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Differential Geometry Meets the Cell

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A new study by Terasaki et al. highlights the role of physical forces in biological form by showing that connections between stacked endoplasmic reticulum cisternae have a shape well known in classical differential geometry, the helicoid, and that this shape is a predictable consequence of membrane physics.

Cells are beautiful structures whose form is tailored to function, but what specifies the form? A century ago, D'Arcy Wentworth Thompson proposed that physical principles such as surface tension could dictate biological form. But then the genome happened, and with it came the desire to explain away questions of cellular structure by telling ourselves that geometry is encoded in the genome. Although the genome is not a blueprint that explicitly encodes shape, the genome does encode proteins that sculpt cellular structures, for example by dictating membrane curvature (Mim and Unger, 2012). The existence of such proteins goes against the concepts of D'Arcy Thompson and appeared to be a final nail in the coffin of his Pythagorean approach to cell biology. But a paper by Terasaki et al. (2013) in this issue of *Cell* breathes new life into the old dream of mathematical biology by discovering that the connections between endoplasmic reticulum (ER) sheets mimic a well-known class of mathematical surfaces and that this shape is in fact predictable from simple physical rules governing membrane energetics.

In their paper, Terasaki et al. (2013) explored the structure of the ER using a new imaging method and obtained a beautiful new structure. In professional secretory cells, the ER forms stacks of membrane cisternae, apparently because this is an efficient way to pack a lot of ER membrane into a small volume inside the cell. Although these stacks have been seen for decades, it was never quite clear how the edges of the cisternae were connected together into one continuous lumen. Using a new method of serial section scanning electron microscopy, the authors discovered a novel arrangement of membranes forming the connectors, which turned out to resemble a mathematical object known as a Helicoid, discovered by Jean Baptise Meusnier in 1776. To visualize a helicoid, start with a fixed axis, draw a line segment perpendicular to the axis, and then rotate the line segment around the axis while moving along the axis to sweep out a surface (Figure 1).

Why would ER stack connectors take this shape? Terasaki et al. (2013) constructed a simple physical model giving the total energy of the ER shape as the sum of two fundamental energetic terms and then solved for the shape that minimizes both energetic contributions simultaneously. The first energy is the bending energy of the sheet surface, which, for symmetrical surfaces like the paired membranes of an ER cisterna, is lowest energy when its average curvature is zero (Helfrich, 1973). For surfaces, one can measure curvature in two orthogonal directions. The "average curvature" refers to the average of the curvatures in these two directions. There are two ways to get an average curvature of zero: either the surface is flat, like a tabletop, or the surface curves up in one direction and down in the orthogonal direction, like a saddle. So the closer the ER membrane could get to one of these zero average curvature shapes, the more energetically favorable it would be.

The second energy term that must be considered is the shape of the edge of the sheet. The path of the edge in 3D space is called the edge line, and the authors use differential geometry methods to derive an energy for bending the edge of a membrane sheet composed of two parallel membranes. Their result is that the edge line will be at its lowest energy when it has a constant, nonzero curvature.

Thus, the lowest energy state for the system would be if the membrane surface has zero average curvature and the edge line has a constant nonzero curvature. Any deviations from these conditions will impose an energetic cost whose value depends on the detailed physical properties of the membrane system. But regardless of the physical details, the lowest energy state can be described quite simply without having to know any numerical parameters whatsoever: the lowest energy state is a shape whose edge has constant curvature and whose surface has zero curvature. In fact, the shape with these properties is well known in the classical literature of differential geometry: the helicoid! The helical shape of the edge has constant curvature, whereas the surface itself has zero average curvature because it has a saddle-like shape at every point.

The fact that the helicoid shape is predicted without having to know the value of any physical constants is one of the most beautiful and surprising results of this paper. It is not very shocking that physical properties of cellular components contribute to their shape—even the most committed geneticist would have to grant this point. But usually when one talks about modeling the relation between physical forces and biological structures, one ends up having to know, or at least estimate, the value of various physical constants like elastic moduli, rate constants, and so on. But in this case, the fundamental form of the helicoidal shape does not rely on knowing such constants, and so in this sense, it may be said that the shape of the ER connectors comes from mathematics rather than physics.

How unusual are structures like this? Helicoid-shaped defects have been predicted to occur in liquid crystals (Kamien and Lubensky, 1996), but helicoids are just one example of a larger class of surfaces, known as minimal surfaces, characterized by zero average curvature. Whereas helicoids are not seen that often, another minimal surface, the gyroid, arises in a huge number of contexts. The gyroid contains helical twists similar to the helicoid but, whereas the helicoid is periodic along one axis, the gyroid is periodic in three perpendicular axes. Gyroids are seen in many self-assembled surfaces, such as in diblock copolymers, for example (Bates and Fredrickson, 1999). Biologically occurring gyroids have been reported in butterfly scales (Michielsen and Stavenga, 2008). Although the scales themselves are formed of chitin, the chitin deposition occurs in invaginations of the plasma membrane separated by tubules of smooth ER (Ghiradella 1989), suggesting that, again, the elastic properties of biological membranes may drive the formation of complex-looking minimal surfaces. Under conditions of stress or viral infection, ER can form periodic structures (Snapp et al., 2003; Goldsmith et al., 2004), some of which represent triply periodic minimal surfaces (Almsherqi et al., 2006). An important difference is that these prior descriptions were in pathological system, whereas Terasaki et al. (2013) have found a minimal surface to describe normal ER stacks in healthy cells.

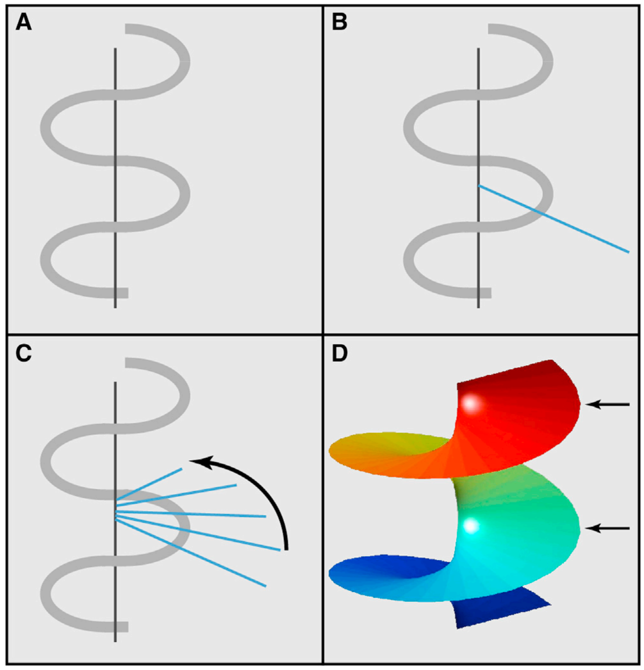

Figure 1. Visualizing a Helicoid
(A–D) To construct a helicoid, start with an axis (A) and then draw a helix around it, like the snake in a caduceus. Draw a line running from the axis through the helix and perpendicular to the axis (B). Draw similar lines through all points on the helix, so that the lines trace out a surface as they rotate up the helix (C). The result is a helicoid (D), the structure discovered in the connections between ER cisternae by Terasaki et al. (2013). In the ER, successive stacked cisternae would be fused to the helicoid periodically as indicated by arrows.

Maybe ER stack connectors are special cases in that simple math and physics won't explain all or even most cellular structure. The jury is still out. The fact that Terasaki et al. (2013) needed advanced microscopy methods to visualize their structure suggests that we might not see recognizable mathematical forms because we don't yet know how to look for them.

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