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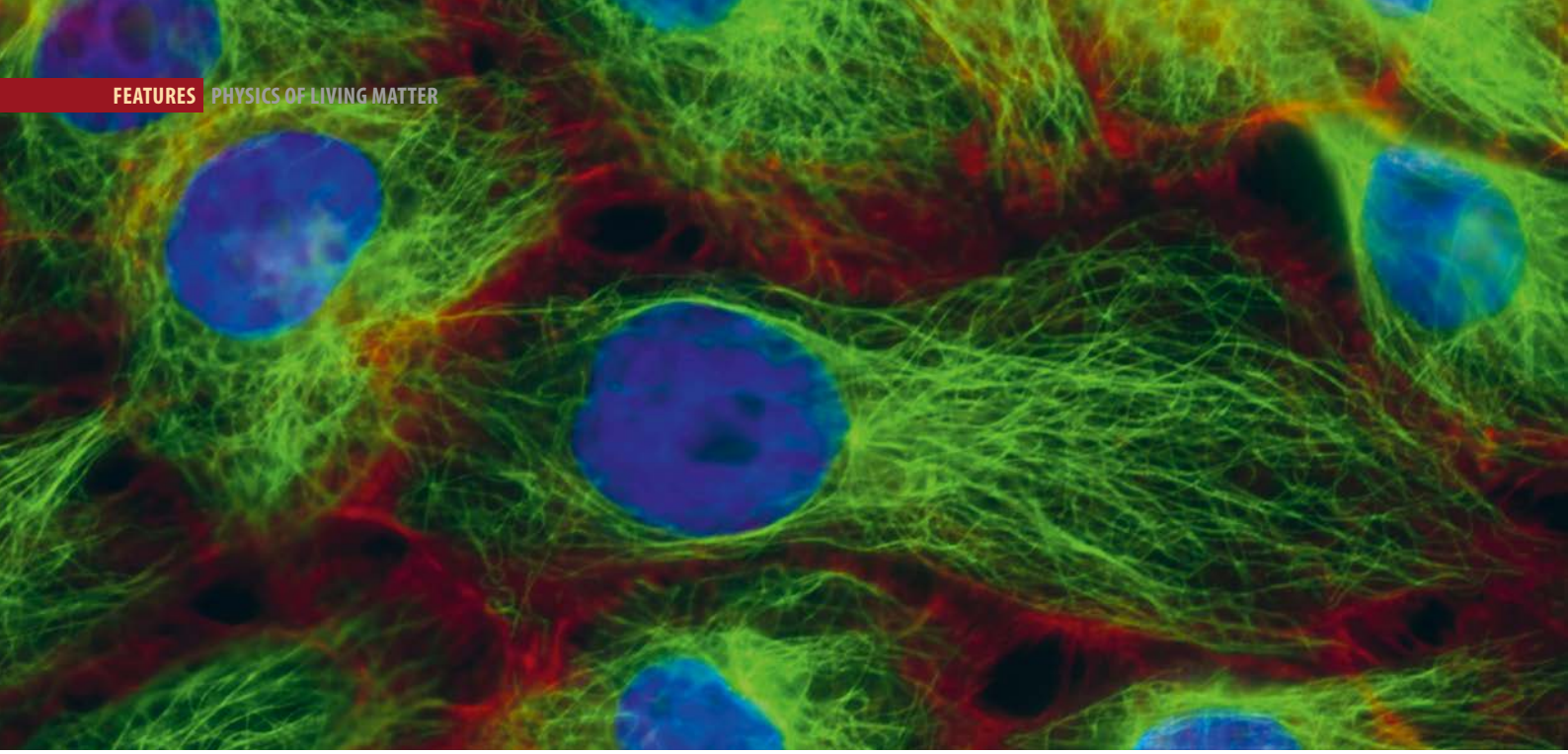

MECHANICS IN BIOLOGY

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Mechanics plays a key role in life, from simple tasks like providing protective shielding to highly complex ones such as cell division. To understand mechanical properties on the organism level, we need to zoom in to its constituent cells, then zoom back out to see how they collectively build tissues.

When multi-cellularity first evolved, organisms gained an important ability: they could let their cells specialise. In a single-cell organism, the one cell by necessity has to be able to perform all essential functions to stay alive. Driven by evolutionary pressure, it will usually optimise for growth and division. For almost all cells in a multi-cellular organism, however, the current organism represents the end of their road: even though they may divide a couple times more during the organism's life span, when the organism dies, they die as well. However, their genetic information can live on, if the organism as a whole has reproduced. Therefore, the cells have the freedom to specialise in a way that helps the organism thrive, by collecting more and different kinds of food, defending against predators and invaders, and increasing the chances that the organism will successfully reproduce.

Arguably the most extreme form of specialisation in animal tissues is in their mechanical properties. The Young's modulus of human brain tissue is less than 1 kPa, while that of the cortical bone in the skull protecting it is more than 10 GPa. This huge difference moreover has to be re-developed every time a new organism is created, as all animals develop from a single fertilised egg[1]. To illustrate, let's consider the development of a chicken heart. A chick embryo needs a heart from the second day of development onwards, as at that point it has grown too big for oxygen to diffuse through its entire body. The initial 'heart' is a simple tube, pumping by contracting like you'd pump water through a hose by moving your hand along it. As the chick develops over the next two weeks (when it hatches), the stiffness of the heart goes up by a factor 20 and it develops into the familiar four-chamber structure (similar to the human heart), including the necessary topological changes, all the while pumping blood around [1]. To achieve this remarkable feat, the embryo follows a strongly regulated developmental programme, while maintaining the ability to adopt to unexpected outside effects.

[1] The story for plants is quite different. Plant cells have a cell wall that gives them rigidity, making the difference in stiffness between various parts of the plant, while non-negligible, much smaller than between those of animals. Moreover, plants can also be easily cloned, but when they grow from seeds, they undergo a similar development process including significant changes in mechanical properties.

So how do tissues get their mechanical properties? Ultimately these come from the cells that make up the tissue, through their internal mechanics, their adhesion to each other, and through the extracellular matrix that these cells build around themselves [2,3].

Internal cell mechanics

Eukaryotic cells (all cells with a nucleus, including animals, plants and fungi, but also simple single-cellular organisms like yeast) have an internal cytoskeleton: a network of several types of polymers that give the cell mechanical structure (see figures 1 and 2). The cytoskeleton mainly consists of three components: microtubules, actin, and intermediate filaments. Microtubules are hollow structures with a persistence length much larger than the size of a typical cell. Actin filaments in contrast consist of two fibers wrapped around each other creating a much more flexible structure. During the growth phase of the cell, the microtubules typically form a radial network, while the actin filaments form a cortical structure along the periphery of the cell (figures 1c and 2a). Both microtubules and actin fibers are polar, allowing for directed transport along them by molecular motors. During cell division, the roles are reversed and motors pull on microtubules connected to chromosomes to divide the duplicated DNA over the two daughter cells (figure 1a); an actin ring around the middle of the cell subsequently contracts, again under the action of motor proteins, to actually divide the cell (figure 2b). While actin and microtubules are found in all eukaryotic cells and have close analogs in bacteria and archaea, there are many different types of intermediate filaments that are more specialised. As their name suggests, these filaments have a stiffness in between those of actin and microtubules. They are nonpolar, making the increase of the stiffness of the cell their primary function.

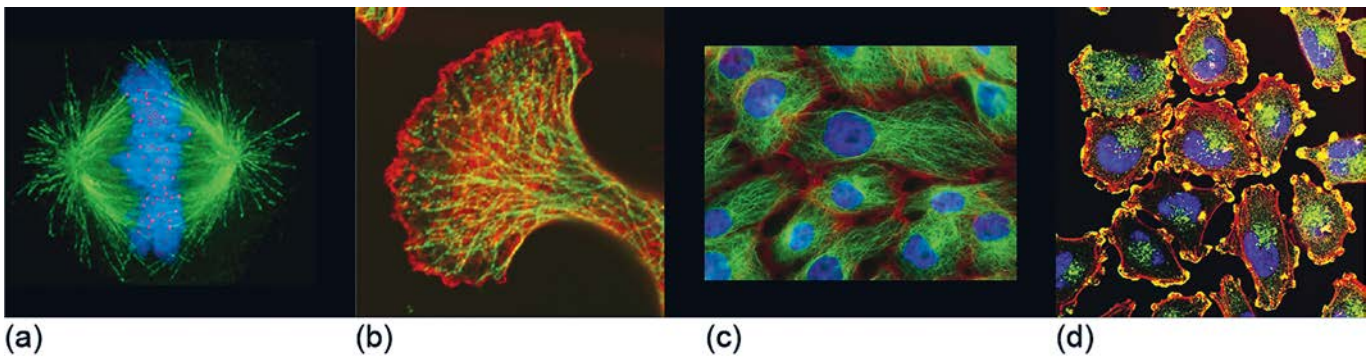
Unlike the bony skeleton in an adult animal, the cytoskeleton of a cell is highly dynamic. All filaments in it continually grow and shrink by adding or removing monomers. This growth and shrinkage can happen at the same end, but also on opposite ends, leading to treadmilling motion of the filament as a whole. Through branching and crosslinking, the filaments create networks in the cell that give the cell its stiffness [4]. Unlike conventional large-scale materials though, the cell will adapt to its environment; if the cell grows under mechanical load, its elastic modulus goes up, and stem cells placed on substrates of different stiffness differentiate into different cell types matching the outside environment [5,6].

Mechanics of tissues

Cells don't just have internal mechanics: they also connect to other cells to form tissues. Links to other cells can be made directly through mechanical junctions between molecules protruding from the cell surface. In particular in developing tissues, many of these junctions are reversible, allowing cells to bind more or less strongly depending on the needs of the developmental programme. A currently outstanding hypothesis is that cells may sort due to differential adhesion, which would be a purely mechanics-based mechanism [7].

As tissues develop, cells specialise and become more strongly anchored to their position[2]. In neuronal tissues, these connections remain relatively weak, and continue developing throughout the organism's life, as part of the ever-ongoing learning process. In most other tissues, to increase the stiffness and provide an anchoring platform, cells develop an extracellular matrix of crosslinked polymers, with a many-layered structure (figure 2c). Ultimately all hard structures in the body are made from

▾ **FIG. 1: Cytoskeletal elements in the cell. Cells get their material properties from biopolymers that continually grow, branch, and shrink, exerting forces as they do so, and providing overall stiffness to the cell. (a) Mitotic spindle in a dividing cell. Microtubules (green) pulling on chromosomes (blue) during cell division. (b) Lamellipodium of a crawling cell, with microtubules (green) and actin filaments (red). (c) Cells in a breast tissue sample, showing the nuclei (blue), microtubules (green) and actin filaments (red). (d) Metastatic melanoma cells, which have broken free from a primary tumor and can invade surrounding tissue. Next to nuclei (blue), actin filaments (red) and actin regulators (green), these cells contain podosomes (yellow), actin-rich structures used to attach the cell to a surface and spread on it. Figure (a): public domain (Wikimedia commons), (b-d) National Cancer Institute (Unsplash).**



[2] The most common such transition from motile to polarised epithelial cells is known as the mesenchymal-epithelial transition (MET); together with its reverse process, the epithelial-mesenchymal transition (EMT) it is likely the most studied transition process in biology, as it occurs in development, wound healing, tumor metastasis, and the induced reprogramming of pluripotent stem cells.

such materials [8], including not just the bones, but also the stiffer layer under epithelial tissues, which are found at the boundaries inside the body, in *e.g.* the skin, the cornea, and the gut. Epithelial tissues have highly nonlinear mechanical properties, as you can test easily for yourself by stretching your skin, which deforms easily at first but stiffens up at the centimeter scale. These properties originate from both the internal mechanics of the constituent cells [9] and the viscoelastic nature of the extracellular matrix [10], combining the elastic response of solid materials on short time scales with a stress-relaxing fluid-like response at longer times.

Because cells in epithelial tissues continually get renewed, they divide relatively frequently. For healthy cells, the number of divisions is limited; once a cell has reached the maximum, it will undergo apoptosis, programmed cell death. Errors in copying the genetic information of the cell can however prevent apoptosis and change the internal structure of the cell, resulting in different mechanical properties, two hallmarks of tumor formation (figure 1d). Fortunately, most of these cells never grow to life-threatening tumors, as they fail to penetrate the surrounding tissue, thanks to a simple but highly effective mechanical mechanism: by building up the hydrostatic pressure around them, healthy cells can keep the tumor in check, causing it to shrink and ultimately disappear. Recent modeling efforts have shown how mechanics can be used to better understand and ultimately suppress tumor development in cases where it does go wrong [11,12], underlining once again the importance of this basic physics concept for the study of life.

About the author

Timon Idema is an Associate Professor of theoretical biophysics at Delft University of Technology. His research focuses on collective dynamics, ranging in scale from molecules to colonies. He has written an open textbook on Mechanics and Relativity and recently received the J.B. Westerdijkprize for his teaching efforts.

References

[1] S. Majkut *et al.*, *Curr. Biol.* **23**, 2434 (2013)

[2] T. J. C. Harris, J. K. Sawyer and M. Peifer, *Curr. Top. Dev. Biol.* **89**, 55 (2009)

[3] A. R. Harris, A. Daeden and G. T. J. Charras, *Cell Sci.* 1**27**, 2507 (2014)

[4] D. A. Fletcher and R. D. Mullins, *Nature* **463**, 485 (2010)

[5] D. E. Discher, P. Janmey and Y. Wang, *Science* **310**, 1139 (2005)

[6] A. J. Engler, S. Sen, H. L. Sweeney and D. E. Discher, *Cell* **126**, 677 (2006)

[7] F. Fagotto, *Semin. Cell Dev. Biol.* **107**, 130 (2020)

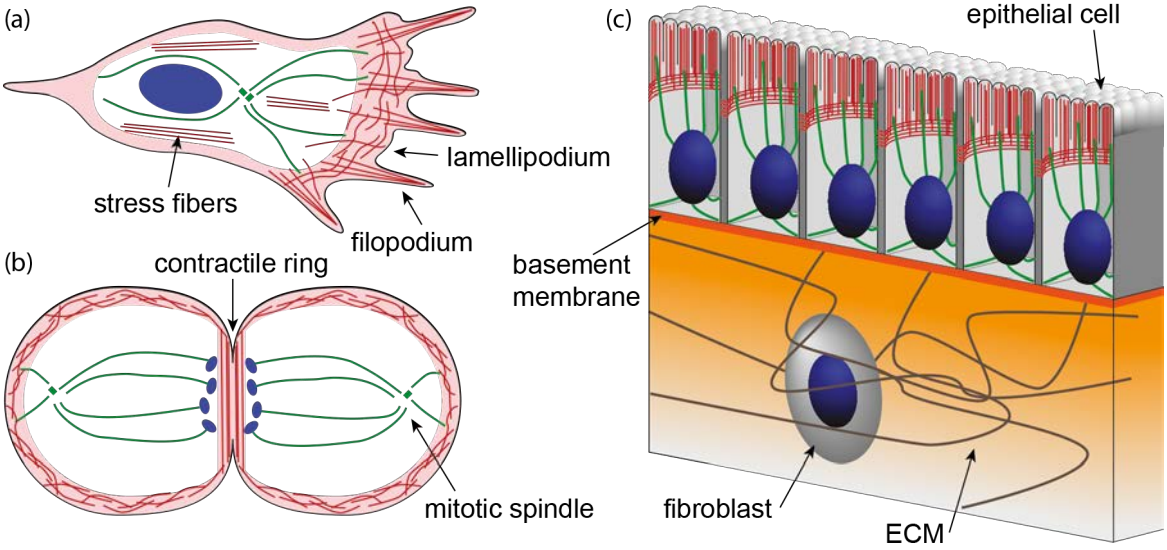
[8] A. Salhotra, H. N. Shah, B. Levi & M. T. Longaker, *Nat. Rev. Mol. Cell Biol.* (2020)

[9] N. Khalilgharibi *et al.*, *Nat. Phys.* **15**, 839 (2019)

[10] O. Chaudhuri, J. Cooper-White, P. A. Janmey, D. J. Mooney and V. B. Shenoy, *Nature* **584**, 535 (2020)

[11] L. A. Harris, S. Beik, P. M. M. Ozawa, L. Jimenez and A. M. Weaver, *Curr. Opin. Syst. Biol.* **17**, 24 (2019)

[12] P. Van Liedekerke *et al.*, *PLOS Comput. Biol.* **15**, e1006273 (2019)



▲ **FIG. 2:** Cells in isolation and in tissue. (a) Crawling cell. At the leading edge of the cell, actin filaments form a network that exerts forces on the cell, resulting in the creation of flat lamellipodia (cf. figure 1b) and rod-shaped extrusions known as filopodia. In the cell body, actin stress fibers (red) and microtubules (green) give the cell mechanical structure. The nucleus (blue) is carried along as cargo. Figure by Lucas de Kam. (b) In a dividing cell, the microtubules organise into a mitotic spindle (cf. figure 1a), which exerts forces on the chromosomes (blue), pulling them apart during division. A contractile actin ring (red) then splits the cell. (c) Cells form epithelial tissues at the various surfaces in a body, such as the gut, blood vessels, and the skin. The cartoon shows a simple columnar epithelium with a clear polar structure, in which the cells not only have an internal biopolymer network, but are also laterally connected to other cells, and supported by a basement membrane. Underneath the membrane fibroblast cells build an extracellular matrix (ECM) of other biopolymers, forming connective tissue between one epithelium and the next. Tissues get their mechanical properties from a combination of the intercellular (cytoskeletal) and extracellular polymer networks.