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

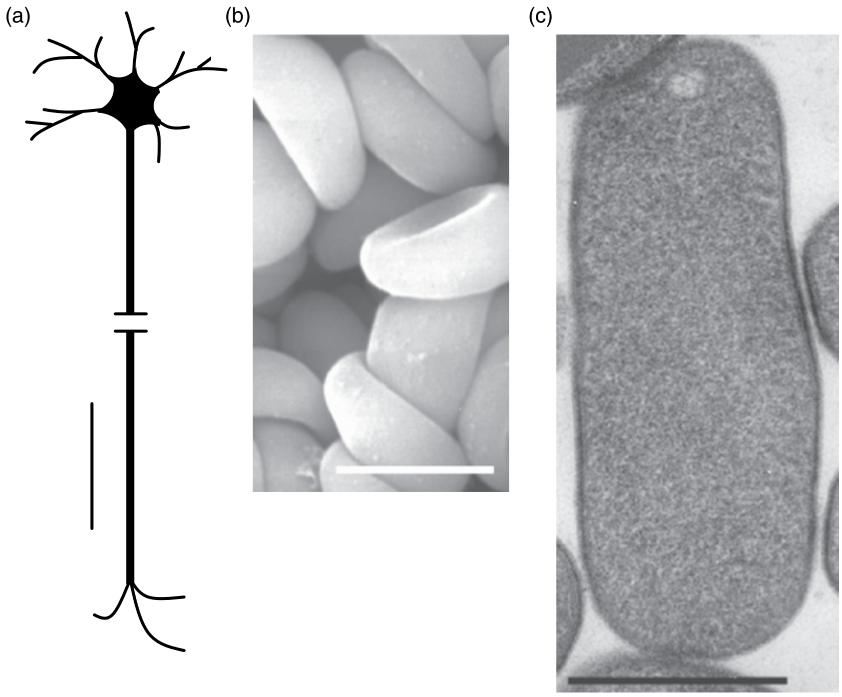

Fig. 1.1 Examples of cell shapes. (a) A neuron is a highly elongated cell usually with extensive branching where it receives sensory input or dispatches signals; indicated by the scale bar, its length may be hundreds of millimeters. (b) Mammalian red blood cells adopt a biconcave shape once they lose 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

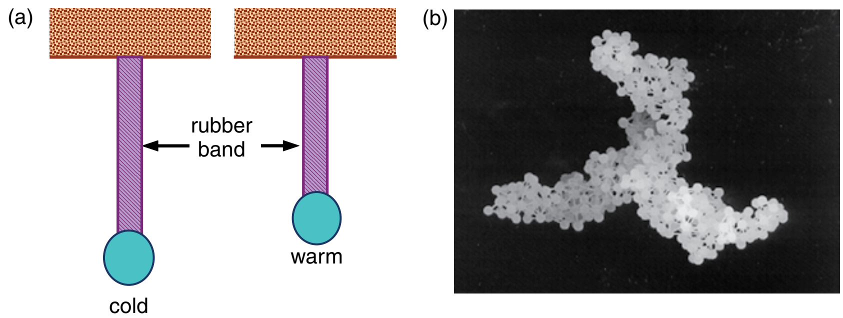

Fig. 1.2 (a) When natural rubber is heated, it becomes more resistant to stretching, an effect which can be demonstrated by hanging an object from an elastic band. When heated, the elastic band contracts, causing the object to rise. (b) A fluid membrane extends arms and fingers at large length scales,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

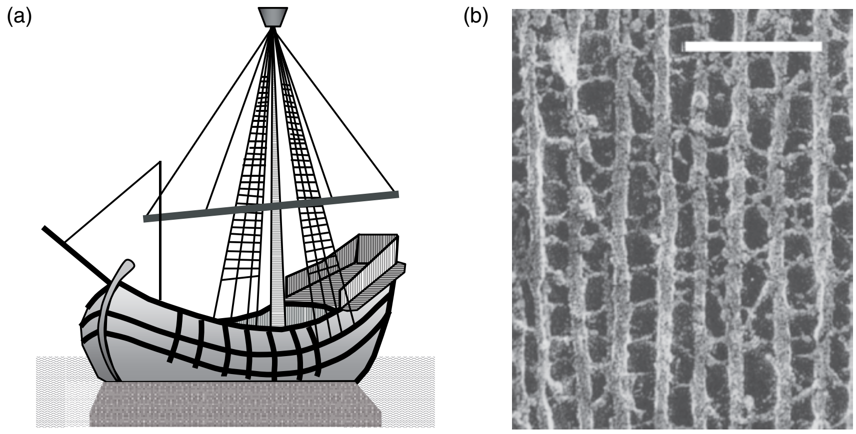

Fig. 1.3 (a) An early fifteenth-century merchant ship displays the efficient use of materials in the design of the reinforced hull and rigging (original illustration by fifteenth-century engraver Israel von Mekenem; redrawn by Gordon Grant in Culver, 1992; ©1994 by Dover Publications). (b) Cross-linked 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.

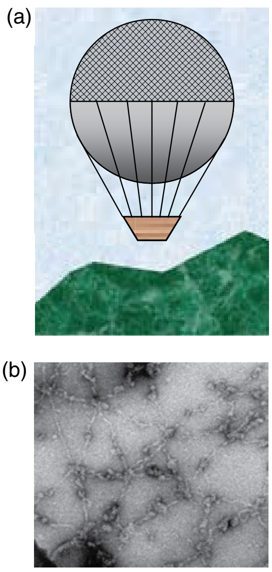

Fig. 1.4

(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

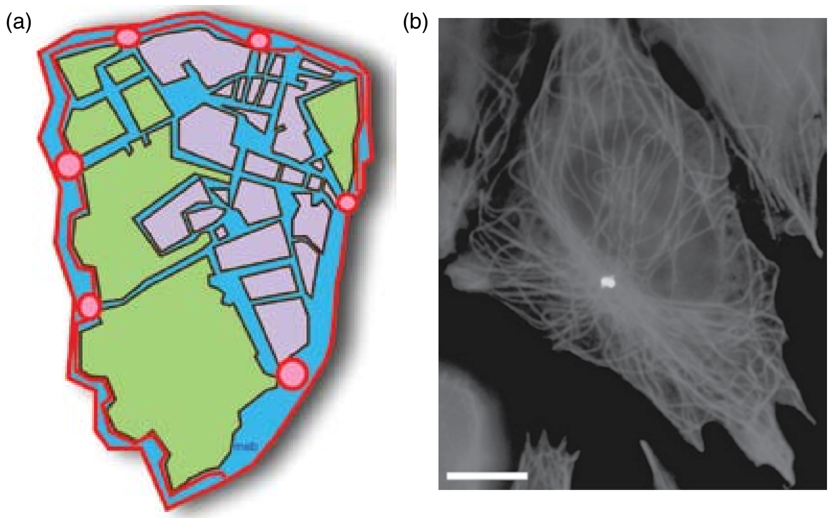

Fig. 1.5 (a) Plan of Quebec in the eighteenth century. Streets within the city walls (red) form an irregular web, with entry points indicated by red disks. (b) The array of microtubules in a cultured fibroblast helps organize the cell's organelles and provides transportation corridors (bar is 10 μm; 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;