NATURE'S BUILDING CODE : THE BAUHAUS SCHOOL OF CELL DESIGN

by David H. Boal

The Earth formed as a planet about 4.5 billion years ago (Ga) and until about 3.8 Ga, its surface was ceaselessly pounded by gravitationally captured material [1]. The impact of meteorites and asteroids, with dimensions of meters to kilometers, fractured and heated the emerging land masses, in some instances releasing enough energy to vaporize an ocean several thousand meters deep. What form of life could have survived, let along thrived, in such an environment? If the answer to this question is "none", then how long after the end of these hadean times did recognizable life emerge? Not long!

Graphite in ancient rocks in Greenland (3.8 Ga) show isotopic abundances consistent with biological processes [2]. The oldest candidates for fossilized cells discovered yet [3] are dated at 3.46 Ga. Although these microfossils are not as mechanically complex as the eukaryotic (nucleated) cells of our bodies, neither are they just inflated spheres. Unless life originated elsewhere in the universe, such that Earth was the lucky recipient of perhaps billions of years of experimental evolution performed before the formation of the solar system, then cell design and construction must be simple and robust: given an appropriate environment, life would arise on Earth or elsewhere in a time scale short compared to the lifetime of a "garden-variety" star [4].

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This article is about Nature's building code. By considering the construction of man-made buildings and bridges, we can extract some architectural principles that are relevant to the building of a cell. Knowing the objectives of the design, a minimal set of construction materials and methods can be formulated. Of course, cellular designs must satisfy more constraints than those imposed on office towers which need not compete with each other for physical survival (although one could argue that similar economic principles govern the longevity of a building - an edifice that is maladapted to its environment is a candidate for demolition and replacement). Here, we develop a partial inventory of the simplest designs for obtaining a specified set of cellular shapes and functions. As this catalogue is verified and extended, it will provide us with a tool for assessing candidate structures for extraterrestrial organisms, a task of increasing importance as the National Aeronautics and Space Administration (NASA) continues its efforts to bring Martian rocks to Earth.

STRATEGIES FOR HOUSE CONSTRUCTION

Let's think for a moment about the appearance of houses in our local neighbourhoods. My part of the world is still dominated by stucco bungalows, while the city where I grew up, several thousand kilometres to the east, was once characterized by two-storey Georgian row housing. Although the appearance of these houses is rather different, the construction principles, and the economic forces from which they arise, are similar.

Construction materials - Most of the building materials of a conventional house must be *readily available*. If not obtainable in near finished form, the materials must at least be produced at low cost to be *economically competitive*. Further, the materials must be specialized according to task: say, bricks for walls, wooden planks and beams for floors and glass for windows. Where the materials are subject to stress or failure, they must be *easy to repair*.

Design - The design of market housing must be *easy to implement* in order to minimize labour costs. The simpler the design, the fewer blueprints are needed, and for much of the modernist era, the more appealing the appearance. "Less is more" is an often-quoted aphorism of Bauhaus architect Ludwig Mies Van der Rohe. The design must also be *adaptable* to changing market demand; for example, the design could allow for a change of room sizes during construction, as requested by a purchaser, or could allow for renovation long after purchase.

Construction Price remains an important determinant of housing sales, and so construction methods that are *cost efficient in labour and materials* tend to be the most common. Cost efficiency in labour translates into designs that require little assembly (the ideal of *self-assembly* is not within reach).

Scanning back over the previous three paragraphs, we see that the italicized words apply equally well to the design and construction of cells as they do to mass-market housing. There are obvious exceptions for specialized buildings, and this will apply as well to the two hundred different cell types of the human body, for example. Let's now examine how each feature - materials, design and construction - appears in Nature's building code. A more detailed treatment of these topics can be found in Ref. [5].

CONSTRUCTION MATERIALS

Filaments

Most construction materials in the cell can be classified as filaments or sheets. We'll deal with filaments first, although they need not appear in the simplest of cell designs. By "filament" we mean a structural element that is narrow in two spatial

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dimensions, and long in the third, like a rod or a rope. What used to be a common example of the use of rods and ropes for efficient construction are the rigging and masts of a sailing ship. Reflecting Newton's third law, the rods and ropes are arranged in tension-compression couplets, with the masts being compression-bearing elements while the ropes are tension bearing. From a design standpoint, this is much more materials efficient than attaching the mast to the hull of the boat with boards or other rigid elements to prevent the mast from twisting or falling.

Cells make use of a variety of protein filaments for structural elements, the four most common are displayed in Table 1. For actin and tubulin, individual globular polymers (each less than 10 nm across) are joined together to form what looks like a multistranded rope, while for spectrin, the filament resembles many beads on a string, where the "bead" is a region in which the string has folded back on itself locally in the shape of the letter z. When so folded, each spectrin string is about 100 nm in length. The table illustrates that the diameter of structural filaments is in the range of a few to 25 nanometers. This is just what we would expect for the common forces present in the cell, as can be established by the following calculation. If a rod of length L is subjected to a pair of compressive forces F at each end, directed along the axis of the rod, it will buckle when F exceeds [6]

$$F_{buckle} = \pi^2 YI / L^2, \qquad (1)$$

where Y is the Young's modulus of the material and I is the moment of inertia of the cross section; for a solid rod of radius R

$$I = \pi R^4/4. \qquad \text{(solid rod)} \qquad (2)$$

Typical forces in the cell from molecular motors are 5 pN, a typical filament length is 5 μm for a cell diameter, and the Young's modulus of a typical biomaterial is 10^9 J/m^3 (compared to steel at 2×10^{11} J/m^3). Putting all this together shows that a biofilament would need a radius of 11 nm to avoid buckling under common conditions in the cell, fortuitously close to the microtubule radius of just over 12 nm. Thus, microtubules provide the stiffest structural element generally needed by the cell, and they can be ganged together to provide extra strength for special situations.

Other biofilaments are much less rigid, as can be seen by their persistence lengths in Table 1; the persistence length ξ_p characterizes the length scale over which a filament bends. If we denote the tangent vector to a curve (or filament) at a location s along the arc by $\mathbf{t}(s)$, then we expect the dot product of tangent vectors at neighbouring positions on the curve to be close to one. This product decreases towards zero, perhaps changing sign, as the separation increases and samples the twists and bends of the shape. Averaging over separations $\Delta s = |s_1 - s_2|$ along the filament, one expects the correlation between tangent vectors to decay exponentially as [7]

$$\langle \mathbf{t}(s_1) \cdot \mathbf{t}(s_2) \rangle = \exp(-\Delta s/\xi_p). \qquad (3)$$

The persistence lengths of the common biofilaments displayed in Table 1 span an impressive range, allowing just a small number of filament types to play a variety of structural roles. The reason why the persistence length varies so strongly can be found in standard polymer textbooks [7], which establish that

$$\xi_p = YI / k_B T \qquad (4)$$

TABLE 1

CHARACTERISTICS OF COMMON STRUCTURAL FILAMENTS IN THE CELL (FROM REF. [5])

Filament	diameter (nm)	persistence length (lnm)
spectrin	few	10 - 20
F-actin	8	10-20 x 10^3
intermediate filaments	~10	variable
microtubules	25	1-6 x 10^6

for a rope undergoing thermal undulations at temperature T. The fact that ξ_p scales like R^4 underlies the dramatic range in ξ_p for a modest range in R.

Membranes

Before the twentieth century, the walls of larger buildings generally had two purposes: to bear the load of the roof and higher storeys and to isolate the interior of the building from its environment (weather in cold climates, enemy attack...). This strategy is not particularly efficient in materials, as can be seen by comparing to the design of hot air balloons, which appeared in the 1800s. There, a thin membrane isolates the contents of the balloon, and a stress-bearing rope network reinforces the membrane as needed. This idea of separating the stress bearing function from the isolation function became common in twentieth century architecture with the introduction of curtain wall construction - where the load bearing components are columns and the wall is a glass "membrane" attached to the floor plates. An early example of this is the Fagus factory of Bauhaus architects Walter Gropius and Adolf Meyer built in 1911. Materials efficiency is vital to the cell, which has to synthesize its own molecular building blocks, so it's no surprise that the cell adopts membrane plus network designs.

For cells, the membrane is based upon the lipid bilayer - a back-to-back sandwich of lipid molecules [8]. Lipids such as the dual chain phospholipids of our cells have a hydrophilic head group which lines the outside of the sandwich facing its aqueous environment, and a pair of hydrocarbon chains, which are hydrophobic and form the interior of the sandwich. The bilayers of modern cells have a thickness d of about 4 or 5 nm, although their chemical composition is heterogeneous. Now, a two-dimensional sheet like a bilayer has several mechanical parameters which, by means of simple models, can be related to d and the surface tension γ of one leaflet of the bilayer in an aqueous environment.

Area compression resistance K_A This parameter is the two-dimensional analogue of the three-dimensional bulk modulus and describes how the free energy density, F, changes when there is an area change ΔA:

$$\Delta F = K_A (\Delta A / A)^2 / 2, \qquad (5)$$

where $\Delta A / A$ is the area strain. With a little model-building, one can show that [9]

$$K_A \cong 4\gamma. \qquad (6)$$

Bending resistance κ_b Sheets can be characterized by two principal curvatures, C_1 and C_2, which are the reciprocals of the local radii of curvature. For example, the radius of curvature of a sphere is just its radius R, and $C_1 = C_2 = 1/R$ everywhere on the surface. The simplest expression for the bending energy associated with the deformation of a surface that is flat in its native state is [10]

$$\Delta F = (\kappa_b/2) \int (C_1+C_2)^2 \, dA + \kappa_g \int C_1 C_2 \, dA, \qquad (7)$$

where κ_g is the Gaussian bending resistance. The integral $\int C_1 C_2 dA$ is independent of the shape of the surface for a given topology and can be ignored in some situations. Again, with some model assumptions, one finds

$$\kappa_b \propto K_A d^2 \sim \gamma d^2, \qquad (8)$$

where the second step follows from Eq. (6). The proportionality constant depends on whether the sheet is uniform, or loosely connected leaflets as in a bilayer [9], and has a value less than unity, commonly quoted at 1/24 [11].

Edge tension λ When a membrane is punctured by a hole, its energy generally increases. Defining the boundary of the hole to have a length ℓ the change in the membrane energy caused by the hole is [12]

$$\Delta E = \lambda \ell \qquad (9)$$

for large holes. If the membrane were made of a solid material, then the creation of a hole would expose the hydrocarbon chains of its lipid molecules to water, corresponding to $\lambda = \gamma d$. However, it is possible that the lipids reorganize themselves at the hole to connect the inner and outer leaflets, so a section through a horizontal membrane would look like $\supset$, where the line indicates the locations of the lipid headgroups. In this case, the edge tension would be given by $\lambda = \pi\kappa_b / 2d$, which can be reduced to $\lambda \cong \gamma d/4$ if relations (6) and (8) hold. In either picture,

$$\lambda \sim \gamma d. \qquad (10)$$

Holes need not be circular, and the sampling of oddly shaped holes reduces the free energy from expression (9) by TS, where S is the entropy of the ensemble of holes. Thus, we expect the membrane may become unstable against the proliferation of holes as the temperature rises, a conjecture found by simulations [13] to occur at $\lambda \cong \kappa_B T / a$, where a is the characteristic length scale of the hole (for example, its inplane persistence length). Taking a to be greater than the membrane thickness, the instability is predicted to occur at $\lambda < 10^{-12}$ J/m. In contrast, the measured [14] values of λ lie an order of magnitude above this at 10^{-11} J/m.

Like Goldilocks and the three bears, there is a region for each of these mechanical parameters that is "just right" for the cell, given its composition and competitive environment. In addition to the mechanical parameters, we also need to consider membrane permeability, which increases linearly with thickness. To simplify the discussion, let's reduce the number of variables to just γ and d by using the model results (6), (8) and (10). Table 2 shows how the cell should behave at extreme values of γ and d: The boundaries of what constitute "too fragile" or "too thick" are not straight lines, and depend upon the cell's environment.

TABLE 2

QUALITATIVE BEHAVIOUR OF A CELL EXPECTED FROM ITS MECHANICAL CHARACTERISTICS

	small values	large values
γ	large K_A, hard to stretch	small K_A, easily stretched
d	high permeability (loses nutrients)	low permeability (starves)
$\gamma \bullet d$	small κ_b, floppy membrane small λ, ruptures easily	large κ_b, stiff membrane (harder to divide)

Aggregation threshold

The phospholipids in our cells have predominantly two hydrocarbon chains, rather than single chain fatty acids (see article by Katsaras *et al.*). The reason for this choice of construction material lies partly in the efficiency with which dual chain lipids can be assembled. To quantify this, consider the behaviour of an aqueous solution of lipids in the dilute and concentrated regimes. In the dilute regime, dispersing the lipids individually throughout the solution is favoured by entropy: many spatial configurations are available to the few lipids in solution such that TS is larger than the energy released should they bind into small clumps. In the concentrated regime, there are lipids everywhere, and they can form large aggregates with considerable energy release, outweighing the loss of entropy from their removal from solution. The concentration at which the disperse phase is favoured over the condensed phase is referred to as the critical micelle concentration or critical aggregation threshold (*micelles* are small aggregates of lipids, with their hydrocarbon tails in the interior and the polar headgroups coating the surface). The threshold concentration is proportional to [15]

$$[threshold] \sim \exp(-E_{BIND} / k_B T), \qquad (11)$$

where the binding energy per lipid is roughly $E_{BIND} \sim [area] \bullet \gamma$. For an idealized lipid molecule of cylindrical shape, radius R and length $d/2$, the area exposed to water is

$$[area] \cong 2\pi R / (d/2). \qquad (12)$$

This tells us that for a single molecule of fixed d, dual chain lipids are more deeply bound than single chain lipids and therefore have a lower aggregation threshold. The exponential decay in the aggregation threshold implied by Eq. (11) is seen experimentally, as summarized in Ref. 9.

From the evolutionary standpoint, Eq. (11) indicates that dual chain lipids will be used in membrane formation more efficiently than single chain lipids: a higher concentration of single chain lipids must be achieved than what is needed for dual chain lipids. Of course, the pathway for synthesizing single chain lipids may be shorter than for dual chain, so perhaps cells had a higher concentration of single chain lipids earlier in the Earth's history.

Adhesion

Humans are aggregates of 10^{14} cells, a suitably impressive number considering there are about 10^{11} stars in the Milky Way. Clearly, the construction of multicellular organisms depends

sensitively on the nature and strength of the adhesion forces between cells. One can imagine at least two mechanisms for adhesion, which will be referred to as site-specific and generic here. Site-specific adhesion can arise from proteins on neighbouring cells that can dock with each other. The resulting bond is not as strong as a covalent bond, but may have an energy exceeding 10 k_BT, or require a force of 50 pN to break at zero temperature (see Ref. [16] for a discussion of the meaning of bond breaking forces at finite temperature). In contrast, generic forces arise even between pure bilayers without embedded proteins just because of their charge distributions. This does not mean that the bilayers must be oppositely charged: they can carry the same charge, but be separated by a polar solvent. The theory for such forces is well described in standard sources (for example, Refs. [9] and [17]); under common conditions, the energy density of such generic forces is in the range 10^{-5} J/m^2 at equilibrium separations.

What adhesion energy is expected for a pair of cells, assuming a contact area of 5 μm^2? For site-specific binding at 100 bonds/μm^2 and 15 k_BT per bond, the adhesion energy is 3×10^{-17} J. The corresponding number for generic binding at 10^{-5} J/m^2 is 5×10^{-17} J, of similar magnitude. Assuming that the cell volume is not so large that the membrane has been pulled tight, is the adhesion energy enough to deform the cell? Based on Eq. (7), the energy required to bend a membrane into a sphere of radius R is $8\pi\kappa_b$, ignoring the contribution from the Gaussian rigidity. At $\kappa_b \sim 20\ k_BT$, this bending energy is 2×10^{-18} J, an order of magnitude smaller than the adhesion energy. In other words, the adhesive forces are generally strong enough to deform a cell if there is sufficient contact area.

Membrane ripples

In describing the forces between membranes, we have invoked a picture in which the interacting surfaces are planar. This is not generally the case, because of the softness and fluidity of lipid bilayers. Just like soft polymers wiggle and squirm because of thermal fluctuations, so do membranes, although their detailed behaviour depends on whether they can resist inplane shear deformations. Polymerized membranes, which can resist shear, do undulate although they are flat on long length scales, meaning that their average inplane size scales linearly with their physical length. A metaphor would be a piece of paper that has been wrinkled by a fine mist of water: the inplane size is the length of its shadow on a flat table top, while the physical length is the distance along the paper following its ups and downs. To give this metaphor some mathematical clothes, define the table top as an xy reference plane and define the vertical displacement of the paper as its height $h(x,y)$, which obviously depends on the table-top co-ordinates. For a polymerized membrane of size L x L when pressed flat, the projected length of the paper along the x-axis is linearly proportional to L. The mean height $\langle h \rangle$ scales like $L^{0.65}$, meaning that the ratio of the transverse height to the longitudinal dimension vanishes as L goes to infinity (see Chap. 6 of Ref. [5]).

Fluid membranes do not behave like this because they have no resistance to inplane shear: they are not like a sheet of paper but rather like the coating on your finger after it is dipped in syrup. Thus, they can adopt an arbitrary shape without the folds and creases of a shear-resistant membrane. They have a finite persistence length just like flexible polymers. To describe the undulations of a membrane, define the local mean curvature C_{mean} by

$$2C_{mean} = -(\partial^2/\partial x^2 + \partial^2/\partial y^2)\, h(x,y). \qquad (13)$$

The more violently the height rises and falls with x or y, the larger its second derivative. From Eq. (7), the bending energy is proportional to the square of the curvature through

$$\Delta E = 2\,\kappa_b \int C_{mean}^2\, dA, \qquad (14)$$

ignoring the Gaussian contribution. After some mathematics, the persistence length can be shown to be [18]

$$\xi_p = [\textit{molecular length}] \times \exp(4\pi\kappa_b / 3k_BT), \qquad (15)$$

where [*molecular length*] is the molecular length scale of the membrane's components. One important thing to note about Eq. (15) is that the persistence length increases exponentially with the elastic parameter κ_b, whereas the persistence length of a polymer increases linearly with the Young's modulus, Y in Eq. (4). As one might expect, the thermal fluctuations in the height

$$\langle h^2 \rangle / A \sim k_BT / \kappa_b \qquad (16)$$

grow with temperature.

This rounds out our discussion of the basic mechanical features of the cell. We have omitted topics like cell locomotion and division for the sake of keeping this article focused on the simplest design and construction available to cells (see Ref. [19] for an introduction to cell motion). Having described generic attributes of the cell's construction materials, let's now turn to the question "what designs are available for a given cell shape"?

CATALOGUE OF DESIGNS

The mechanical components described above can give rise to an impressive variety of cellular shapes and sizes. If composed solely of a fluid membrane, the cell boundary can have a shape that is easily deformed in response to its environment or during the final stages of cell division. However, this ease of deformation also tells us that some mechanisms or structural elements, like networks, must be employed if the cell is to have a largely fixed shape. In other words, the boundary is not like a sheet of wood that can be sawn or bent into a particular shape: the thermal fluctuations of Eq. (16) and the changes caused by random external forces can both be significant. The designs that are described in this section incorporate at least the fluid boundary of the cell, and a minimal number of extra components as needed to attain a given shape. The energetics of the shape then involve at least Eq. (7).

Spheres

The fluid membrane bounding a cell is easily bent and unable to maintain a shape on its own. However, even a cell whose only structural element is a membrane can attain a spherical shape by possessing an osmotic pressure difference ΔP across its boundary, thus keeping its volume at the maximal value permitted by the membrane area,

$$V_{max} = A^{3/2} / (6\sqrt{\pi}). \qquad (17)$$

In principle, even the slightest elevated osmotic pressure will generate a sphere (assuming that the enclosed volume can

accommodate it) but some systems may be less than spherical at $T > 0$. The size of the sphere may be constrained by the properties of the membrane material.

Small spheres A homogeneous lipid membrane will be under stress when bent into a spherical shape: the headgroups and hydrocarbon chains will be displaced from their equilibrium density. Using Eq. (7), the bending energy associated with the spherical shape is

$$E_{\text{sphere}} \equiv 8\pi\kappa_b, \tag{18}$$

where the Gaussian term has as usual, been omitted. If the spherical shape is to be stable, this energy must not exceed the energy of a flat membrane with a circular edge, $2\pi R\lambda$ according to Eq. (9). Because the energies of the flat and spherical shapes depend differently on the radius R, there is a minimum radius R_{min} below which the flat state is favoured, namely [20]

$$R_{\text{min}} = 4\kappa_b / \lambda. \tag{19}$$

Invoking the relationship $\lambda = \pi\kappa_b / 2d$, which led to Eq. (10), we have

$$R_{\text{min}} = (8/\pi)\, d. \tag{20}$$

This is not an especially dramatic bound, predicting only R_{min} = 10 nm for bilayers of thickness d = 4 nm.

Large spheres A more useful bound on cell size can be obtained by considering the stress that the membrane must bear at elevated osmotic pressure. For surfaces with principal curvatures C_1 and C_2, the law of Laplace [21]

$$\Delta P = (C_1+C_2)\tau, \tag{21}$$

relates the pressure difference ΔP across the membrane to the two-dimensional stress τ it experiences. For spheres, this leads to

$$\tau = R\, \Delta P / 2. \tag{22}$$

Fluid membranes rupture at just a few percent strain, for which the corresponding surface stress can be obtained from

$$\tau = [strain] \bullet K_A. \tag{23}$$

Eqs. (22) and (23) can be combined to determine the maximum radius at which the bilayer can sustain a given ΔP. Taking 3% strain at failure and K_A = 0.2 J/m^2 as common values, then

$$R_{\text{max}} \approx 10^{-2} / \Delta P, \tag{24}$$

where R and ΔP are in MKSA units. Note that this result is independent of membrane thickness if Eq. (6) holds. For example, if ΔP = 1 atm = 10^5 J/m^3, the maximum allowable radius is 0.1 μm. Clearly, bacteria with radii of order microns need a cell wall to sustain pressures of 10 atm or more.

Prolates and oblates

According to Eq. (7), shapes like prolate (cigar) and oblate (pancake) ellipsoids have higher deformation energies than a sphere. To describe these shapes quantitatively, we define a reduced volume v_{red} as the enclosed volume of a particular shape (with spherical topology) compared to a sphere with the same surface area, or

$$v_{\text{red}} = 6\sqrt{\pi}\, V / A^{3/2}. \tag{25}$$

Numerically solving Eq. (7), one can show that the energy of a shape rises from the mandatory E_{sphere} at v_{red} = 1, to about twice E_{sphere} at $v_{\text{red}} \cong 0.6$. Now, an energy of $2E_{\text{sphere}}$ is the deformation energy of two spheres touching, the ultimate product of the cell division process. Before jumping to the conclusion that this is the point at which a cell must divide, note that the reduced volume of two identical spheres is $1/\sqrt{2}$ or 0.71, notably higher than 0.6. In other words, a pure bilayer cell can safely pass below v_{red} = 0.71 without dividing, which would cost energy to achieve.

Extensive studies [22] have been made of the shapes of synthetic vesicles (pure bilayers of controlled composition) and the red blood cell, whose sole structural components are a membrane and its attached two-dimensional protein scaffolding. Such systems have been taken through a large range of v_{red}, past the biconcave equilibrium shape of the red cell at $v_{\text{red}} \approx 0.6$ towards bowl-like shapes (*stomatocytes*) at very low v_{red}. These shapes can be stabilized either by controlling the enclosed volume, or by modifying the equilibrium curvature of the bilayer. For example, if the chemical composition of the inner and outer leaflets is inequivalent, the bilayer may have an equilibrium curvature which is not zero, referred to as a spontaneous curvature, C_o. The presence of spontaneous curvature modifies the κ_b part of Eq. (7) to read [23]

$$\Delta F = (\kappa_b / 2) \int (C_1+C_2-C_o)^2\, dA. \tag{26}$$

One can see that a positive value of C_o, corresponding to "inward" bending, reduces the bending energy, perhaps below E_{sphere} depending on its magnitude.

Spherocylinders

Many bacterial shapes are approximately cylinders capped at each end by hemispheres (called spherocylinders by some researchers). Defining the cylindrical part to have a length L and radius R, for an overall length of $L + 2R$, the deformation energy of the membrane having such a shape is

$$E_{\text{spherocylinder}} - E_{\text{sphere}} = \pi\kappa_b (1 - RC_o)^2 (L/R), \tag{27}$$

according to Eq. (26). For membranes with zero spontaneous curvature, the energy of a spherocylinder is higher than one of the ellipsoids of revolution; however, the deformation energy vanishes if $C_o = 1/R$. It is difficult to imagine how a fluid bilayer alone can preferentially form a spherocylinder rather than an ellipsoid; in most bacteria, the shape arises from the presence of the cell wall used to strengthen the bilayer against rupture. In modern bacteria, the wall itself is compositionally anisotropic, with strong glycan (sugar) chains running around the girth of the cell and floppy protein chains running longitudinally and linking successive glycans. This composition permits the bacterium to grow without compromising the strength of the wall, as suggested by the tensor form of Eq. (21). Although the surface stress is equal to $\Delta P / 2R$ isotropically at the end caps, it is $\Delta P / R$ around the cylinder and $\Delta P / 2R$ along its length. This anisotropic stress is familiar from boiled sausages, which split longitudinally when they absorb too much water.

Tubes

A variety of bacteria grow within a sheath or tube, which is often a thin layer of strong material. On theoretical grounds, such tubes should be relatively straight if they are constructed with few defects. Let's calculate the persistence length of a thin tube according to Eqs. (2) and (4). For uniform tubes of radius R and thickness t, the moment of inertia of the cross section is

$$I \cong \pi R^3 t \qquad (R >> t) \qquad (28)$$

which can be obtained from Eq. (2) by comparing I for solid tubes of radius R and $R+t$. Placing this into Eq. (4) gives

$$\xi_p = \pi R^3 t Y / k_B T, \qquad (29)$$

which demonstrates that ξ_p grows strongly with radius, even for hollow tubes. As a numerical example, suppose that the tube has R = 1 μm and t = 10 nm, like a modest bacterial cell wall. If $Y = 10^7$ J/m^3, typical of cell wall material but much less than most protein filaments, the persistence length is predicted to be an impressive 80 m! The presence of defects and kinks will undoubtedly decrease this estimate, but it confirms that cellular tubes should appear straight on the scale of hundreds of microns.

Coils

Under what conditions will a tube spontaneously deform into a coil? This question is of general interest in molecular biology because of the presence of coils in large proteins etc. On mesoscopic length scales, the coiling instability of multilamellar tubes has been investigated [24] both theoretically and experimentally. These are uniform tubes made from concentric lamina of lipids - the tubes are "solid" in the sense that they are composed entirely of lipids, but the lamina themselves are two-dimensional fluids. When a particular polymer is attached to the outside of the tube in the appropriate concentration, it spontaneously forms a coiled state, said to be maximally tight in the sense that the repeat distance along the length of the coil is just the diameter of the multilamellar tube. A theoretical model for this phenomenon, based upon equilibrium shapes, has established that a compositional inhomogeneity (like the polymer) which is free to diffuse on the surface of the tube, may cause coiling within a range of densities. If the polymer is too dense, the tube's surface again becomes relatively uniform, suppressing coiling.

For polymerized membranes, one can introduce an inhomogeneous composition in which some of the links possess a spontaneous curvature (say type C for curved) while others do not (say type N for normal). Imagine a triangulated network (all elementary plaquettes are triangles subtended by six-fold vertices) which has been formed into the shape of a straw, with one set of bonds forming rings around the tube and the other two sets spiraling around it at 120° to the rings. Let's take all of the diagonal bonds to have type N. If all the bonds in the ring set are type N or type C, the tube is straight. However, for a range of intermediate concentrations, the tube spontaneously coils. Now, it may be a bit much to demand a biological sheath have this specific composition, but it does provide a mechanism for tubes to form coils spontaneously.

Let's summarize these results. It is easy to imagine strategies that can give rise to spheres and ellipsoids using nothing more than a fluid membrane. On the other hand, a network or some way of segregating compositional inhomogeneities is needed to produce a spherocylinder. Although we did not discuss mechanisms by which a cell might construct a tube, we did establish that such tubes should have a very long persistence length compared to their radius. Designs by which tubes could spontaneously coil appear to involve some architectural ingenuity on the cell's part - certain kinds of compositional inhomogeneities may be sufficient for fluid membranes, but more care must be taken to induce coiling in polymerized membranes or networks.

CONCLUSIONS

This article began with a look at guidelines for materials and designs that are part of conventional building codes for residential construction. How close are these guidelines to the building code of the cell? The raw materials for the cell - at some level, CO_2 and H_2O - are certainly *readily available* on the Earth's surface, but we did not discuss the synthetic pathways for the cell's molecular building blocks: are lipids and proteins energetically inexpensive to produce? We did show, however, that only a *few specialized materials* are needed to create many cellular designs: fluid membranes and filamentous networks can generate an impressive variety of fundamental cell shapes. With their dual hydrocarbon chains, the phospholipids of modern cells have a low aggregation threshold and are very *materials efficient*. This is the result of lipids having a strong affinity for the bilayer phase. With their hydrophobic cores, bilayers resist rupture and are *self-healing* under many conditions.

The catalogue of cell architecture includes many simple designs such as spheres and ellipsoids. Not only can these cells propagate through division, they are *adaptable* to changes in the cell's environment and permit a cell to double in area and volume during its lifetime. Of course, the most evolutionarily advanced cells are far removed from such simple designs, having many internal compartments for specialized tasks as well as networks for dynamic structural organization. In this sense, advanced cells more resemble villages than they do individual houses.

While the core of Nature's building code has remained the same for more than 3 billion years, it has been constantly elaborated. Many of the earliest fossilized cells resemble stacks of coins [3], with each cell adhering to two opposing neighbours, like a tower of pancakes (or a Rollo chocolate bar). By the time the Earth was half as old as it is today, a broader suite of designs can be seen - spheres, prolates, multiplets and tubes - as discovered in microfossils from Canada's Belcher Islands [25]. After another billion years, a variety of robust coils are firmly established. As the inventory of fossilized cells continues to grow, it may be possible to trace the history of various designs as cells compete for, and exploit, new resources in a changing environment.

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