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Editorial

Form, force and flamboyance

Florian Maderspacher

"*The form [...] of any portion of matter, whether it be living or dead, and the changes of form which are apparent in its movements and in its growth, may in all cases alike be described as due to the action of force. In short, the form of an object is a 'diagram of forces' in this sense, at least, that from it we can judge or deduce the forces that are acting or have acted upon it.*"

D'Arcy Wentworth Thompson, *On Growth and Form*

The diagram of forces mentioned in the well-known quote from D'Arcy Thompson's biblical book can be recognised in various guises throughout the reviews in this special issue of *Current Biology* on cell form and physics. The force diagram is perhaps most strikingly apparent in a structure that has not terribly much to do with cell shape *per se* — the mitotic spindle, discussed by Sophie Dumont and Tim Mitchison. This complex apparatus, the prime task of which is the segregation of chromosomes, is determined in its form and function by the forces generated by its molecular machines. It is perhaps a curious twist of history that only now — after decades of deciphering its molecular make-up — we are beginning to understand the spindle as a purely physical, mechanical object, while D'Arcy Thompson could formulate a great deal of his physical principles in blissful ignorance of the underlying biological machinery. And with the current renaissance (or *naissance*) of physical thought in cell biology, Thompson's book might be moving along from the apocryphal towards the canonical.

In the case of cell form, the force diagram is essentially a balance between 'intrinsic' and 'extrinsic' forces. Depending on the cell being studied, the forces can be carried by different cellular structures; intrinsic forces may, for instance, be generated by the cytoskeleton, while extrinsic forces are particularly relevant in multicellular organisms where cells make contacts with their neighbours or the extracellular matrix. Perhaps the most obvious determinants of shape are the walls and membranes that demarcate cells. Take multicellular plants, for instance, discussed by Daniel Szymanski and Daniel Cosgrove, where the rigid cell walls themselves largely determine the shape of a cell and counteract internal forces, mainly generated by osmotic pressure which creates turgor on the inside. In animal cells, which lack a rigid cell wall, the membranous confines of the cells also counteract intrinsic forces, and they were long thought to be mainly organised by the scaffold of the cytoskeletal cortex, acting much like an 'inside wall'. But, as Joshua Zimmerberg and colleagues point out, membrane intrinsic properties, such as membrane composition, and their direct regulation also contribute to the shape cells take. Particularly in animal cells, however, another pivotal extrinsic factor in the force diagram comes into play — the adhesive contacts that cells make with their environment. These play a central role, not only for cell shape, but also for the dynamic interactions in which cells engage, particularly during embryonic development, as discussed by Carl-Philipp Heisenberg and Ewa Paluch.

The predominant transducers of the 'intrinsic' forces that shape cells — the various components of the cytoskeleton — have been particularly well studied in migrating cells, which are the focus of the review of Alex Mogilner and Kinneret Keren. The

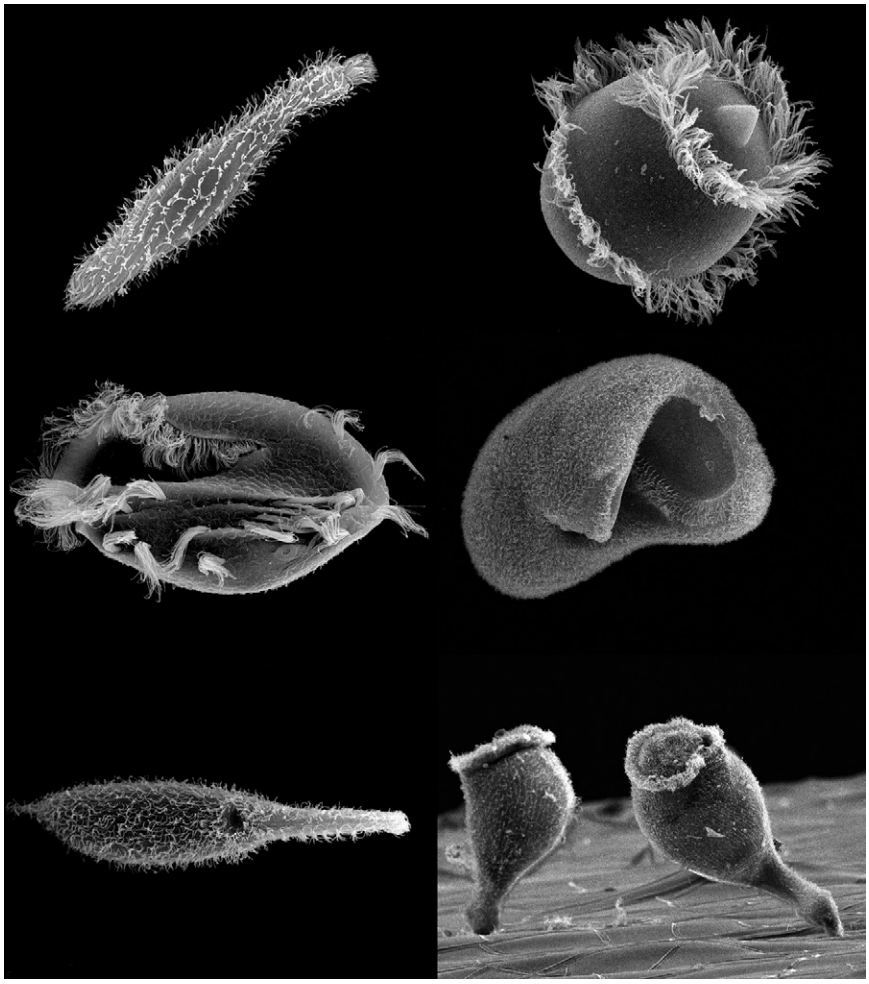

Figure 1. Ciliate cell shape diversity.

Electron micrographs of various ciliates, from top left to right bottom: *Lacrymaria sp*., *Didinium sp*., *Euplotes sp*., *Bursaria sp*., *Dileptus sp*., and *Stentor sp*. *Stentor* image by Lindy Cacciapo, all other images by Aaron Bell.

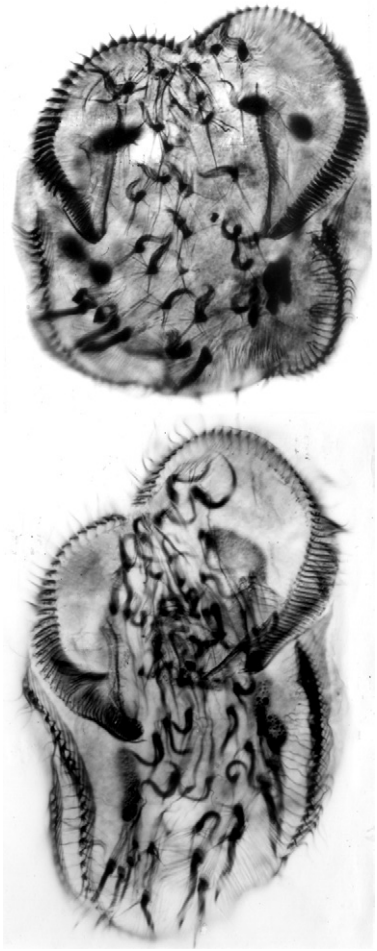

Figure 2. Cortical inheritance in a ciliate.

Mirror-image doublet cells of the ciliate *Stylonychia mytilus*. Such duplications can be induced by surgical manipulations and can be propagated over generations. Photos by Xinbai Shi and Joseph Frankel. Reproduced with permission from Shi, X. and Frankel, J. (2007). Morphology and development of mirror-image doublets of *Stylonychia mytilus.* J. Protozool. *37*, 1–13 (upper panel) and Frankel, J. (1992) Intracellular handedness in ciliates. Ciba Foundation Symposium *162*, 73–93 (lower panel).

cytoskeletal actin network is crucial for force generation and dynamics, and a multitude of actin-regulating processes has been inferred from studies of motile cells. Microtubules are also important, both as a mechanical counterbalance to actin as well as, by way of associated motor proteins, a delivery line for cytoskeletal and membrane components. And again, adhesion plays an important role here and must be dynamically regulated to allow for net movement of the cells. Such a dynamic regulation — at the level of the cytoskeleton, the membrane and the adhesive contacts — requires that the cell is able to sense forces, a process discussed by André Brown and Dennis Discher.

Behind all its various manifestations in the complex machinery of the cell, the force diagram seems like a good candidate for a fundamental physical principle underlying biological form — though, of course, solid quantitative parametrisations and mathematical formulations are still in their infancy in cell biology. But, its simplicity contrasted with the complexity of the biological 'wetware' perhaps also says something about the relationship of biology and physics as sciences. From empirical data, physicists distil fundamental, all-encompassing laws, whose explanatory power and general validity may be the target of a good deal of 'physics envy' among biologists. Yet, unlike in physics, where, say, the law of gravitation holds for every object under the sun, biology is full of exceptions. Therefore, biologists, as much as they like to find general principles, have also always embraced diversity. In biology, studying diverse systems can be informative in two regards: first, comparison of diverse systems helps clarify which features of a fundamental mechanism are general and which are special; and second, the study of divergent systems may also lead to the discovery of entirely new mechanisms and principles that are not necessarily apparent from the model systems that have been studied so far.

Cell shape has been studied in a good handful of cell types, most of which actually look — no offence — fairly simple in terms of form. Of course, there are exceptions — neurons have rather elaborate shapes — but, by and large, most of the model cells of multicellular organisms can be reduced in first approximation to simple polygons; likewise, for unicellular model organisms, such as yeast and bacteria, the variety of shapes can be reduced to variations of a few basic forms, as D'Arcy Thompson has attempted in his book. Such a reductive step was indispensable for the success of understanding the biology and physics of cell shape in these seemingly simpler organisms, a fact testified by the reviews by Bill Margolin on the bacterial cell wall and by Matthieu Piel and Phong Tran on fission yeast. Yet, in the light of all the knowledge gained from simple model cells, now might be a good time to step back and consider studying the more complex, more flamboyant cellular shapes that are seen in multicellular organisms and especially in the unicellular protists.

The shapes of protist cells have long fascinated biologists. This fascination was initially mainly an aesthetic one and is documented in the beautiful drawings by early microscopists. And indeed, the complexity, variety and beauty of protist cell shapes is astonishing. There are cells with intricate mineral skeletons, such as the radiolarians popularised by Haeckel, or diatom algae. Others, such as several single-celled algae have huge thallic bodies with a complex architecture that often resembles that of multicellular forms. Yet, others, like dinoflagellates or chaonoflagellates, have complex cellular protrusions or highly bizarre shapes. Perhaps the pinnacle of single-celled complexity is marked by the ciliates, which come in various shapes, some of them as sessile forms, and are adorned with complex patterns of cilia (Figure 1).

Of course, even the most burlesque cell shape will ultimately be the result of an interplay between the membrane and actin or microtubule filaments as well as other cytoskeletal proteins. So, in a sense one could argue that, in terms of fundamental, law-like principles of cell shape generation, there's probably little to learn from studying such cells that could not have been learned from yeast or fibroblasts. And indeed, ciliates have been studied fairly little with regard to cell shape. It is quite telling that perhaps the most influential work in this area was done half a century ago, in the pre-molecular age, by Vance Tartar. Tartar worked on the sessile ciliate *Stentor* in a tiny shed named 'Wits End' at the back of his farm. Like most ciliates, *Stentor* possesses a geometrically arranged microtubular cortex with regular rows of basal bodies. In the freedom of his confine, Tartar observed that *Stentors* have an amazing capability for regeneration: they can regenerate into complete cells from as little as one percent of the original cell. But such regenerates will only attain their proper appearance if a fragment of the cortex is included: *Stentors* stripped of their cortex — so called 'endoplasmic spheres' that are able to survive for some days — cannot form a new cortex.

Tartar also conducted numerous surgical manipulations on the large *Stentor* cells and observed their influence on the pattern of cilia on the cell's surface. The rows of cilia

alternate with pigment stripes that get thinner across the circumference of the cell, such that the narrowest and widest stripes meet in an area called the 'locus of stripe contrast'. Such a region of stripe contrast is required for a regenerating *Stentor* to form an oral apparatus through which it feeds; and, when grafted onto another *Stentor* cell, the locus of stripe contrast can organise the neighbouring cortex such that a new oral apparatus emerges or, depending on the position of the graft, conjoined twin cells arise. What's more, such twins can be propagated in culture over many generations. These observations led to the idea of 'cortical inheritance', which means that the geometrical properties of the cell's cortex — and thus ultimately the cell's form — cannot be generated without a physical template of the cortex. Similar effects have subsequently been observed in numerous other ciliates (Figure 2), where for instance, small patches of cortex with inverted polarity or conjoined twins can be passed on through many generations.

Though this phenomenon of cortical inheritance does not directly challenge or even change our view of the fundamental principles of how cell shape is generated, it perhaps provides a glimpse of what might be out there to discover. Once such phenomena are investigated in molecular detail — as is being done in *Tetrahymena* now — we might find both the well-known structural elements in new arrangements and configurations that have not been seen before in model cells as well as entirely new regulators. In a sense, and at the very least, the study of more exuberant cell shapes might simply serve to expand the parameter space for the formulation of physical principles and it may show of what cellular machineries are — and aren't — capable. Much like developmental biologists, who have inferred the fundamental principles of patterning in comparatively simple systems, such as the nematode vulva, or the fly eye, are turning their attention to more flamboyant structures, such as beetle's horns or butterfly wings, this may be a time for those interested in the biology and physics of cell shape to look at more complex cell shapes — and if only to give physicists something to envy biologists for.

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Primer

The mechanical cell

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Many decisions we make are based on our ability to probe the mechanical properties of materials and to measure forces applied to us. We choose ripe fruits in part by squeezing them, make inferences based on the firmness of a person's handshake, and are often attracted or repelled by whether something is soft or sticky, a response of great interest to product designers and cosmetic manufacturers. These sensory abilities depend on our capacity to function as rheometers: we apply forces of controlled magnitude and duration and detect the resulting deformation or rate of flow. That is, we are simultaneously aware of stress (force/area) and strain (deformation) or strain rate when we judge how an object feels or how hard we are pushed or pulled. Cells appear to be equally sensitive to information about force, stiffness and adhesivity. The range of force and stiffness to which different cell types respond and the nature of their responses as they encounter materials with stiffness different from that of the tissue in which they normally reside are as individual as their responses to chemical stimuli.

The ability of cells to respond to external forces or to detect the mechanics of their substrates as they apply internally generated forces depends on the mechanical properties of the cells themselves. The same methods and instrumentation used to measure the mechanical properties of synthetic materials — the province of rheology — have been applied to tissues and isolated cells. In the latter case, modification of traditional methods and invention of new methods have been needed to cope with the small size and fragility of an individual cell. In this primer we shall attempt to summarize some of the current findings in cell mechanics (see Box 1 for glossary of terms) and how they are thought to affect how cells function or malfunction *in vivo*.

Why physics matters for cells

The idea that the physical properties of cells are important for their biological function is nothing new. Many early cell biologists emphasized that defining the physical features of cells is essential to understanding how they function [1]. Cell functions that are defined by the mechanical work done by the cell such as motility and cytokinesis have especially motivated studies of the cell's mechanical properties and mechanisms of force production. But beyond those processes that, like muscle contraction and cell locomotion, clearly do mechanical work and require an elastic cytoplasm or a gelation–solation transition to perform that work, the physical state of the cell has sometimes appeared to be merely a side-effect of the structures and reactions required for the more important genetic and biochemical processes that guide cell function. Recently, however, interest in the physics of cells has been stimulated by evidence from a wide range of studies that external force applied to a cell, and the resistance that extracellular matrices exert on cell-derived forces, also generate signals that are as potent as those of chemical stimuli to direct cell growth, survival, differentiation, and function [2]. Changes in those physical features or in the cell's response to them are beginning to be taken seriously as contributing factors and not just consequences of pathologies such as scarring, fibrotic disease and cancer [3].

A few examples of the importance of external forces are the ability to promote axonal elongation by applying pN to nN scale forces to the tips of the neuronal growth cone, the effects of fluid flow on the morphology and signaling of vascular endothelial cells, and the abrupt loss of bone or muscle mass when forces due to gravity or exercise are reduced. To understand how these forces are transmitted throughout the molecular structures of the cell, and how they might be transduced into biochemical reactions, requires detailed quantitative characterization of the mechanical properties of the cells at the points where these forces are applied. Just as the three-dimensional atomic structure of a hormone receptor is needed to fully understand how that chemical stimulus activates a cellular function, so too is it necessary to define how cells and macromolecules