume that the extended end of the chain cannot pass to the left of the fixed end. In Fig. 1.13, there are six configurations with no extension, four with two units of extension, and only one stretched configuration with four units of extension, where "unit" refers to the length of an individual chain element.

In the absence of bending resistance between links on the chain, all configurations in Fig. 1.13 have the same energy. If no force is applied to the right-hand of the chain, it can move freely among the configurations

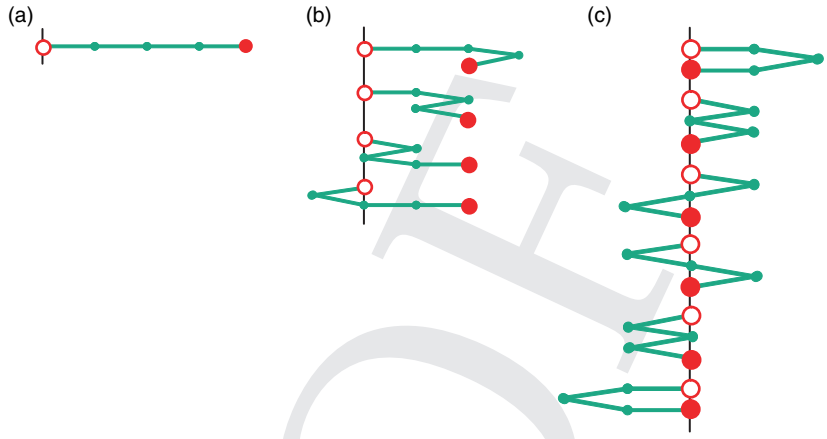


Fig. 1.13 Configurations of a four-segment chain with inequivalent ends in one dimension. The displacement between ends of the chain is 0, 2 and 4 segment lengths in groups (a), (b) and (c), respectively. Switchbacks have been offset for clarity.

without an energy penalty. On the basis of the number of configurations available, the chain is most likely to be found unextended, and least likely to be found fully extended. However, if sufficient force is applied to the right-hand end to pull it by two units of extension to the right, then about half (six out of eleven) of the original configurations of the chain are difficult to access. That is, pulling on the chain reduces its entropy because the system can sample fewer configurations: the chain resists extension for entropic reasons, not energetic ones. Of course, if one attempts to pull the chain beyond four units of extension by stretching an individual link, the resistance will be energetic as well as entropic.

Elasticity arising from the resistance to entropy loss, as we have just described, is well established in polymer physics (Flory, 1953). We will show that entropy also contributes to the elasticity of flexible membranes, not just filaments. From the examples above, we see that the deformation resistance of stiff materials is dominated by energy considerations, while that of soft materials is also influenced by entropy.

1.4 Forces inside and outside the cell

During their lifetime, almost all cells experience forces and stresses that arise as part of the efficient operation of the organism. For instance, the cytoplasm of a bacterium is laden with proteins and ionic compounds that raise its osmotic pressure with respect to the cell's external environment. The high concentration of molecules and ions increases chemical reaction rates in the cytoplasm, but forces the bacterium to surround itself with a

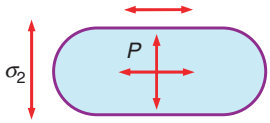


Fig. 1.14

The pressure P within a mechanically simple cell like a bacterium is opposed by the surface stress σ_2 within the cell boundary. As a three-dimensional quantity, P has units of energy per unit volume, whereas the two-dimensional stress has energy per unit area.

cell wall to avoid rupture. Similarly, the cytoplasm is sufficiently viscous that molecular diffusion is slow; consequently, larger cells must find a way of transporting important molecular components through the cytoplasm faster than the time scale of diffusion. Such directed transport of cargo-laden vesicles requires the generation of force to overcome viscous drag on the vesicles. Lastly, during cell division, forces must be exerted in nucleus-bearing cells to segregate sister chromatids.

Consider the bacterium shown in Fig. 1.14. Its cytoplasm is at an elevated pressure P that has units of force per unit area or energy per unit volume; for some bacteria, P can range above 10 atmospheres (10^6 J/m^3). The pressure exerts a force per unit area on the boundary of the cell that is the same at any location, schematically represented by the single-headed arrows in the diagram. The cell wall, which can be viewed as a two-dimensional sheet for our purposes, experiences a surface stress σ_2 having units of energy per unit area, not the energy per unit volume of (three-dimensional) pressure. In Fig. 1.14, surface stress is indicated by the two-headed arrows drawn parallel to the cell boundary. To within some simple numerical factors that will be derived in Chapter 10, σ_2 is proportional to the product RP, where R is the radius of the cell. For a bacterium of radius 1 μm, this shows that the surface stress is in the range of 1 J/m^2. The bacterial cell wall is relatively stiff and can accommodate a surface stress of this magnitude without significant deformation.

Compared to a cell wall, the boundary of the human red blood cell is soft: its plasma membrane easily deforms as the cell passes through narrow capillaries, and its cytoskeleton helps restore the cell to its rest shape once passage is complete. The cytoskeleton of the mature red cell is particularly simple, as it is effectively a two-dimensional mesh attached to the plasma membrane; it does not crisscross through the volume of the cell. The magnitude of the deformation that a red cell can sustain is demonstrated in Fig. 1.15(a), which displays the cell's shape as it is drawn up a micropipette by suction. Part (b) is an image of the density of the membrane-associated cytoskeleton, to which fluorescent molecules have been attached, showing how the cytoskeleton becomes ever more dilute, and hence less visible in the image, as it stretches up the pipette. Part (c) is a computer simulation of a similar deformation, based on a model in which the elasticity of the cytoskeleton arises from the entropy of its thin filaments. The images indicate the magnitude of the deformation to which the materials of a cell can be subjected without failure: the fluid membrane permits the cell to squeeze into a narrow pipette, and the density of the cytoskeleton itself evidently drops by a factor of two along the length of the aspirated segment of the red cell.

As described more fully in Chapter 11, the cell has designed a number of molecular motors for generating force. Consider the origin of Watt's steam engine for a moment: the fundamental motion is the expansion of a

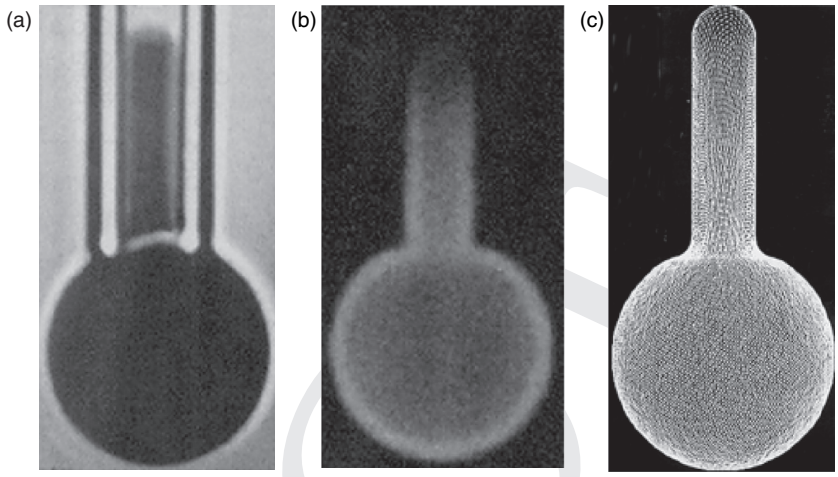


Fig. 1.15

Deformation of a human red blood cell as it is drawn up a pipette approximately 1 μm in diameter. Part (a) is a bright-field microscope image of the cell and the pipette, while (b) is a fluorescence image showing the density of the cytoskeleton. Part (c) is a computer simulation of the experiment, based on the entropic contribution of the cytoskeleton [(a) and (b) reprinted with permission from Discher *et al*. (1994); ©1994 by the American Association for the Advancement of Science; (c) from Discher *et al*. (1998)].

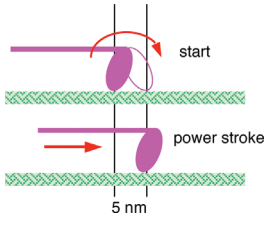


Fig. 1.16

Schematic representation of a myosin motor (magenta) pulling itself along an actin (green) filament. From its initial position, the myosin detaches from the filament, then reattaches at a location about 5 nm away, before the power stoke pulls it. The red arrows indicate the direction of motion. The orientation of the myosin head with respect to its tail is the same at the end of the power stroke as at the initial location.

gas causing the linear motion of a sliding piston within a cylinder. Yet the development of the steam engine to be more than just a poorly controlled means of pumping water from ditches came with the creation of mechanical means of obtaining rotational movement from it (for example, the offset drive of the wheels of a train engine) and the invention of the governor to control the engine's speed. These ideas also apply to a molecular motor in the cell, where the fundamental motion is linear as it *pulls* itself along a filament, a motion that has been adapted to create the push of cell division. An example of the actin/myosin motor is displayed in Fig. 1.16, where the protein myosin undergoes changes in conformation as it pulls itself along an actin filament. Further, the rotor/stator design of modern rotary motors also appears in the multi-component motor that drives the motion of flagella, the whips that propel some types of bacteria.

There are many examples in which the role of molecular motors is to overcome the drag forces arising in the cell's viscous environment, both internally and externally. In fluid mechanics, a quantity called the Reynolds number indicates the relative importance of viscosity in the motion of an object – the Reynolds number is a measure of the inertial force compared to the force from viscous drag. A dimensionless quantity, the Reynolds number depends on the viscosity of the environment and the size of the moving object, among other things. If the Reynolds number of the motion is much less than unity, the motion is dominated by viscous effects. For

most situations in the cell, the Reynolds number is remarkably small: one-millionth or less!

Let's estimate the magnitude of drag forces present in the cell. At low speeds, drag is proportional to the product of the speed and width of the moving object, among other things, meaning that drag forces can span a range of values. Taking a representative system that is treated as an example in Chapter 2, the drag force experienced by a spherical bacterium of radius 1 μm moving at a speed of 20 μm/s in water is 0.4 pN, where pN is a piconewton of force, or 10^{-12} N. This is the force that the bacterium's flagella, its propulsion unit, must generate in order to keep the cell moving. Tiny as this force may appear to be, it is substantial on the cellular level and if the flagella were suddenly disabled, the cell would come to a complete stop in a distance much smaller than an atomic diameter. This is the nature of life at low Reynolds number: the lack of inertial effects strongly influences the strategies a cell must employ in order to swim, even in a low viscosity fluid.

Just as with everyday machinery, the motion of molecular motors is repetitive, a series of steps in which chemical energy is converted into mechanical energy. Familiar from introductory physics courses, the work done by the motor in a specific step is equal to the usual product of force and distance for linear motion, or torque and angle for circular motion. Using a step size of 5 nm, and a force of 4 pN as representative values, the corresponding work per step is 2×10^{-20} J. This can be compared to the energy available per hydrolysis of ATP (adenosine triphosphate, the cell's most common energy currency) of 8×10^{-20} J. In other words, the hydrolysis of a single ATP molecule is sufficient to drive a motor through one step.

The remaining concept that we wish to address in this section is the magnitude of the thermal energy scale compared to the typical mechanical energies in the cell. Let's consider the imaginary box of molecules in Fig. 1.17, each molecule of mass m roving at random throughout the box at a density sufficiently low that the molecules form an ideal gas. The molecules are free to collide with each other, exchanging momentum and kinetic energy when they do so, such that they possess a distribution of speeds and kinetic energies. That is, the speed of the particles is not fixed at one particular value, but rather forms a distribution, with few molecules traveling very slowly, few traveling very fast, and many traveling in some intermediate range. Quantities such as the mean speed and kinetic energy of this molecular gas can be calculated *via* statistical mechanics, which shows that the mean kinetic energy of a molecule is $(3/2)k_BT$ in three dimensions, where k_B is Boltzmann's constant (1.38×10^{-23} J). For a gas at room temperature (20 °C), the combination $k_BT = 4 \times 10^{-21}$ J.

How does the thermal energy scale compare to the energy scales in the cell? One benchmark is the work done per step in a typical molecular motor, which we calculated as 2×10^{-20} J, or about five times k_BT. This is not

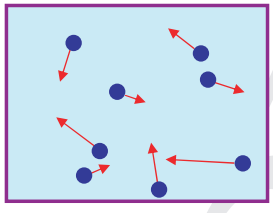


Fig. 1.17

Schematic drawing of an ensemble of particles moving within a confined geometry. The particles exchange energy and momentum by colliding with each other and the walls of the container, which is kept at a fixed temperature T.

unexpected: if the work done by the motor were less than $k_B T$, the motor would be ineffective, as random thermal fluctuations would overwhelm its work and the motor would move randomly. In contrast, isolated molecules that are much smaller than proteins are more influenced by thermal effects. For example, we will demonstrate in Chapter 3 that the varying positions of the links of a polymer arising from thermal fluctuations contribute to the elasticity of the polymer. Thus, the thermal energy scale is generally not too far removed from other energy scales in the cell, and effects arising from thermal fluctuations may be important.

Summary

Many of the design principles that have been developed for structures such as buildings and bridges are equally applicable to the architecture of the cell. For example, the efficient usage of available materials may be most readily achieved through composite systems, in which the required functionality is obtained only from the combined properties of the individual structural elements. We see this strategy in the design of the cell, where the plasma membrane provides the necessary barrier for confining the cell's contents and is reinforced as necessary by networks and walls to withstand the stresses of the membrane's environment. We observe that at least one linear dimension (i.e. width or thickness) of most structural elements of the cell is very small, say 4–5 nm for the thickness of a membrane or 8–25 nm for the diameter of many biofilaments, so that most mechanical components of the cell are soft in some respects because of their small dimensions. Further, the resistance of soft biological materials to deformation may be a hundred times less than conventional hard materials such as metals. In thermal equilibrium, soft filaments and sheets oscillate and undulate because the energy required for modest changes in shape is available in the cell. The presence of soft materials is required not only for the everyday tasks of the cell but also for its growth and division, necessitating the development of a much broader building code than what is applicable to human engineering.

In the next several chapters, we investigate the generic characteristics of soft filaments and sheets. The cytoskeleton is one of the primary topics of this text, and Part I is entirely devoted to the behavior of flexible filaments, both in isolation (Chapters 3 and 4), and as they are welded into networks (Chapters 5 and 6). Part II approaches our second principal topic, membranes, in a similar vein: the molecular structure and self-assembly of bilayers are treated in Chapter 7, while membrane undulations and interactions are the subjects of Chapters 8 and 9. Throughout

Parts I and II, many prominent features of soft structures are shown to be rooted in their entropy, and are most easily understood by means of statistical mechanics. An introduction to the statistical concepts needed for the text is given in Chapter 2, while Appendices C and D provide additional background material from statistical mechanics and elasticity that underlie Parts I and II.

We assemble these isolated ropes and sheets into some simple, but complete, cells in Part III. The shapes of biological structures such as vesicles and mammalian red blood cells are interpreted with the aid of mechanical models in Chapter 10. The motion of a cell, including its molecular basis, is the subject of Chapter 11. We then devote the last two chapters of the text to cell growth and division, including mechanisms for the transcription and replication of DNA as well as for the control of the division cycle.