Spring 3-28-2022

Materials science and mechanosensitivity of living matter

Alison E. Patteson
Syracuse University

Merrill E. Asp
Syracuse University

Paul A. Janmey
University of Pennsylvania

Recommended Citation

Alison E. Patteson, Merrill E. Asp, Paul A. Janmey; Materials science and mechanosensitivity of living matter. Appl. Phys. Rev. 1 March 2022; 9 (1): 011320. https://doi.org/10.1063/5.0071648

REVIEW ARTICLE | MARCH 28 2022

Materials science and mechanosensitivity of living matter

Alison E. Patteson ; Merrill E. Asp ; Paul A. Janmey

Applied Physics Reviews 9, 011320 (2022)
https://doi.org/10.1063/5.0071648
CHORUS

Applied Physics Reviews REVIEW scitation.org/journal/are

Materials science and mechanosensitivity of living matter

Cite as: Appl. Phys. Rev. **9**, 011320 (2022); doi: 10.1063/5.0071648
Submitted: 15 September 2021 · Accepted: 8 February 2022 ·
Published Online: 28 March 2022

Alison E. Patteson,[1] Merrill E. Asp,[1] and Paul A. Janmey[2,a)]

AFFILIATIONS

[1]Physics Department and BioInspired Institute, Syracuse University, Syracuse NY, 13244, USA
[2]Institute for Medicine and Engineering and Departments of Physiology and Physics & Astronomy, University of Pennsylvania, Philadelphia PA, 19104, USA

[a)]Author to whom correspondence should be addressed: janmey@mail.med.upenn.edu

ABSTRACT

Living systems are composed of molecules that are synthesized by cells that use energy sources within their surroundings to create fascinating materials that have mechanical properties optimized for their biological function. Their functionality is a ubiquitous aspect of our lives. We use wood to construct furniture, bacterial colonies to modify the texture of dairy products and other foods, intestines as violin strings, bladders in bagpipes, and so on. The mechanical properties of these biological materials differ from those of other simpler synthetic elastomers, glasses, and crystals. Reproducing their mechanical properties synthetically or from first principles is still often unattainable. The challenge is that biomaterials often exist far from equilibrium, either in a kinetically arrested state or in an energy consuming active state that is not yet possible to reproduce de novo. Also, the design principles that form biological materials often result in nonlinear responses of stress to strain, or force to displacement, and theoretical models to explain these nonlinear effects are in relatively early stages of development compared to the predictive models for rubberlike elastomers or metals. In this Review, we summarize some of the most common and striking mechanical features of biological materials and make comparisons among animal, plant, fungal, and bacterial systems. We also summarize some of the mechanisms by which living systems develop forces that shape biological matter and examine newly discovered mechanisms by which cells sense and respond to the forces they generate themselves, which are resisted by their environment, or that are exerted upon them by their environment. Within this framework, we discuss examples of how physical methods are being applied to cell biology and bioengineering.

TABLE OF CONTENTS

I. INTRODUCTION

The evolution of living matter has been shaped by physical as well as chemical environmental factors, and presumably both have determined the physical properties of biological matter. These properties include the sizes, shapes, and mechanical properties of the cells and extracellular materials that comprise different life forms and the mechanisms by which cells detect and respond to physical stimuli. Living organisms are able to create materials and structures that are

far from equilibrium, either in a kinetically arrested state[11,12] or in an energy consuming active state[17] to produce mechanical responses that are often not yet attainable in synthetic materials, and for which quantitative theories analogous to those that guide development of synthetic materials are only beginning to be developed.[18] Much more is known about the biochemical and genetic mechanisms that underlie cell biology and physiology than about how cells and multicellular systems respond to physical stimuli, but genetics and chemistry alone are not sufficient to explain the form or function of cells and tissues. The rapid growth of mechanobiology and the reemphasis on mechanical studies of biological material have led to many demonstrations of selective responses of different cell types and tissues to physical cues.[20–24]

Here, we review recent advances in physical biology with an emphasis on how cells from a broad range of organisms form materials with controlled mechanical properties and how they respond to mechanical forces. Much of the recent emphasis in mechanobiology has focused on the responses of animal cells to factors, such as substrate stiffness, substrate viscoelasticity, and exogenous forces derived from other cells or external factors, largely because of the importance of these physical effects to diseases, such as cancer,[28] fibrosis,[21,29] and cardiovascular disease.[30] However, it is likely that nearly all cell types have mechanisms to sense and respond to mechanical stresses.[31] Therefore, we consider mechanobiology in widely diverse biological systems including animals, plants, protists, fungi, and bacteria.

II. STRUCTURAL PROPERTIES OF LIVING SYSTEMS FROM A POLYMER PHYSICS PERSPECTIVE

How a cell deforms in response to external forces or internally generated forces depends on the mechanical properties of the cells themselves and on the extracellular environment in which cells are placed when they form multicellular tissues or colonies. The mechanical properties of cells do not uniquely define the mechanical properties of the multicellular structures they form. Most animal cells are softer than the tissues in which they are found. The shear stiffness of fibrous tissues, for example, is largely dominated by the extracellular matrix not the cells themselves, although the presence of cells modulates the configuration of the tissue and how the tissues relaxes upon applied stress.[8] In contrast, biofilms formed by bacteria are often softer than the individual cells,[32] and fungal biofilms are generally as stiff as the individual cells.[34] The interface between cells and matrix is a site of active remodeling. Cells can remodel a matrix from within. Cells can cross-link, degrade, or actively pull on the fibers, and these processes can occur in response to mechanical forces and other stresses. For example, animal cells respond to artificial matrix by chemically and mechanically remodeling it, altering its stiffness, apparently to produce some optimal state.[36] Similar adaptations occur in bacteria and plant cells. Examples include the mechanical adaptation of biofilms by matrix production in response to fluid shear [37] and anisotropic expansion of plant cells by tension-dependent remodeling of the cell wall.[39]

The molecules that are important for the strength of biological materials are often long chain macromolecules or polymers. From the perspective of polymer physics, these structural molecules are generally stiff or semi-flexible filaments and are often highly charged polyelectrolytes. In animal cells, for instance, DNA and the three cytoskeletal polymers—F-actin, microtubules, and intermediate filaments[40]—are all polyelectrolytes. Many biopolymers are too rigid to be described as random coil polymers. Filaments such as F-actin and DNA are soft enough to be significantly deformed by thermal energy and can be classified as semi-flexible polymers. These polymers resist deformations by entropic mechanisms.[41,42] Stiffer biopolymers, such as collagen or microtubules, however, are better modeled as rigid objects. They resist deformation by enthalpic mechanisms involving stresses on chemical bonds.[43,44] At the scale of cross-linked networks of these biopolymers, the distinction between semiflexible and rigid is not absolute, but depends on the relation between the persistence length of the filament and the distance between crosslinks. For example, an actin filament in a dense network might be better modeled as a rigid rod [43] even though at larger length scales it is thermally fluctuating.[42] Flexible, random coil polymers are also present in biological structures. Examples include the protein elastin in the arterial wall, hyaluronan in the vitreous body of the eye, the polysaccharides pectin in plant cell walls, chitin in the wall of fungi and the exoskeleton of insects, and of course rubber, which is a mixture of polyisoprenes. Some flexible biopolymer chains and less flexible polysaccharides like cellulose, assemble into fibers that are stabilized by hydrogen bonds to form stiff or semiflexible filaments. True rubberlike elasticity, characterized by a linear relation between stress and strain over a wide range of strains, is a rarity in biological materials. Most soft tissues either stiffen or soften when deformed to biologically relevant strains, and the response can be very different for shear and uniaxial deformations. Stiffer materials in plants, fungi, and bacteria generally have a very small elastic limit and often rupture at modest strains. Even the polyisoprene of the rubber tree and other latex-forming plants is not used for mechanical purposes but rather appears to function as a barrier to predators and protection from environmental, non-mechanical stresses.[46]

Biological materials are rarely composed of polymer networks alone but are instead often composites of fiber networks with cells or particles embedded at variable volume fractions within the pores of the network. The widespread systems of fiber networks with globular inclusions range from intracellular actin networks filled with ribosomes of size $\sim$100 nm and extracellular collagen filament networks filled with $>10\,\mu$m diameter cells to fungal systems or mycelia filled with millimeter-sized particles of the soil in which they grow.

Figure 1 illustrates the prevalence of fibrous networks and inclusions within their meshwork, using examples from four different kingdoms. Three mammalian examples are shown in Figs. 1(a)–1(f), specifically (i) the actin cytoskeleton [Fig. 1(a)], which forms part of the fibrous network of the cytoplasm [Fig. 1(b)], (ii) the collagen matrix [Fig. 1(c)] that forms the fibrous component of many tissues [Fig. 1(d)], and (iii) fibrin [Fig. 1(e)] which makes up blood clots [Fig. 1(d)]. In the cell, the actin cytoskeleton has a mesh size of $\sim$300 nm,[4] as shown in the reconstituted actin network in Fig. 1(a). The cell environment is crowded, filled with actin but also intermediate filaments (red) and microtubules (green) that encapsulate organelles, such as clusters of ribosomal particles (blue and yellow) and parts of the endoplasmic reticulum (gray) [Fig. 1(b)].[6] In animal tissues, the main constituent of the extracellular matrix is collagen [Fig. 1(c)].[15] In fat tissue, as an example, the large, nearly spherical cells are entrapped in a relatively sparse network formed by the collagen fibers [Fig. 1(d)].[16] In a blood clot, the matrix is comprised of fibrin [Fig. 1(e)], encapsulating various types of blood cells within it and contracting around them due to the activity of blood platelets.[27]

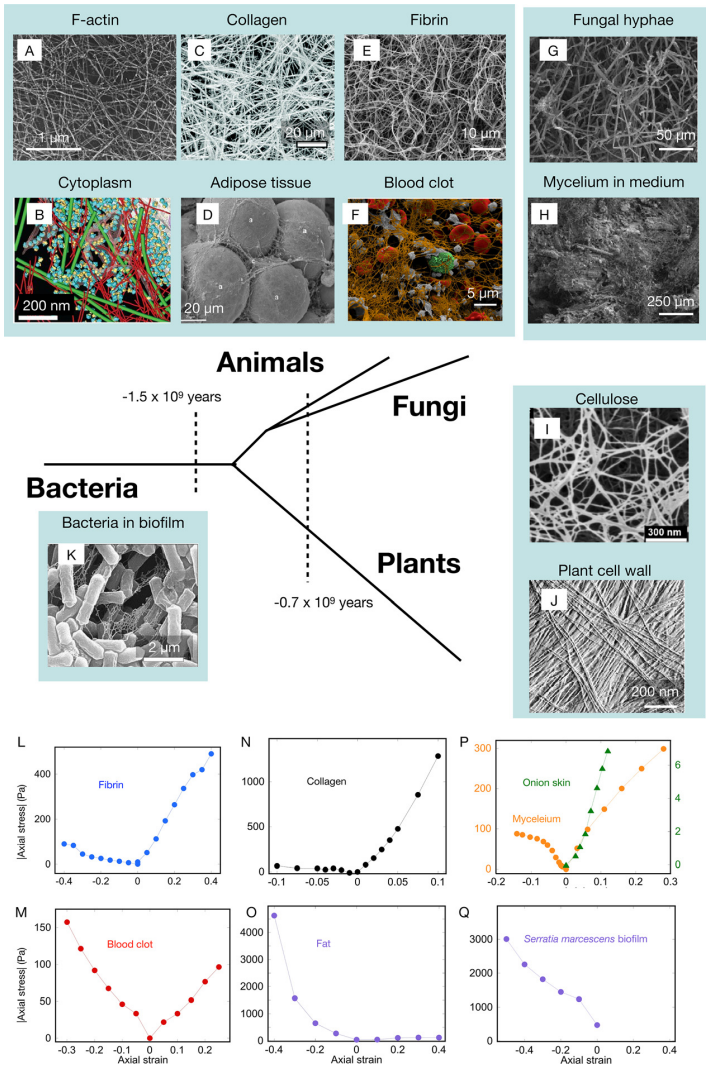

FIG. 1. Fibrous networks and inclusions in diverse biological materials. (a) Purified cytoskeletal actin filaments[4] and (b) a reconstructed image of the composite of cytoskeletal polymers and intracellular particles near the edge of the nuclear membrane.[6] (c) Purified collagen network[15] and (d) adipocytes within a sparse collagen network in fat tissue.[16] (e) Purified fibrin[25] and (f) a blood clot[27] showing cells trapped within the fibrin network that contracts around them. (g) Long filamentous protrusions of fungal cells[5] and (h) the mixture of fungal hyphae and the organic or inorganic particles within which they form a mycelium.[5] (i) Purified hemicellulose filaments[33] and (j) the complex of dense cellulose fibers and interspersed polysaccharides that form the skin of an onion cell.[35] (k) Bacteria held together by flexible extended exopolysaccharides in a biofilm.[38] Axial stress at different levels of axial strain (negative strain: compression; positive strain: extension) for collagen[10] (l), fat[7] (m), fibrin[10] (n), blood clot[8] (o), onion skin[35] mycelium[45] (p), and *Serratia marcescens* biofilm (q). (a) Reproduced with permission from Niederman *et al.*, J. Cell Biol. **96**, 1400–1413 (1983). Copyright 1983 Rockefeller University Press. (b) Reproduced with permission from Mahamid *et al.*, Science **351**, 969 (2016). Copyright 2016 American Association for the Advancement of Science. (c) Reproduced from Sauer *et al.*, Soft Matter, **15**, 3055 (2019). Copyright 2019 Author(s), licensed under a Creative Commons Attribution (CC BY) license. (d) Reproduced from Panettiere *et al.*, Eur. J. Histochem. **55**(2), 85–89 (2011). Copyright 2011 Author(s), licensed under a Creative Commons Attribution (CC BY) license. (e) Reproduced with permission from Janmey *et al.*, J. R. Soc. Interface **6**(30), 1–10 (2009). Copyright 2009 The Royal Society. (f) Reproduced with permission from Weisel and Litvinov, Res. Pract. Thromb. Haemost. **5**, 38–50 (2021). Copyright 2021 John Wiley & Sons, Inc. (g and h) Reproduced from Silverman *et al.*, Cloth. Text. Res. J. **38**(2), 119–133 (2020). Copyright 2011 Author(s), licensed under a Creative Commons Attribution (CC BY) license. (i) Reproduced with permission from Prakobna *et al.*, J. Mater. Sci. **50**, 7413 (2015). Copyright 2015 Springer Nature. (j) Reproduced with permission from Zhang *et al.*, Science **372**, 706 (2021). Copyright 2021 American Association for the Advancement of Science. (k) Reproduced with permission from the Obana *et al.*, J. Bacteriol. **196**, 1540–1550 (2014). Copyright 2014 American Society for Microbiology.

Biomaterials consisting of fiber network and inclusions are also found in fungi [Figs. 1(g) and 1(h)], plants [Fig. 1(j)], and prokaryotes [Fig. 1(k)]. Panel 1G shows a network of fungal hyphae formed in liquid medium,[5] illustrating the similarly between the structure of the open network of fungal hypha and that of the fibrin strands, although an important difference is the much larger length scale of the fungal network compared to that of the fibrin network. Panel 1H shows the more biologically realistic setting of the fungus, with the solid matrix that it forms around the solid particles and nutrients in which it grows, to form the fungal mycelium, a common material formed by both fungal and plant systems within the soil and other solid matrices.[5] Numerous similar dense structures are formed under different conditions depending on the species of fungus and the type of particle inclusion.[45,47,48] Figure 1(i) shows a reconstituted network of chemically modified cellulose fibers, the major constituent of many plant systems,[33] and Fig. 1(j) shows the much denser and oriented system of cellulose fibers that forms in the wall of the onion skin,[35] in which the cellulose fibers are held together by other protein and polysaccharide complexes and arranged into multiple layers with orderly differences in the alignment of filaments between different layers. The composite of extracellular polymers, usually polysaccharides and cells that constitute bacterial biofilms, is illustrated in Fig. 1(k).[38]

One striking feature of the three animal polymer networks and those of plant cellulose and fungal hyphae is that the isotropic networks of these fiber-like structures share many similarities. The filaments within the meshwork are nearly straight between network cross-linking points, and the connectivity of these networks at points where filaments intersect is relatively low, generally between three and four, and much lower than the isostatic point of stability in three dimensions,[49,50] which would be a connectivity of six.[50,51] This low connectivity and the rigidity of the polymer strands have been shown by multiple theories to produce mechanical responses that are highly variable with the magnitude of deformation and very different in both magnitude and strain dependence from the mechanical responses of soft materials formed by flexible polymers.[52] The major difference among these different open mesh works is the difference in their length scales, with mesh sizes of a few tens of nanometers for the dense cellulose networks to a few micrometers for networks formed by fibrin or collagen, to tens of micrometers for networks formed by fungal hyphae. The common feature of open meshworks surrounding particles with similar length scales is likely to be modified by factors, such as the relation between the mesh size and the filament persistence length or the size of the particle relative to the mesh size. These features are likely to determine if the mechanical resistance is primarily entropic or enthalpic, or if the network response is continuous or limited to specific filaments. Bacterial biofilms differ from the cell-fiber construct examples in that the exopolysaccharides of the biofilm are generally more flexible and less fibrous than the extracellular filaments formed by animal or plant systems or the stiff filamentous networks formed by fungal colonies.

While there are a number of similarities among these biological materials, it is important to note that the tissues and other macroscopic materials made from these fibrous components differ strongly in the size and mechanical characteristics of the inclusions within them. Typically, animal cells, which lack a rigid cell wall, have elastic moduli similar to those the extracellular matrix networks in which they are imbedded. The inclusions in mycelium or plant walls can vary greatly in their size, shape, and rigidity. The relative contributions of the fibrous networks and the mechanical properties of the inclusions within them to the emergent mechanical properties of the composite can depend on many factors and can vary significantly. This is an open area of current theoretical and experimental study.[53]

III. MECHANICAL RESPONSE OF BIOLOGICAL MATERIALS

A. Resistance to uniaxial strain

While the shear mechanics of fibrous networks alone have received extensive study, the effects of inclusions within fiber networks are still being characterized. There are several model systems for combinations of fibers and cells or particles. Most are from animal derived systems, largely because these systems have been more widely studied. Figures 1(l)–1(q) illustrate some of the differences between open fiber networks and fiber networks with inclusions that become evident by comparing the responses of these materials to uniaxial compression or extension. Figure 1(l) shows that a purified collagen network exhibits relatively linear stress–strain response in tension and a more nonlinear but much weaker resistance to deformation in compression. The large difference in compression and extension results from the fact that stiff fibers, such as collagen and fibrin, buckle under compression but undergo much stiffer resistance to deformation in stretching.[10,54] The low connectivity between fibers also contributes to an increased resistance to extension. This occurs as stresses are placed on the network junctions during extension,[12,55,56] accounting for the larger apparent Young's modulus in tension than in compression. In contrast, intact tissues, in which collagen forms the bulk of the extracellular matrix but cells occupy most of the volume, respond to uniaxial deformation very differently from the purified collagen network, and similar to the response of the fibrin network with inclusions that constitutes the blood clot. Figure 1(m) shows that for fat tissue [7,8] the relation between stress and strain is nonlinear even at relatively modest strains of a few tens of percent, and that the tissue is much stiffer in compression than in tension, the opposite of the response of the open collagen network.

Qualitatively similar mechanical responses are seen in fibrin networks both with and without inclusions. Figure 1(p) shows that, like collagen, fibrin networks have nearly linear responses to uniaxial strain in both tension and compression, but the resistance to extension is greater than it is in compression. This is consistent with the expectation that fibrin fibers will buckle in compression but stretch in tension. When particles such as red blood cells are enmeshed within a contracting fibrin network, as in blood clots [Fig. 1(f)], the differences between uniaxial tension and compression fade [Fig. 1(o)], and the material becomes similarly stiff in compression as in extension.

The general features of resistance to uniaxial strains are also observed in fungal networks that form mycelium-based materials embedded with inclusions [Fig. 1(p)], which is orders of magnitude stiffer than blood clots or soft animal tissue.[45] The initial stress–strain relations are similar for compression and extension, but this material softens at large compressive strains [Fig. 1(p)]. This could possibly be due to plastic deformation, whereas it maintains a nearly linear stress–strain relation in extension. The fungal systems are particularly interesting and adaptable to practical application as renewable construction or packaging materials. The rigid cell wall of the fungus is comprised largely from a dense network of chitin polymers, which imparts the cell with a Young's modulus of ∼GPa when tested by

indentation.[34] The response to tension of plant cell walls, formed of a composite of collagen fibers containing softer islands of pectin and other polymers,[35] is shown in Fig. 1(p). Like other tissues, the cellulose-based cell walls in onion skin exhibit a range of linear response, but there is also an apparent stiffening at very small strains. Bacterial biofilms are nearly linear in response to compression to at least to strains of 50% [Fig. 1(q)].

The results of these uniaxial mechanical tests illustrate how profoundly particle inclusions alter elastic responses of the fibrous network that includes them. Such studies have also demonstrated that most of the mechanical resistance depends on the fiber network, because enzymatic digestion of fibrin strands or collagen fibers under conditions that leave the embedded cells or particles intact, almost completely reduces the elastic response of that tissue, leaving largely a viscous response as cells slide past each other.[57] The elastic properties of the open networks in uniaxial deformation are themselves highly time and length dependent because of the significant poroelastic response of these hydrogels to uniaxial stresses. The data in Fig. 1 all derive from measurements at steady state when the poroelastic relaxation is essentially complete, but other studies have shown how strongly the response of collagen and fibrin networks depends on the rate of uniaxial deformation, and the importance of time-dependent changes in network and tissue stiffness has recently been reviewed elsewhere.[20]

B. Shear modulus in compression and extension

The unusual responses of fiber networks with and without inclusions are more obvious from measurements of the shear modulus when samples are compressed or stretched. Figure 2(a) shows an example of the experimental method in which a hydrogel or a tissue is attached to two parallel plates that can be moved vertically to impose static uniaxial compressions or extensions, at the same time that the low strain shear modulus is measured by oscillation.[58] Figure 2(b) shows that collagen networks exhibit a highly nonlinear relation between shear modulus and uniaxial strain. In compression the shear modulus decreases, consistent with the low slope of the stress strain curve shown in Fig. 1, and it strongly increases as the sample is stretched. The change in shear modulus with compression is attributed to filament buckling, and the increase in stretch is attributed to the increased contribution of crosslinks to the shear modulus as forces are applied to them in the tensed sample.[11,56] The response of the shear modulus to uniaxial stress in the fiber network is strongly modified when volume conserving objects are placed within it [Fig. 2(b)]. When cells are embedded in the network, such as in adipose tissue or liver, the materials stiffen when they are compressed, but not when they are stretched.[8,59,60] Reversal of stiffening in extension and softening in compression of collagen gels also occurs if isolated cells are cultured within the collagen network to form a simplified artificial tissue construct.

A similar pattern of responses is also seen in fibrin-containing materials. Figure 2(c) shows that gels formed by the fibrous polymer fibrin, like collagen networks, soften in compression but stiffen in extension. In contrast to the open fibrin network, fibrin containing approximately 30% volume fraction polysaccharide beads exhibits the opposite response to uniaxial deformation: the fiber and bead composite becomes stiffer in compression but does not stiffen much if at all in extension. A very similar response to uniaxial deformation is observed in contracted blood clots, in which the fibrin strands have wrapped

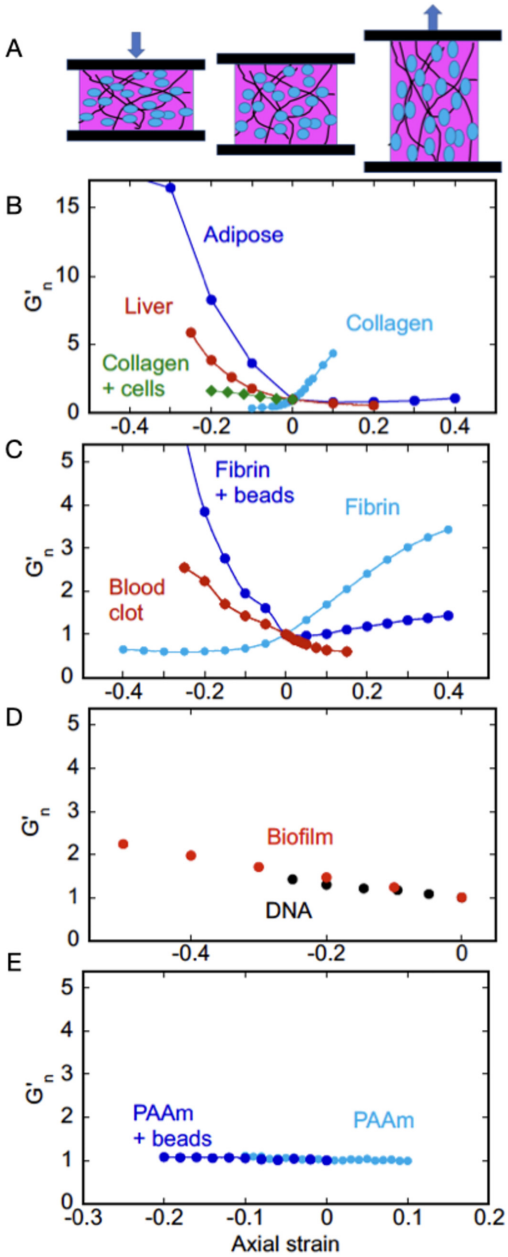

FIG. 2. Change in shear modulus with uniaxial compression or extension. (a) Schematic for application of static uniaxial strain and dynamic shear measurements.[5] Dependence of shear modulus on axial strain for (b) collagen with and within cellular inclusions, fat, and liver;[7,8] (c) fibrin with and without inclusions and whole blood clot;[8,10] (d) crosslinked DNA and Serratia marcescens biofilm; and (e) crosslinked polyacrylamide with and without particle inclusions.[8]

around red blood cells. The shear modulus increases with compression but decreases slightly with extension.

In contrast to the systems of stiff filaments, bacterial biofilms [Fig. 2(d)], which have to date only been studied in compression, exhibit a relatively weak stiffening that is mimicked by crosslinked purified DNA, which is often part of the external polymer network of the biofilms. Figure 2(e) shows that, as expected for a simple linear elastic material like a polyacrylamide gel, the shear modulus remains constant when the uniaxial strain is imposed and is not affected by inclusion of large spherical particle at volume fractions below the jamming transition.[8]

The transition from compression softening fiber networks to compression stiffening composites of fiber networks with embedded cells or particles has been interpreted by a number of different theoretical studies (reviewed in Ref. 60) If the particles are relatively soft compared to the fibers, then when the composite is macroscopically compressed, volume-conserving particles decrease in length along the strain direction, but biaxially expand in the orthogonal plane. This biaxial extension drags with it the fiber network to which the inclusion is attached, and open fibrous networks, such as fibrin or collagen, exhibit a very strong stiffening effect when deformed by biaxial stretch.[61] This effect dominates over softening due to the limited number of fibers buckling and results in compression stiffening.[8] An alternative theory considers the case where the particle inclusions are stiffer than the network that surrounds it. Here, a different mechanism based on formation of force chains and highly nonuniform deformation fields again leads to stiffening in compression, even when the fibers that account for the elastic response by themselves would soften in compression.[59] When fibers are isostatically connected, then another mechanism due to resistance to the bending angle induced in the crosslinked network can also lead to compression stiffening.[62] The striking effect of these models and experiments is that the bulk of the elastic response comes from the fiber network itself, and not from the stiffness of the particles within it, until very high volume fractions where the particles form percolating networks or become jammed, which would also lead to compression stiffening by a separate mechanism, but not one that is feasible at the low volume fractions of particles at which conversion of softening to stiffening is observed. Similar experiments of shear modulus under static uniaxial loading do not yet appear to have been done with fungal, plant, or bacterial systems, but the prediction is that the fibers within the materials would carry the most load during shear measurements, and that the response to uniaxial strain will depend on the constraints that particles within the network impose on the relaxation modes that the fibers can access as a sample is macroscopically deformed.

Not all fibrous networks soften in compression. For example, electrospun fiber networks of fibrinogen stiffen in compression, whereas the randomly polymerized form of fibrinogen, fibrin, soften in compression.[63] Similarly, networks formed by self-assembly of amphiphilic gemini molecules into radial asters with a common core and diverging semiflexible extensions that grow long enough to interpenetrate into neighboring asters, also form elastic solids that stiffen in compression.[64] The stiffening of electrospun fibrin networks appears to be due to their greater connectivity, and perhaps their regular geometry, and the aster-like networks resemble composites in having dense nodes surrounded by sparser networks, even though they are formed by a single material.

IV. FORCES GENERATED BY LIVING SYSTEMS

Biological matter employs multiple mechanisms to do mechanical work. Plants and other photosynthetic organisms use energy derived from absorbed photons that then is converted to chemical energy sources eaten by other organisms and eventually converted to proton gradients, adenosine triphosphate (ATP), or a small number of other high energy out of equilibrium systems. Although the sources of energy and the mechanisms for producing mechanical work are similar in various organisms, the levels of force and the distances over which forces are exerted by animals, plants, bacteria, and fungi vary over a wide range. Examples of the force generating systems in biology are summarized in Figs. 3 and 4 and in Table I. The magnitudes of mechanical stresses generated by various organisms are shown schematically in Fig. 5.

A. Force generation in eukaryotic systems

In animal cells, there are several physically distinct mechanisms of force production that lead to coordinated movement, often involving mechanisms that reorganize the cortical cytoskeletal network. Probably the most direct and familiar are the molecular motors, such as myosin or kinesin, in which a conformation change in a large protein, coupled to ATP hydrolysis to adenosine diphosphate (ADP) and release of phosphate causes one part of a protein that is bound to a stationary filament or membrane to move relative to another part of the protein that is bound to a cargo or to another filament [Fig. 3(a)]. Typically, the movement of a single such force-production event, or step, is a few nm long and generates a few pN of force, consistent with the amount of chemical energy (~14 kT or 57 pN·nm) of ATP hydrolysis under biological conditions. Similar, slightly smaller, forces can also be produced by the addition of subunits to growing filaments of actin or tubulin, in which asymmetric filament growth requires ATP or guanosine triphosphate (GTP) hydrolysis to avoid microscopic reversibility,[65] but in which a conformational change driven by nucleotide hydrolysis does not perform the mechanical work. Instead, thermal fluctuations of the filament end are exploited by the adding subunits to generate force against a barrier, such as the cell membrane in a mechanism termed the thermal or Brownian ratchet[66] [Fig. 3(b)]. Coordinated formation and contraction of an acto-myosin network at the cell periphery can produce internal pressures [Fig. 3(c)].

Motor-filament systems can be built into larger organized structures, such as the microtubule-based cilium, in which motors drive sliding of microtubules past each other [Fig. 3(d)], the actin-based sarcomere in the muscle [Fig. 3(e)] or the microtubule-based mitotic spindle.[67] Coupling many motor proteins in series and parallel can produce much larger forces and move much longer distances. A single sarcomere, consisting of hexagonally packed actin and myosin filaments, can generate 10–100 pN,[68] depending on its rate of contraction, and a typical skeletal muscle can generate hundreds of kPa of stress.[69]

The interpretation of these single molecule force generating mechanisms as strictly analogous to the mechanisms of macroscopic machines, and the language of these studies, characterized by terms, such as lever arm, duty cycle, or stall force reinforces the similarity between molecular motors and their macroscopic counterparts. There are also some important differences. Molecular motors function in water, and thermal energy (~4 pN·nm) is on the same order as the work done in a single motor step. Therefore, the idea that productive

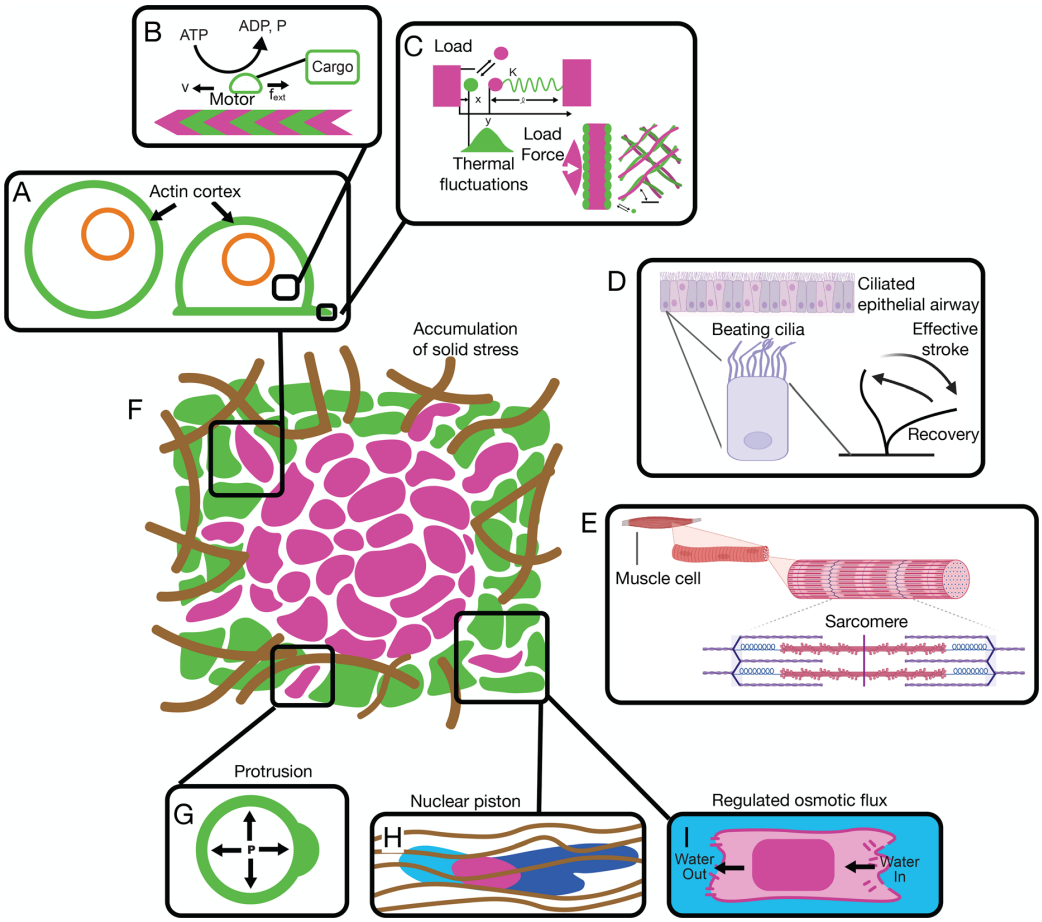

FIG. 3. Force generation mechanisms in biological systems. Linear movement along a filament is achieved by ATP-hydrolyzing motor protein enzymes (a) or by the addition of monomer units to a growing rigid filament using rectified thermal motions (b). Collective movement of the actomyosin network in the cell cortex generates contractile stresses and intracellular pressures (c). Coordinated sliding of stiff microtubules along each other within a bundle generates flexing motions that drive wavelike motions in cilia (d) and myosin-dependent sliding of actin filaments within a sarcomere leads to linear contraction (e). When cells are attached to a substrate or within a 3D tissue (f), local weakening of the cell cortex allows intracellular pressure to drive directional extension (g). Resistance to intracellular water flow by the large and relatively rigid nucleus can generate pressure gradients between front and back of the cell that enable protrusion, with the nucleus acting as a piston (h). Active, local regulation of water flow can also generate cell motility in 3D using osmotic pressure rather than cytoskeletal motors as the driving force (i). Created in part with BioRender.com (BioRender, 2022).[172]

work can be done by harnessing thermal energy using nonuniform interaction fields between, for example, myosin motors and actin filaments, has also been proposed to contribute to the work done during a motor step.[70] The anionic polyelectrolyte properties of the track on which motor proteins run, F-actin or microtubules, and the polycationic sites at the motor head that interacts with the filaments contribute additional modes of interaction that distinguish molecular motors from traditional machines. For example, the strong salt dependence of the weak binding state of myosin to F-actin, involving polycationic regions of myosin and the anionic surface charge of F-actin,[71] has similarities with the condensation of polyvalent counterions to a linear polyelectrolyte that can work together with the stronger, more specific myosin–actin docking sites that determine the strong binding state.[72] The movements generated by ATP-consuming molecules can lead not only to controlled unidirectional movement, as on a filament track, but also to random non-thermal motions[73] that generate anomalous diffusion and other features of active matter systems like cell monolayers,[74] cytoplasmic mixing,[75] or bacterial swarms.[76]

On the larger length scale of whole cells or tissues, these molecular mechanisms can work together with processes, such as water flow and osmotic pressures, to generate a large range of mechanical stresses over much larger length scales. In growing mammalian tumors or embryos, for example, the metabolic synthesis of new cellular materials and the resulting motor driven forces produce solid stresses on the

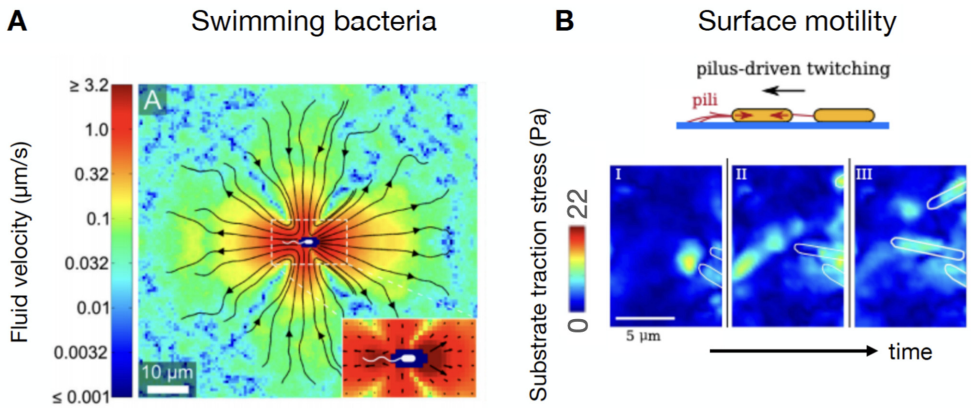

FIG. 4. Force generation in bacteria. (a) Flagellated bacteria swim using a flagella rotatory motor that propels the cell body forward. The viscous drag on the cell body is equal and opposite to the viscous drag on the bacteria flagella, such that bacteria impose an extensive force dipole or stresslet on the surrounding fluid. (b) On surfaces, many bacteria move use type iv pili to move. These pili are adhesive appendages, which extend and retract from the cell envelope. In both these cases, researchers have embedded small fluorescent beads to trace the local deformations of the ambient fluid or cell substrate, which deform as a result of the stresses imposed by the cells. A was adapted from Drescher *et al.*, Proc. Natl. Acad. Sci. **108**(27), 10940 (2011).[3] Copyright 2011 Author(s), licensed under a Creative Commons Attribution (CC BY) license. B was adapted from Sabass *et al.*, Proc. Natl. Acad. Sci. **114**(28), 7266 (2017).[13] Copyright 2017 Author(s), licensed under a Creative Commons Attribution (CC BY) license.

order of hundreds of Pa. These stresses are evident from the splaying out of incisions made on the surface of an excised tumor. The solid stresses generated by human tumors are sufficient to deform the normal tissue surrounding the growing tumor leading to collapse of blood vessels and other pathologic changes.[28,77] Individual animal cells can generate hydrostatic pressures on the order of kPa by contracting their actomyosin-based cortex [Figs. 3(c) and 3(g)]. Localized contraction, or localized weakening of the cortical cytoskeleton, is used by many cells in 3D to generate directed motility, often in a process called blebbing.[78] Cells can also use contractility to pull against the stiffer nucleus, using it as a piston to generate pressure gradients that can lead to directed motion [Fig. 3(h)].[79] Because of the large ionic differences between the inside and the outside of animal cells, active control of ion flux or water flow is enabled by specific transmembrane protein complexes. As a result, controlled movement of water into one end of the cell and out of the other can also generate motility by a mechanism that does not require acto-myosin activity [Fig. 3(i)].[80,81]

The ionic imbalance across biological membranes that separate the inside from the outside of cells can generate forces that are much larger than those generated by motor proteins that move along a filament track. The upper limit to actomyosin-generated stresses at the cell membrane appears to be on the order of kPa (Fig. 5), which is comparable to the osmotic pressure generated by less than 1 mM monovalent salt. In vivo, concentration differences across the cell wall are often hundreds of mM, allowing for potentially much larger pressures. Plants and fungi, which have much stiffer cells walls than animal cells, often use water flow and ion concentration gradients to produce large pressures that can deform the cell wall and allow growth and protrusion. Under many growth conditions, fungi will extend long protrusions termed hyphae that have typical diameters of 1 μm but are mms in length. The forces generated by fungal hyphae, such as formed by *Candida albicans*, are in the range of 1 MPa,[82] and sufficient to penetrate soft elastomers, blood vessels, and surgical implants, which makes them clinically dangerous if they infect a compromised host. Fission yeast generate similar levels of stress,[83] and other fungi, such as *Magnaporthe grisea*, can generate 8 MPa protrusive force,[84] which enables them to invade rice grains and break through relatively rigid materials, such as polyvinyl chloride. These large stresses cannot be generated by protein motor systems, but instead rely on generation of osmotic pressures inside the fungus that are directed into movement in a specific direction by selective softening of the fungal wall at the site of protrusion.[85] Single plant cells also generate >MPa internal pressures, and the pressure inside the cell is an important regulator of the cell's rheology, as it pushes against the cell wall and resists further deformation.[86] The high local stress generated by these pressures enables a relatively soft plant to slowly break through a rigid barrier formed by compacted soil or pavement.

B. Force generation in prokaryotic systems

Force generation by prokaryotes presumably evolved before eukaryotes appeared. Some of the force-generating mechanisms of prokaryotes share features with eukaryotic systems, but the major cytoskeletal fibers and motor proteins, such as myosin, dynein, and kinesin, are missing in bacteria, which use alternative structures and force generating strategies. While much of the research conducted in bacteria focuses on a few key model organisms, such as *Escherichia coli* and *Pseudomonas aeruginosa*, many aspects of the force-generating and mechano-sensing mechanisms discussed in this Review are conserved over many species.

1. Swimming

The physical world of cells is quite different from our own. Bacteria are small (~1 μm) and typically live in fluidic environments.

TABLE I. Force generation in biological systems.

Force/energy	Examples	Protein/structure involved	Magnitude of force/stress	References
ATP hydrolysis by motor proteins with large conformational changes	Muscle contraction ciliary; beating in epithelia; rotation of flagella	Myosin/F-actin kinesin or dynein / microtubules Flagellar rotors / cell wall	1–10 pN / motor protein ∼ 100 kPa for skeletal muscle	112
Surface tension	Softening of cell cortex leads to more spreading	Activation of actin disassembly/inactivation of myosin		113
Thermal ratchet	Protrusion or filipodia and lamellae at the leading edge of animal cells	Actin assembly at the leading edge of cytoskeleton	∼2 pN per monomer addition ∼ kPa at filopod tip	66, 114, 115
Actomyosin contraction or osmotic pressure coupled to local cortical softening	Protrusion in animal cells plant wall or hyphae extension in plants and fungi	Increased internal pressure coupled to local destabilization of actin cortex in animal cells or cell wall softening in plants, fungi, and bacteria	∼100–1000 Pa for single animal cell ∼100 MPa for fungal hyphae	78, 86
Cell-generated pressure difference	Nuclear piston	Actin/myosin/small GTPases drive contraction that pushes nucleus	kPa	79, 116
Regulated water transport	water or ion flux at cell membrane: in at front, out at rear	aquaporin/ion channels	kPa	80, 81, 117
Pressure due to increased mass/ osmotic swelling	Volume change as cells multiply during development or tumorigenesis	General metabolism and cell division	100 Pa in brain	118
Sarcomere/muscle	Muscle contraction	Sliding of arrays of myosin (thick) filaments along array of F-actin	10–100 nN per sarcomere; 100 s of kPa in muscle	68, 69
Waving of cilia	mucus flow at surface of ciliated epithelial cells	Microtubules in bundle within core of cilium slide past each other due to dynein motors	0.2 nN per cilium	119
Swimming and swarming Flagella rotary motor driven by a proton motive force	*E. coli*	Torque generating unit: MotA/MotB complex; cytoplasmic ring (C-ring): FliM, FliN, and FliG	2000 pN·nm; 200 pN·nm per stator; 10 pN per motor	91
Gliding or twitching surface motility-Type IV pili	*P. aeruginosa*	PilY1	10 pN	113
Substrate buckling	*Vibrio cholerae* and *Pseudomonas aeruginosa* biofilms	Matrix components maintaining cell–cell cohesion and cell–surface adhesion	Individual wrinkles—30 mN/m; Whole colony buckling—100 kPa	79, 116
Osmotic pressure	*Vibrio cholerae* biofilms; *E. Coli* swarms	Non-crosslinked extracellular polymeric substances (EPS) in biofilms; possibly lipopolysaccharide in swarms	2 kPa in biofilms	80, 81, 117, 120

This is the realm of low Reynolds number, where fluid viscosity dominates. The Reynolds number, $Re = \rho UL/\mu$, is given by the ratio of inertial forces ($\rho U^2/L$) to viscous forces ($\mu U/L^2$), where U is a typical fluid speed, L a typical length scale, ρ the density of the fluid, and μ the fluid viscosity. Our intuition of motion is built in a world of high Reynolds number ($\mathrm{Re} > 10^4$), where inertia dominates and objects in motion tend to stay in motion. Due to their small size and slow speeds, the Re of a bacterium is on the order of 10^{-4}. At these low Reynolds numbers, viscosity quickly damps out motion. As described by Purcell, the analogous low-Re case for humans is trying to swim in a pool full of molasses and only being able to move any part of your body at 1 cm/min.[87]

One of the earliest forms of motility and most common among bacteria species is the flagellar propulsion system [Figs. 4(a) and Table I; see also Fig. 9].[88] The bacterial flagella is a thin helical filament driven at its base by a molecular rotary motor.[89] The rotating filament generates a thrust that propels the cell body forward against viscous

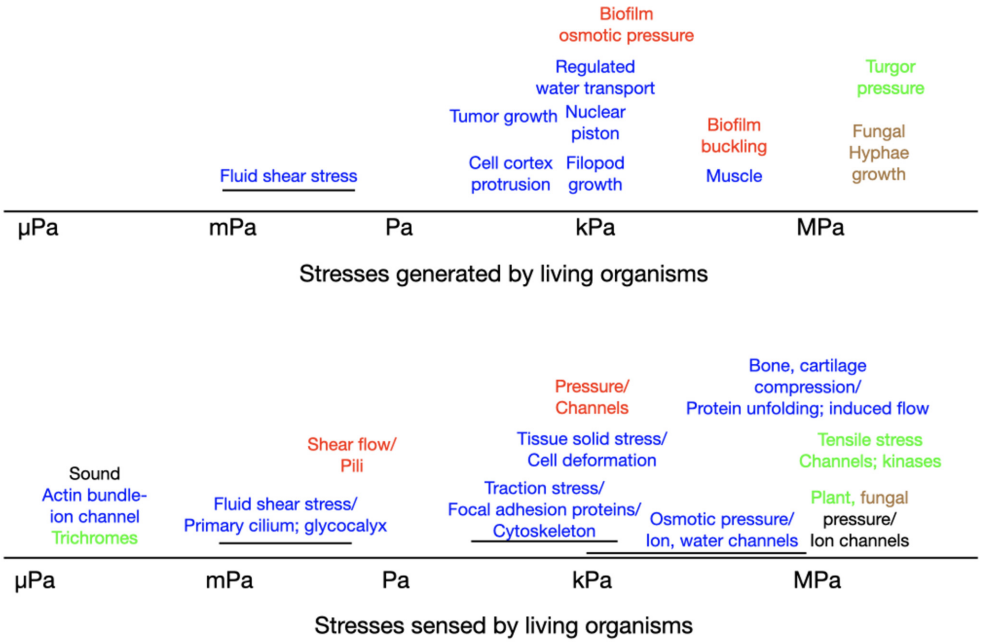

FIG. 5. Magnitudes of stresses generated and sensed by living organisms. Red: bacteria; Blue: animals; Green: plants; Brown: fungi.

drag. Typical flagella rotation rates are 100 Hz, propelling the cell forward at 10 μm/sec in water.[90] The motor operates at nearly constant torque of approximately 4500 pN·nm.[91] In a Newtonian fluid, the torque is proportional to the fluid viscosity and flagella rotation rate ω. If the fluid is as viscous as honey, the flagella rotate slowly. In water or other low-viscosity fluids, the flagella rotate quickly. In this way, the bacteria flagella could in principle read out the viscosity of the ambient fluid based on the rotation rate of the flagella.

2. Movement on surfaces

Whereas bacteria swimming is typically individual, surface living is communal. Most surface-dwelling bacteria live in biofilms, which are slow-growing largely sessile communities of bacteria protected by a self-secreted extracellular polymeric substance matrix.[92,93] The conversion of swimming to surface motility occurs by a coordinated genetic reprogramming that is triggered by mechanosensing mechanisms discussed in Sec. V and Fig. 7. One of the most commonly studied appendages for bacteria surface motility are the type IV pili (Table 1). Type IV pili enable a type of surface motility known as twitching in *Pseudomonas* and *Neisseria* and social gliding in *Myxococcus xanthus*. Type IV pili are motorized adhesins that bind to surfaces and other cells. Swimming cells possess a small number of these pili that can adhere to surfaces when bacteria come into contact. These small appendages (5–8 nm in diameter, several micrometers in length) extend and retract, binding and unbinding with surrounding surfaces to enable net motion.[94] Single pili generate retraction forces on the order of 10 pN[95]—and at the collective cell level up to 50–100 pN[13] [Fig. 4(b)], and thus serve as points of force transfer between the cell and its environment.

3. Collective biofilm expansion

The onset of biofilm formation corresponds to a shift from single cell to collective structures. Single cells are more susceptible to environmental stresses in comparison with the slime-filled biofilm communities they construct, which offer more protection against shear flows,[96] toxins (e.g., antibiotics and disinfectants),[97] and invasion by other microbial species.[2] Biofilm formation typically proceeds through a series of steps[93,98,99] [Fig. 7(a)]. One of the first steps is irreversible attachment to a surface. Once attached, bacteria begin growing and dividing, forming a dense monolayer and producing extracellular polymeric substances (EPS). The EPS is composed primarily of long polysaccharides that give the colony its strength and adhesion.[100,101] Over time, three-dimensional biofilm structures emerge,[102] and the biofilm matures. In the final stages of a biofilm lifecycle, parts of the biofilm detach and disperse, releasing mature cells into the environment and allowing the cycle to begin again. Biofilm growth thus depends on several physical factors that mediate cell-cell interactions and the properties of the biofilm as a whole.

The mechanical properties of the biofilm are largely dominated by the composition of the extracellular matrix.[100,101] Biofilms are viscoelastic in nature. Their mechanical response to constant shear stress is consistent with that of organic polymers and other viscoelastic

biological fluids.[103] Over shorter time periods on the order of seconds, biofilms can respond to shear like elastic solids, whereas the behavior of linear viscous fluids is seen at longer times.[96] Depending on bacterial species and the degree of expression of different components of the EPS matrix, the storage modulus G' for mature biofilms can vary over several orders of magnitude, from 0.1 kPa to over 10 kPa.[100] Biofilms can adapt to the mechanical forces in their environment: biofilms grown under higher shear are cohesively much stronger than those grown under lower shears.[96]

While the EPS matrix has traditionally been considered passive in the context of biofilm expansion, new work is showing a number of ways by which the EPS matrix supports and generates force production within a growing biofilm. In particular, EPS supports internal stress generation[104–106] and osmotic pressures that facilitate biofilm growth.[2,107] Internal stress in the network is generated as cells grow and divide in the EPS matrix, stretching and compressing the matrix. The EPS matrix is highly viscoelastic[100,103] and can support and transmit these mechanical stresses at length scales relevant to the whole biofilm structure. Friction between the biofilm and its substrate further increases stress.[108] These internal stresses cause the biofilm to fold and form macroscopic wrinkles over the timescales of days (Table 1).[104–106,109] The wrinkles relieve internal stress in the biofilm and have been shown to be triggered in localized region of cell death where the biofilm is thinner and weaker.[109] Intriguingly, these wrinkles open up channels in the biofilm through which fluid can flow.[104] This facilitates the biofilm growth by enhancing nutrient transport throughout the biofilm at rates much higher than diffusion alone. In recent work by Cont *et al.*, *Vibrio cholerae* biofilms were shown to deform soft substrates and disrupt epithelial tissue[110] (Table 1) through a buckling instability reminiscent of Euler buckling where the internal compressive stress trigger transverse deformations.

EPS production increases biofilm expansion.[2,107] This might be surprising given the strong viscoelastic properties of the EPS that might resist outward growth of the biofilm. However, new work shows that EPS production enhances biofilm expansion by generation of osmotic pressure gradients.[2,107] Most biofilm studies are conducted on nutrient-filled agar substrates, and the high local concentrations of polymer molecules in the biofilm produce an osmotic pressure difference between the biofilm and the agar substrate. This pressure gradient causes a flow of nutrient-rich fluid from the substrate into the biofilm, causing the biofilm to swell and expand. Over time, secreted polymer molecules cross-link to form the EPS matrix, which reduces their osmotic effect. Thus, EPS osmotic pressures at the expanding edge of the biofilm and cross-linking of the matrix in the core together control the morphology and growth of the biofilm. The effects of osmotic pressure are evident when growing bacteria on substrates of varying agar concentrations. Biofilms are more spread on softer less-concentrated agar substrates compared to harder more-concentrated agar substrates [Fig. 7(b)].[2,106,111] This effect is attributed to the smaller agar gel pore size: as agar concentration increases, the agar gel pore size decreases, limiting the rate of nutrient-rich fluid transport through the substrate and to the biofilm, decreasing biofilm growth.

V. BIOLOGICAL RESPONSE TO PHYSICAL STIMULI

Some of the mechanisms that cells use to produce force can also be used as sensors of force or sensors of the resistance of the environment to cell-generated forces. For example, the primary cilium is a microtubule-based protrusion at the surface of some epithelial cells that is similar to the cilia that produce waving motions to transport surface fluids when the microtubules are moved by motors, except the primarily cilium lacks the motor proteins that can actively move microtubules. When external fluid flows rather than cytoplasmic motors bend or rotate the primary cilium, ion channels can be activated or protein domains unfolded to initiate intracellular signals.[121] Bacteria have similarly adapted their flagella and pili to both produce force and respond to it, as discussed in Sec. IV B and Table II. These and many other structures have evolved to enable cells to sense and respond to their mechanical environment.

The magnitudes of stress that activate specific sensors in different organisms vary over a very large range, from >MPa for the turgor pressure and tensile stresses that distend the cell walls of plants, bacteria and fungi or compress our joints when we walk to <0.1 Pa stresses caused by fluid flow of blood or urine at the surfaces of vascular endothelial cells or renal epithelial cells to the μPa levels that move the surfaces of the hair cells in the ear when we perceive sound. Examples of the types of mechanical stresses to which biological objects respond are summarized in Table II. Despite the wide range of stresses, some of the sensors in these diverse force settings are nearly the same. For example, the ion channels piezo-1 or 2 function as a mechanosensor in animal cells[122] as well as plants[123,124] to alter conductance of Ca^{2+}, which elicits many acute responses in nearly all cell types. Bacteria do not express piezo isoforms, but they do express other mechanosensitive channels,[125] some also expressed in plants,[126] that alter ion conductance in response to force. In each case the ion channels are composed of transmembrane proteins that are embedded in the lipid bilayer that either forms the plasma membrane surface of an animal cell or underlies the much stiffer polysaccharide and protein-based cell walls of bacteria, fungi, and plants. Much larger stresses are needed to strain stiff cell walls than are needed to deform the plasma membrane, but in each case similar magnitudes of strain are transmitted through the lipid bilayer to the ion channel protein complex. Several ion channels including piezo-1 can be activated either by stresses within the plane of the lipid bilayers or by applying point forces to proteins domains that lie either inside or outside the cell.

Numerous mechanisms have been reported to be involved in the ability of animal cells to detect the viscoelastic properties of the surface or matrix to which they adhere as well as to sense the forces applied to them by other cells or global effects, such as gravity. Some of the mechanisms involve the same complex structures that generate forces, and others involve multiprotein complexes that change structure, binding affinity, or dissociation rates when forces are applied to them. The molecular complexes and reactions of mechanosensing by animal cells have been extensively reviewed elsewhere[23,127] and are summarized in Table II. Here, we discuss in more detail some examples of mechanical response in bacteria and plants and illustrate those aspects of mechanosensing that appear to be most widely conserved among different life forms.

A. Mechanosensing by plants and similarities to mechanosensing by animal cells

Some examples of the way that plant cells respond to mechanical forces are shown in Fig. 6. In the example shown in Fig. 6(a), bending or stretching forces are applied to a multicellular system, such as a plant rootlet, to induce expansion over one or more of the cell walls.

TABLE II. Mechanisms of mechanical sensing in biological systems.

Force/energy	Examples	Main protein/structures involved	Magnitude of force/stress	Example References
Turgor pressure	Plant or fungal cell growth	Ion channels	MPa	84, 128, 82
Fluid shear stress	Blood flow in vasculature Urine flow in kidney	Primary cilium, glycocalyx	0.01–1 Pa	121, 129, 130, 131
Actomyosin contractility against viscoelastic substrates	Stresses at focal adhesions	Actomyosin/integrins/cytoskeletal linkers formation of catch bonds in cell-matrix linkers	50–100 000 Pa	132, 23, 127
Vibrations / sound	Hair cell protrusions in animals trichomes in plants	Acoustic waves bend actin bundles to put tension on tip links in ear cells or rotate trichrome structures in plant cells	>20 μPa	133, 134
Hydrostatic pressure	Hypertension, glaucoma, and arthritis	Cardiovascular function, balance of inflow and outflow in eye, brain, gravitational stress on joint fluid	0.2 kPa–5 MPa	135
Osmotic pressure	Cell and tissue swelling	Ion or water channels	kPa–MPa	19, 80
Solid stress	Compression of normal tissue by growing tumor	Deformation of neurons, constriction of blood flow	0.1–10 kPa	77
Tensile stresses in plants	Stretching of cell walls due to growth or internal pressure	Cellulose/pectin transmit stress to transmembrane proteins (channels/kinases) that alter function	10 s of MPa	136
Compressive stress in cartilage and bone	Compression at cartilage/bone interface of joints during walking	Collagen/glycosaminoglycan networks transmit force to alter cell membrane protein structure or expose cryptic binding sites. Induce flow in internal fluid channels	1–10 MPa	137, 138
Shear flow sensing	*E. coli*	FimH that comprises the adhesive tip pf type 1 pilus	0.2 Pa	139
Pressure or other forces generated by flow or motility bend, shear, or stretch the cell envelope	*E. coli* membrane proteins	Mechanosensitive channels, possibly CpxA/CpxR and NlpE	kPa	140, 141

Figure 6(b) shows the result of applying a bending force to the tip of a plant root to induce curvature in the original straight rootlet. As the force deforms the root, there is an influx of calcium on the convex side of the bend but not on the concave side.[14] The time course of the calcium influx shown in Fig. 6(c) occurs within seconds and is accompanied by a similar transient change in pH. Both calcium and pH levels undergo a second wave of increase and then decay to nearly resting levels after several minutes. The mechanism by which calcium influx or changes in pH occurs is illustrated in Fig. 6(d). The plasma membrane of many plant cells contains a wide array of different mechanosensitive ion channels. As bending or stretching forces are applied to the cell wall either by direct application of force or by global expansion due to osmotic pressure, these ion channels can be opened, resulting in the initial increase in the ions that the channels conduct. Once the initial mechanically stimulated chemical signal has been initiated, the consequences of the initial rise in calcium or other signal then activates the multitude of downstream effectors and feedback systems that are often similar to those induced by chemical stimuli.[142,143]

Specific structures involved in activation of ion channels by forces exerted at the lipid bilayer/cell wall interface are shown in more detail in Fig. 6(e). As also shown in Fig. 1(j) the plant cell wall is a complex composite formed largely of stiff cellulose fibers that are linked by a variety of softer polymers including pectin and other polysaccharides that bridge the space between the collagen fibers.[26] These materials are linked through multiple types of linkers to the outer surface of transmembrane proteins embedded in the cell membrane. As forces deform the stiff cell wall, the much softer lipid bilayer follows to adopt the same strain as the inner surface of the plant wall. As the lipid bilayer is strained, proteins move with respect to each other or undergo local unfolding that then leads to the activation of multiple types of ion channels that conduct both cations and anions selectively.[19,123] Additional transmembrane proteins, such as those that contain

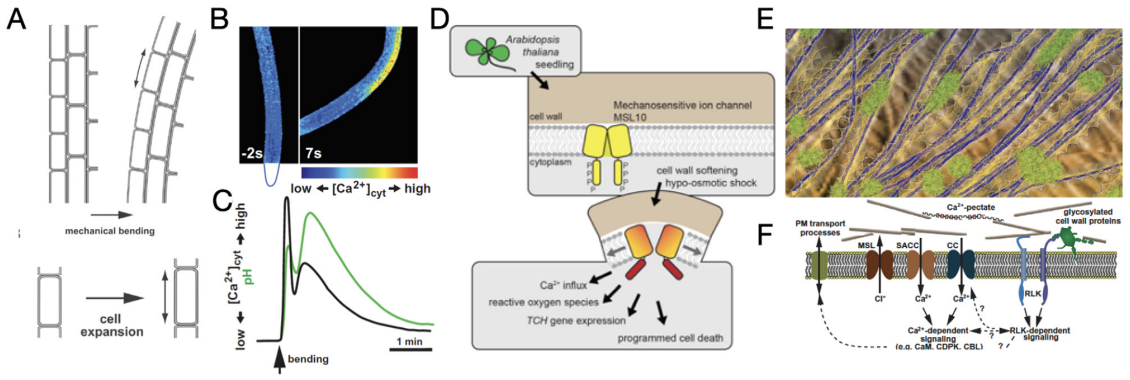

FIG. 6. Activation of intracellular signals by bending or stretching cell walls. (a) Plant cell walls and their underlying lipid bilayers can be stretched or by bending multicellular structures or by the pressures of cell growth. (b) When an elongated plant rootlet is bent, local calcium levels rise at the convex surface. (c) The rise in Ca^{2+} and pH triggered by the bending force is transient and actively regulated by the cell. (d) Force-induced ion influx depends on changes in stricture and conductivity of transmembrane ion channels within the lipid bilayer in contact with the cell wall. (e) Schematic illustrating the composite nature of the plant cells wall and the underlying lipid bilayer. 3 nm diameter long still cellulose fibers (blue) form the framework of the cell wall and are connected by xyloglucan (green) and pectin (yellow) polysaccharides. (f) These structures then bind the externally facing domains of transmembrane proteins. As forces deform the cell wall, they are transmitted to the membrane proteins that in turn alter ion influx, polysaccharides kinase activity, and other functions that transduce the physical stimulus to intracellular biochemical reactions. Derived from Ref. 14 (a–c and f) Ref. 19 (d) and Ref. 26 (e). Figure 6(a)–6(c) and 6(f) reproduced with permission from Monshausen and Haswell, J. Exp. Bot. **64**, 4663–4680 (2013). Copyright 2013 Oxford University Press. Figure 6(d) reproduced with permission from Basu and Haswell, Curr. Biol. **30**, 2716–2728 (2020). Copyright 2020 Elsevier. Figure 6(e) reproduced with permission from Cosgrove, J. Exp. Bot. **67**, 463–476 (2016). Copyright 2013 Oxford University Press.

intracellular kinase activity, can also change function as they are deformed when the cell wall moves. Once the initial mechanically activated signal occurs, the vastly complex network of intracellular chemical signals is activated, and changes in metabolism, cell growth, and cell division are initiated just as they might be in response to chemical signals. Similar mechanisms are very well documented in animal cell systems.[143] Although the magnitudes of force (Fig. 5) and the specific proteins engaged in mechanotransduction in plants are often different from those in animals, the basic strategies they employ, such as changes in protein confirmation, influx of ions, activation or inactivation of protein kinases and phosphatases, and other similar aspects of signal transduction are often conserved.

B. Mechanosensing in bacterial systems

Like eukaryotic cells, bacteria have a range of structures that can detect mechanical stresses of different magnitudes ranging from small fluid shear stress to large osmotic pressures as summarized in Table II and Fig. 7.

1. Mechanosensing by flagella

The bacteria flagella motor is a fascinating molecular machine, and its physical and biological functions, such as flagella bunding, run-and-tumble motion, and chemotaxis, have been reviewed elsewhere.[144] Here, we provide perspective on flagellar bacteria swimming as a mode of mechanosensing, in which we define mechanosensing as the ability of the cell to detect changes in the mechanical features of its environment and then respond to these changes, and the challenges ahead in understanding how bacteria adapt to swimming in real complex environments.

Bacteria have rigid cell walls, no active cytoskeletal motors, and express far fewer proteins than animal cells—so the extent to which they can sense their mechanical environment and adapt to those conditions has been disputed.[145] Consistent with this idea is the conventional view of the bacteria flagella rotatory motor as a structure that operates at a single value of constant torque. New work is revealing that the bacteria flagella motor is not static but dynamic and assembles and dissembles torque-generating units in response to changes in mechanical load.[24,146,147] The typical *E. coli* flagella motor is comprised of 6–11 torque-generating stator motor proteins MotB.[24] These molecular components exchange between the working motor and the cellular pool of soluble units.[146] The typical turnover time of gfp-labeled MotB molecules bound to the motor has been measured with fluorescence recovery after photobleaching and is approximately 30 sec. One way to apply load to the bacterial motor is to use bacteria mutants that form only short flagella stubs and tether beads to them, which are probed either passively by varying bead size[24] or actively via magnetic traps.[147] These experiments show that the number of MotB stator motor proteins bound to the motor increases with the applied load on the motor, and the larger the number of MotB motor proteins, the larger the torque the motor generates. These studies provide direct evidence that the bacteria flagella motor serves as a mechanosensing molecular machine and is capable of adapting to changes in mechanical load on the motor.

How do bacteria increase motor stator units upon increased mechanical loads? One possible explanation is that the turnover of motor proteins is mechanosensitive, that is, the rates of association or dissociation of motor proteins depends on the mechanical load. In a recent study,[148] the kinetics of the stator units were measured as a function of mechanical load on the motor, and the lifetime of the stator unit was found to increase with the applied load. These results

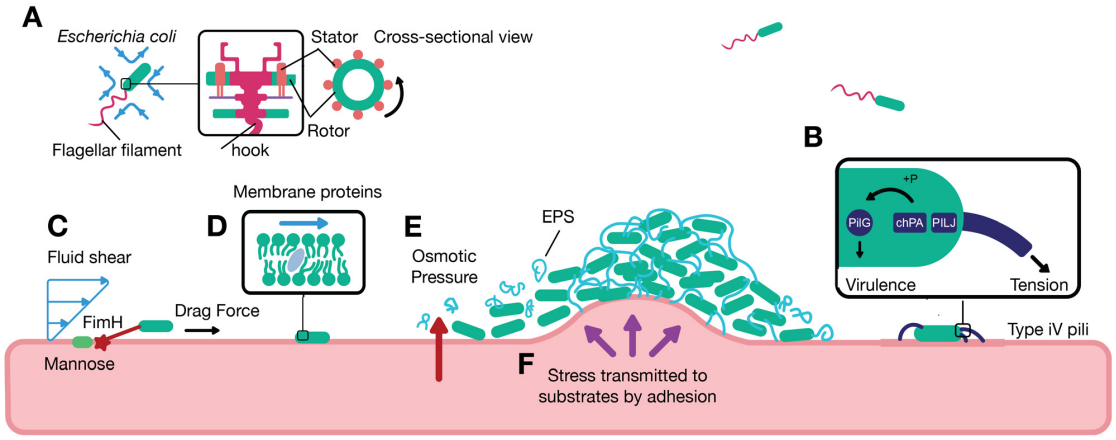

FIG. 7. Mechanosensing strategies by bacteria. (a) The bacteria flagellar motor powers cell swimming. The motor is comprised of a rotor and torque-generating stator proteins that must overcome the resistance from viscous drag on the flagella to propel the cell. (b) Cell surface motility is enabled by type IV pili. Type IV pili adhere to external surfaces and the tension in the pili is thought to be readout by cell as part of the biofilm formation and virulence cell signaling pathways. (c) Fluid shear stresses can be sensed by the adhesion of bacteria to surface by small type 1 fimbriae and (d) deflection of cell membrane proteins. (e) Secretion of EPS molecules that act as osmolytes generates osmotic pressure gradients. These pressure gradients induce fluid flows with a flux of fluid from the porous substrate into the growing biofilm. (f) Growing biofilms generate internal compressive stress that can bend and buckles their underlying substrate.

suggest that the motor stator units act as catch bonds. Catch bonds are bonds strengthened upon applied forces rather than weakened. This behavior can occur, for instance, when applied loading drives conformational changes that expose hidden binding sites. Catch bonds tend to strengthen stress-activated signals and are well-recognized in mammalian cell systems for their ability to strengthen adhesions[132,149] or cytoskeletal networks on demand.[150] The bacteria flagella motor now is an early evolutionary example of catch-bond behavior in the prokaryotic kingdom.

While the bacteria flagella motor has been studied at the molecular scale in great detail, understanding physical effects at the level of the swimming cell presents its own unique challenges. Some of the first experiments to determine the effect of fluid viscosity on bacteria swimming speed occurred in the 1970s and found a surprising result—an increase in bacteria swimming speed in more viscous environments[1,151] (Fig. 8). This result is surprising because the physics of low Reynolds number Newtonian fluid mechanics is quite clear—cell swimming speed is expected to decrease with fluid viscosity. In a Newtonian fluid, the viscous torque on the cell flagella is proportional to $\mu\omega$. Assuming the bacteria motor operates at constant torque, the cell will adjust to highly viscous environments by reducing the motor rotation rate, as experimental data on swimming bacteria suggests.[90] At low Reynolds number, the cell swimming speed varies with the flagella rotation frequency $v \propto \omega$. As viscosity increases, the bundle rotation rate ω and correspondingly cell speed is decrease as μ^{-1}.

What might cause this increase in cell swimming? Fluid viscosity is typically modified by the addition of biocompatible polymers and macromolecular agents, such as methyl cellulose or polyvinylpyrrolidone, to the buffer medium. Initial reports suggested that if the polymers formed a loose quasi-rigid network, then bacteria could swim through solvent-filled pores in the network and push of the walls of the network to increase swimming speed.[151] However, this explanation fails to explain the increase in cell swimming speed observed in dilute polymer solution well below the overlap concentration needed for gel formation.[152,153]

One experimental limitation is the lack of biocompatible polymer systems to systemically design Newtonian fluids of varying viscosity at

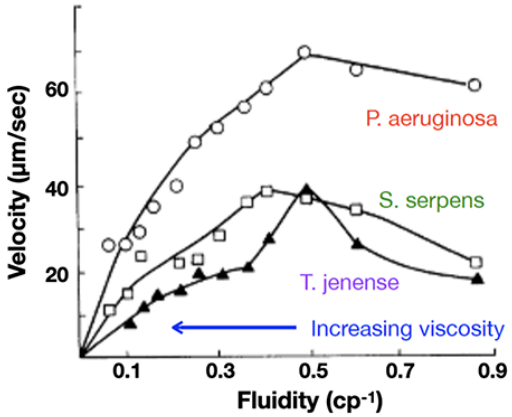

FIG. 8. Physical effects of the environment on bacteria swimming speed. Experiments showing the effect of viscosifying agents on bacteria swimming speed. Polymers polyvinylpyrollidone and methylcellulose were added to bacteria solution to increase fluid viscosity, 1/fluidity. The results show that the addition of the macromolecules initially increases cell swimming speed, despite increases in the fluid viscosity (right-to-left on x axis). For high viscosities, swimming speed decreases with viscosity as expected. This figure was adapted from and reproduced with permission from the Schneider and Doetsch, J. Bacteriol. **117**, 696–701 (1974).[1] Copyright 1974 American Society for Microbiology.

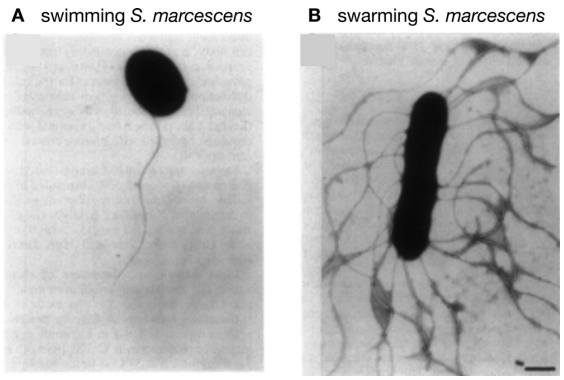

FIG. 9. Surface contact induces bacterial differentiation. Morphology of *Serratia marcescens* in (a) liquid and (b) solid media. Under the right conditions, surface contact can induce swimming cells to differentiate into a hyper-flagellated elongated swarming state. Images are electron micrographs. Scale bar, 1 μm. The figure was adapted from and reproduced with permission from the Alberti and Harshey, J. Bacteriol. **172**, 4322–4328 (1990).[9] Copyright 1990 American Society for Microbiology.

the scale of a single bacteria. Typical polymer molecules (~60 nm) can be as large or larger than the flagella width (20 nm) that is rapidly rotating on the order of 100 Hz.[153] In the past few years, there have been a number of proposed models that attribute the increase swimming speed to non-Newtonian fluid dynamics. These include local shear thinning viscosities around the cell, viscoelastic stresses, and local polymer depletion around the chiral moving cell. While there have been advances in high-throughput bacteria swimming analysis[153] and fluorescence imagining of polymers under transient fluid flows,[152] it is still difficult to resolve both the cell and fluid polymer dynamics and link the local fluid properties to the cell swimming speed.

Nonetheless, there are some conceptually simple experiments that could lend insight. For instance, fluorescently labeling a subset of the macromolecules in the ambient fluid could reveal whether there is a depletion or—as predicted under some conditions—accumulation of polymer molecules near the cell and its flagella. A second approach would be to measure the deformations of the material around the moving cell. A freely swimming bacterium induces fluids flows. The bacterium is both force free and torque free and thus the resulting flows are force dipoles, which decay as $1/r^2$, or higher order multipoles. Determining the velocity field around the bacterium in a non-Newtonian solution would shed light on the appropriate fluid constitutive models to describe the interaction between the cell and its environment. The fluid flow around a bacterium can be resolved by the use of small inert particles as tracers of the surrounding flow, as demonstrated by Drescher *et al.*[3] for Newtonian fluids, approach (Fig. 4).

2. Bacterial mechanosensing on surfaces and within biofilms

One of the most striking examples that bacteria can sense changes in their physical environment is their ability to transition from life in fluids to life on surfaces. When a bacterium makes contact with a surface, it initiates a program of gene expression and cell differentiation (Figs. 9 and 10) that promotes biofilm formation and virulence factors.[99,154]

If surface contact is a mechanical stimulus, then cells need a transduction system to convert mechanical cues into biochemical signals. The bacterial flagellum is one candidate mechano-sensor for initial contact with a surface. The bacteria flagella motor could sense a change in torque on the flagella as a cell nears a surface and would certainly feel an increased load once a bacterium adheres to the surface. While the bacteria flagella motor is a remarkable machine for free swimming, it is not widely employed by bacteria for surfaces. As a biofilm begins to develop, flagellar gene transcription is inhibited, and most cells lose their flagella and swimming ability. It has been proposed that the main function of the flagella in biofilm formation is to bring cells close to the surface where they can bind and adhere to surfaces through other appendages that they have evolved to adhere and move on surfaces. Interesting, the chiral nature of the flagella-bundle rotation tends to trap swimming bacteria near solid surfaces for much longer times compared to simple diffusion,[155] which may allow deployment of "just-in-time" adhesion to the surface.[156] It should be noted that some species of bacteria—under the right conditions with high nutrient availability—can adopt a highly motile hyper-flagellated phenotype and differentiate into swarming cells that rapidly colonize a surface, but this flagella-based swarming motility is oppositely regulated from the much more common and conserved phenotype of slow growing biofilm formation.[157]

While neither the physical nor molecular mechanisms of bacteria surface sensing are fully understood, new work is illuminating the pathways by which type IV pili and associated proteins transduce mechanical signals into biochemical networks that initiate biofilm formation. In *Pseudomonas aeruginosa*, two distinct yet cooperative systems have been identified. The first is mediated by the type IV pili biogenesis factor PilY1, located at type IV pili and in the outer membrane of the cell envelope.[158] PilY1 regulates surface-associated behaviors, such as twitching, cyclic diguanosine monophosphate (cyclic-di-GMP) signaling, and biofilm formation.[159] Cyclic-di-GMP is an intracellular signal that is known to increase upon surface adhesion and leads to EPS production.[160] It further promotes surface sensing by increasing friction with the surface.[161] *P. aeruginosa* lacking PilY1 do not increase cyclic-di-GMP signaling in response to surface attachment and cannot activate virulence and EPS production upon surface contact.[158] The second mechanosensitive element is the functioning type IV pili itself that transmits signals to the Chp chemosensory system.[141] The Chp system regulates cAMP production and transcription of hundreds of genes, including key virulence factors and the quorum sensing system.[162] Quorum sensing is the ability of bacteria to detect the presence of a high density of neighbors, an important condition for the full switch to biofilm life.[163] The two systems, PilY1 and type IV pili, thus activate two distinct biochemical signals that are both important preconditions for proper biofilm formation. Cellular differentiation from planktonic to biofilm life involves the induction of many hundreds of genes that are very energetically expensive.[158] The requirement of two distinct conditions to be met for biofilm formation ensures the cells are in the right conditions before such a high-cost commitment.

How do PilY1 and type IV pili transduce mechanical surface signals? One plausible explanation is that the cell is able to recognize and readout force-induced conformational changes of these two structures.

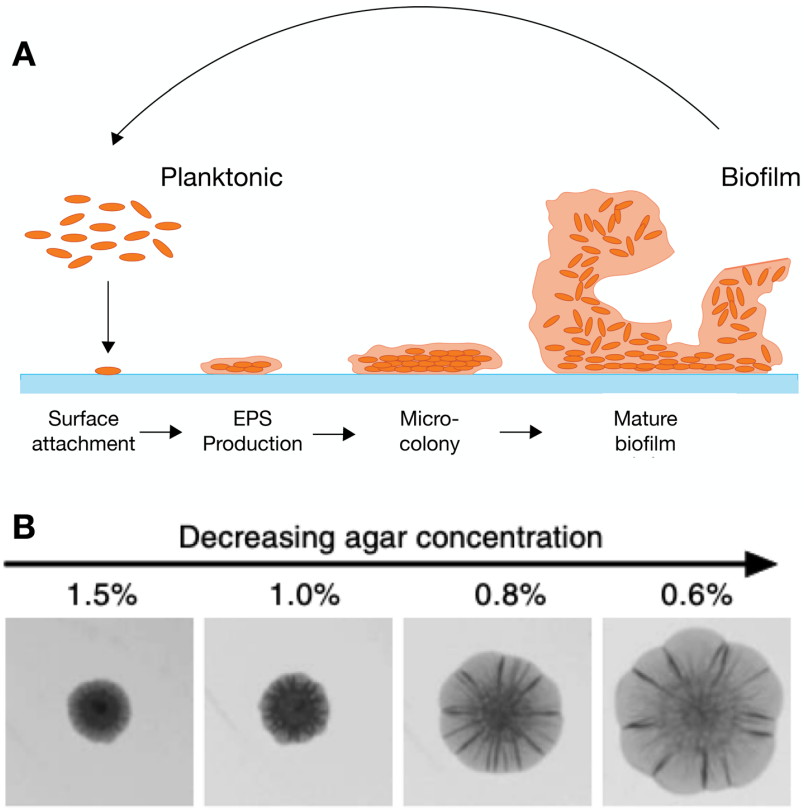

FIG. 10. Biofilm development. (a) Schematic representation of the different stages of biofilm development. (b) Biofilm expansion increases with decreasing agar concentration. This figure was adapted and reproduced with permission from Yan *et al.*, Nat. Commun. **8**, 327 (2017).[2] Copyright 2017 Springer Nature.

PilY1 is an envelope protein that shares a domain with the mechanosensitive von Willebrand factor protein A.[158,161] In animal cell systems, the von Willebrand factor protein A activates by binding to the cell surface and then unraveling from shear flows in the blood stream. Thus, it is tempting to speculate that the vWA domain on PilY1 similarly activates chemical pathways for bacteria upon stretched conformation changes. Likewise, stretching has been shown to induce conformation changes in type IV pili. For instance, in Neisseria gonorrhea, stretching type IV pili reduces its width and the force-induced conformational changes reveal hidden epitopes previously buried in the pili.[164] Surface sensing by type IV pili requires not only physical stretching of the pilus fiber but its internalization by the pili retraction machinery,[141] at which point the stretched-out conformational state may be readout by the Chp system that activates many downstream virulence factors.

The bacterial flagella and type IV pili are on a small but growing list of mechanosensing elements expressed in prokaryotes. There are other candidate surface sensing transduction systems, such as envelope proteins that sense surface shear or pressure (Table 3, Fig. 7)[140] and small type 1 fimbriae (~0.3–1.5 μm in length) adhesive fibers (Table 3, Fig. 7), which are also known to exhibit classic catch-bound behavior by enhancing surface adhesion under heavier shear flows.[139,165]

VI. PRACTICAL APPLICATIONS OF BIOMATERIAL MECHANICS

Perhaps the most obvious utility of characterizing the material properties of living materials is to identify the design principles that nature uses to construct solid tissues and other complex systems. One recurring theme in biomaterials is the common finding of long interpenetrated, but sparsely connected, networks made from structural elements that span the scale from protein polymers such as the cytoskeleton, to polymer bundles such as in the extracellular matrix, to filamentous cellular structures such as those formed by fungi, bacteriophages, or plant rootlets. One obvious advantage of forming materials from highly elongated structural elements is that it is possible to form elastic or viscoelastic solids at very low volume fraction compared to the amount of polymer that is necessary to form a gel or an elastomer of similar stiffness using flexible polymers. For example, it is possible to make hydrogels with 0.1% volume fraction collagen fibers that have similar elastic moduli as gels formed from 5% gelatin, which is a flexible, denatured form of collagen. Therefore, production of cells and tissues that can withstand the forces of gravity or water flow, for example, can be accomplished by relatively modest amounts of protein synthesis needed to create the cytoskeleton or the extracellular matrix. Of course, other strategies, such as encapsulating materials within a

rigid cell wall, can also minimize the use of materials to create structurally robust biological materials.

Defining the responses of biological materials to various geometries of deforming stresses is important for design of bioengineered materials that can either replace damaged structures, such as blood vessels or cartilage, or mimic the physiologic conditions in which cells grow and differentiate and thereby create better platforms for stem cell differentiation, drug testing, and other biomedical applications. Understanding the biomechanical response of other living systems has also proved instrumental in creating better environments for plant development, or production of fungal-based materials for various applications. For example, it is now possible to synthesize small block copolymers that assemble into semiflexible filaments and form strain stiffening networks similar to those formed by F-actin or fibrin[166] and combination of these networks with nanoparticle crosslinked expands the capability to tune network geometry and mechanical response.[167] From the opposite perspective, understanding the mechanical features that promote fungal or bacterial growth is important to design materials and implants that prevent deleterious formation of biofilms and proliferation of pathogens.

A combination of fibrous biomaterials with organic or inorganic fillers is also being increasingly considered as renewable courses of construction materials and other high-performance materials, such as for use in footwear or protective garments.[48] The potential to produce materials with high tensile and shear resistance, but with reduced volume fraction that allow for air or water flow[168] is also a potential advantage of combining fibrous materials with inclusions. The strategy has the added benefit of being able to use final mycelium, for example, to encapsulate waste material granules for production of bricks.[169] The potential of controlled production of fibrous materials by 3D printing for bioengineering and other applications has also been recently reviewed.[170]

The responsiveness of cells to physical stimuli is increasingly used to design better materials to interface with living systems. For example, one of the limiting factors in implanting electrodes or shunts into the central nervous system or other soft animal tissues is that the rigid surface of metal or ceramic implant rapidly leads to activation of cells that form fibrous capsules around the material and degrade them over time. These so-called foreign body responses can be suppressed by soft biomaterials that do not activate the mechanical signals that initiate fibrotic response.[171]

VII. CONCLUSION

Living matter has evolved many structures with mechanical properties that maximize biological functions and survival. A common feature of biological tissues over all kingdoms is the formation of long and often fibrous polymers that form viscoelastic networks both inside the cell, as in the cytoskeleton, and outside the cell, as in extracellular matrices. The combination of cells or other particles within fibrous networks provides these biological materials with mechanical responses that are often unlike those of synthetic materials. The ability to tune mechanical response by altering the balance of particles and network, change network geometry, and apply forces to the composite material provides living matter with its unique ability to adapt to different conditions. Learning how nature performs these tasks will lead to improved strategies to make new, adaptable, and sustainable materials with a vast array of possible applications.

ACKNOWLEDGMENTS

We are grateful to Dr. Robert Bucki for help with the DNA network data shown in Fig. 2. This work was supported by grants from the U.S. National Institute of General Medical Sciences (No. GM142963 to A.E.P and No. GM136259 to P.A.J.), the U.S. National Science Foundation Center for Engineering Mechanobiology (Nos. CMMI-154857 and MCB 2026747 to A.E.P.), and the Materials Research Science and Engineering Center (No. DMR-1720530).

AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

[1]W. R. Schneider and R. Doetsch, J. Bacteriol. **117**(2), 696 (1974).
[2]J. Yan, C. D. Nadell, H. A. Stone, N. S. Wingreen, and B. L. Bassler, Nat. Commun. **8**(1), 327 (2017).
[3]K. Drescher, J. Dunkel, L. H. Cisneros, S. Ganguly, and R. E. Goldstein, Proc. Natl. Acad. Sci. **108**(27), 10940 (2011).
[4]R. Niederman, P. C. Amrein, and J. Hartwig, J. Cell. Biol. **96**(5), 1400 (1983).
[5]J. Silverman, H. T. Cao, and K. Cobb, Cloth. Text. Res. J. **38**(2), 119 (2020).
[6]J. Mahamid, S. Pfeffer, M. Schaffer, E. Villa, R. Danev, L. K. Cuellar, F. Forster, A. A. Hyman, J. M. Plitzko, and W. Baumeister, Science **351**(6276), 969 (2016).
[7]L. A. Mihai, L. Chin, P. A. Janmey, and A. Goriely, J. R. Soc. Interface **12**(110), 0486 (2015).
[8]A. S. G. van Oosten, X. Chen, L. Chin, K. Cruz, A. E. Patteson, K. Pogoda, V. B. Shenoy, and P. A. Janmey, Nature **573**(7772), 96 (2019).
[9]L. Alberti and R. M. Harshey, J. Bacteriol. **172**(8), 4322 (1990).
[10]A. S. G. van Oosten, M. Vahabi, A. J. Licup, A. Sharma, P. A. Galie, F. C. MacKintosh, and P. A. Janmey, Sci. Rep. **6**, 19270 (2016).
[11]S. Arzash, J. L. Shivers, A. J. Licup, A. Sharma, and F. C. MacKintosh, Phys. Rev. E **99**(4), 042412 (2019).
[12]K. A. Jansen, A. J. Licup, A. Sharma, R. Rens, F. C. MacKintosh, and G. H. Koenderink, Biophys. J. **114**(11), 2665 (2018).
[13]B. Sabass, M. D. Koch, G. Liu, H. A. Stone, and J. W. Shaevitz, Proc. Natl. Acad. Sci. **114**(28), 7266 (2017).
[14]G. B. Monshausen and E. S. Haswell, J. Exp. Bot. **64**(15), 4663 (2013).
[15]F. Sauer, L. Oswald, A. Ariza de Schellenberger, H. Tzschatzsch, F. Schrank, T. Fischer, J. Braun, C. T. Mierke, R. Valiullin, I. Sack, and J. A. Kas, Soft Matter **15**(14), 3055 (2019).
[16]P. Panettiere, D. Accorsi, L. Marchetti, A. M. Minicozzi, G. Orsini, P. Bernardi, D. Benati, G. Conti, and A. Sbarbati, Eur. J. Histochem. **55**(2), 85 (2011).
[17]C. P. Brangwynne, G. H. Koenderink, F. C. MacKintosh, and D. A. Weitz, Trends Cell. Biol. **19**(9), 423 (2009).
[18]C. P. Broedersz and F. C. MacKintosh, Rev. Mod. Phys. **86**(3), 995 (2014); H. Hatami-Marbini and M. Rohanifar, Biophys. J. **120**(3), 527 (2021); H. Lopez-Menendez and L. Gonzalez-Torres, J. Mech. Phys. Solids **127**, 208 (2019); C. Storm, J. J. Pastore, F. C. MacKintosh, T. C. Lubensky, and P. A. Janmey, Nature **435**(7039), 191 (2005).
[19]D. Basu and E. S. Haswell, Curr. Biol. **30**(14), 2716 (2020).
[20]O. Chaudhuri, J. Cooper-White, P. A. Janmey, D. J. Mooney, and V. B. Shenoy, Nature **584**(7822), 535 (2020).
[21]A. Santos and D. Lagares, Curr. Rheumatol. Rep. **20**(1), 2 (2018).
[22]S. Goulas, M. V. Gelfand, and I. Carmi, Dev. Cell **56**(2), 155 (2021); D. Basu and E. S. Haswell, Curr. Opin. Plant Biol. **40**, 43 (2017); V. Vogel, Annu. Rev. Physiol. **80**, 353 (2018).

[23]J. A. Espina, C. L. Marchant, and E. H. Barriga, FEBS J. **120**, 53–65 (2021); A. Inman and M. Smutny, Semin. Cell Dev. Biol. **120**, 53–65 (2021).
[24]P. P. Lele, B. G. Hosu, and H. C. Berg, Proc. Natl. Acad. Sci. **110**(29), 11839 (2013).
[25]P. A. Janmey, J. P. Winer, and J. W. Weisel, J. R. Soc. Interface **6**(30), 1 (2009).
[26]D. J. Cosgrove, J. Exp. Bot. **67**(2), 463 (2016).
[27]J. W. Weisel and R. I. Litvinov, Res. Pract. Thromb. Haemost. **5**(1), 38 (2021).
[28]H. T. Nia, L. L. Munn, and R. K. Jain, Science **370**(6516), eaaz0868 (2020).
[29]B. Piersma, M. K. Hayward, and V. M. Weaver, Biochim. Biophys. Acta Rev. Cancer **1873**(2), 188356 (2020).
[30]J. D. Humphrey and M. A. Schwartz, Annu. Rev. Biomed. Eng. **23**, 1 (2021).
[31]P. A. Janmey, D. A. Fletcher, and C. A. Reinhart-King, Physiol. Rev. **100**(2), 695 (2020); R. J. Pelham, Jr. and Y. Wang, Proc. Natl. Acad. Sci. U. S. A. **94**(25), 13661 (1997).
[32]J. Pattem, M. Davrandi, S. Aguayo, B. Slak, R. Maev, E. Allan, D. Spratt, and L. Bozec, Sci. Rep. **11**(1), 16234 (2021).
[33]K. Prakobna, V. Kisonen, C. L. Xu, and L. A. Berglund, J. Mater. Sci. **50**(22), 7413 (2015).
[34]D. Q. Pham, S. J. Bryant, S. Cheeseman, L. Z. Y. Huang, G. Bryant, M. F. Dupont, J. Chapman, C. C. Berndt, J. P. Vongsvivut, R. J. Crawford, V. K. Truong, A. S. M. Ang, and A. Elbourne, Nanoscale **12**(38), 19888 (2020).
[35]Y. Zhang, J. Y. Yu, X. Wang, D. M. Durachko, S. L. Zhang, and D. J. Cosgrove, Science **372**(6543), 706 (2021).
[36]C. Loebel, R. L. Mauck, and J. A. Burdick, Nat. Mater. **18**(8), 883 (2019).
[37]K. Drescher, Y. Shen, B. L. Bassler, and H. A. Stone, Proc. Natl. Acad. Sci. U. S. A. **110**(11), 4345 (2013).
[38]N. Obana, K. Nakamura, and N. Nomura, J. Bacteriol. **196**(8), 1540 (2014).
[39]E. S. Castle, J. Cell. Comp. Physiol. **10**(1), 113 (1937).
[40]P. A. Janmey, D. R. Slochower, Y. H. Wang, Q. Wen, and A. Cebers, Soft Matter **10**(10), 1439 (2014).
[41]C. Bustamante, J. F. Marko, E. D. Siggia, and S. Smith, Science **265**(5178), 1599 (1994); F. C. MacKintosh, J. Kas, and P. A. Janmey, Phys. Rev. Lett. **75**(24), 4425 (1995).
[42]J. Kas, H. Strey, and E. Sackmann, Nature **368**(6468), 226 (1994).
[43]P. R. Onck, T. Koeman, T. van Dillen, and E. van der Giessen, Phys. Rev. Lett. **95**(17), 178102 (2005).
[44]A. J. Licup, A. Sharma, and F. C. MacKintosh, Phys. Rev. E **93**(1), 012407 (2016); E. Ban, V. H. Barocas, M. S. Shephard, and C. R. Picu, J. Appl. Mech. **83**(4), 0410081 (2016); G. Zagar, P. R. Onck, and E. Van der Giessen, Macromolecules **44**(17), 7026 (2011).
[45]M. R. Islam, G. Tudryn, R. Bucinell, L. Schadler, and R. C. Picu, Sci. Rep. **7**(1), 13070 (2017).
[46]A. A. Agrawal and K. Konno, Annu. Rev. Ecol. Evol. Syst. **40**(1), 311 (2009).
[47]M. Haneef, L. Ceseracciu, C. Canale, I. S. Bayer, J. A. Heredia-Guerrero, and A. Athanassiou, Sci. Rep. **7**, 41292 (2017).
[48]I. Irbe, I. Filipova, M. Skute, A. Zajakina, K. Spunde, and T. Juhna, Polymers (Basel) **13**(7), 1086 (2021).
[49]W. G. Ellenbroek, V. F. Hagh, A. Kumar, M. F. Thorpe, and M. van Hecke, Phys. Rev. Lett. **114**(13), 135501 (2015); L. Theran, A. Nixon, E. Ross, M. Sadjadi, B. Servatius, and M. F. Thorpe, Phys. Rev. E **92**(5), 053306 (2015).
[50]R. Rens, M. Vahabi, A. J. Licup, F. C. MacKintosh, and A. Sharma, J. Phys. Chem. B **120**(26), 5831 (2016).
[51]J. Feng, H. Levine, X. Mao, and L. M. Sander, Soft Matter **12**(5), 1419 (2016).
[52]A. Sharma, A. J. Licup, R. Rens, M. Vahabi, K. A. Jansen, G. H. Koenderink, and F. C. MacKintosh, Phys. Rev. E **94**(4–1), 042407 (2016).
[53]M. R. Islam and R. C. Picu, Phys. Rev. E **99**(6–1), 063001 (2019).
[54]P. A. Janmey, M. E. McCormick, S. Rammensee, J. L. Leight, P. C. Georges, and F. C. MacKintosh, Nat. Mater. **6**(1), 48 (2007); H. Kang, Q. Wen, P. A. Janmey, J. X. Tang, E. Conti, and F. C. MacKintosh, J. Phys. Chem. B **113**(12), 3799 (2009).
[55]A. J. Licup, S. Munster, A. Sharma, M. Sheinman, L. M. Jawerth, B. Fabry, D. A. Weitz, and F. C. MacKintosh, Proc. Natl. Acad. Sci. U. S. A. **112**(31), 9573 (2015).
[56]M. Vahabi, A. Sharma, A. J. Licup, A. S. G. van Oosten, P. A. Galie, P. A. Janmey, and F. C. MacKintosh, Soft Matter **12**(22), 5050 (2016).
[57]M. Perepelyuk, L. Chin, X. Cao, A. van Oosten, V. B. Shenoy, P. A. Janmey, and R. G. Wells, PLoS One **11**(1), e0146588 (2016).
[58]F. Eskandari, M. Shafieian, M. M. Aghdam, and K. Laksari, Ann. Biomed. Eng. **49**(1), 276 (2021).
[59]J. L. Shivers, J. Feng, A. S. G. van Oosten, H. Levine, P. A. Janmey, and F. C. MacKintosh, Proc. Natl. Acad. Sci. U. S. A. **117**(35), 21037 (2020).
[60]D. W. Song, J. L. Shivers, F. C. MacKintosh, A. E. Patteson, and P. A. Janmey, J. Appl. Phys. **129**(14), 140901 (2021).
[61]E. Ban, H. Wang, J. M. Franklin, J. T. Liphardt, P. A. Janmey, and V. B. Shenoy, Proc. Natl. Acad. Sci. U. S. A. **116**(14), 6790 (2019); S. Zhang, X. Cao, A. M. Stablow, V. B. Shenoy, and B. A. Winkelstein, J. Biomech. Eng. **138**(2), 021013 (2016).
[62]M. C. Gandikota, K. Pogoda, A. van Oosten, T. A. Engstrom, A. E. Patteson, P. A. Janmey, and J. M. Schwarz, Soft Matter **16**(18), 4389 (2020).
[63]I. Laidmae, K. Erglis, A. Cebers, P. A. Janmey, and R. Uibo, J. Mater. Sci. Mater. Med. **29**(12), 182 (2018).
[64]Q. Xie, Y. Zhuang, G. Ye, T. Wang, Y. Cao, and L. Jiang, Nat. Commun. **12**(1), 4277 (2021).
[65]A. Wegner, J Mol Biol **108**(1), 139 (1976); A. Wegner and J. Engel, Biophys. Chem. **3**(3), 215 (1975).
[66]C. S. Peskin, G. M. Odell, and G. F. Oster, Biophys. J. **65**(1), 316 (1993).
[67]G. Civelekoglu-Scholey and J. M. Scholey, Cell. Mol. Life Sci. **67**(13), 2231 (2010).
[68]F. C. Minozzo, B. M. Baroni, J. A. Correa, M. A. Vaz, and D. E. Rassier, Sci. Rep. **3**(1), 2320 (2013).
[69]D. E. Rassier, B. R. MacIntosh, and W. Herzog, J. Appl. Physiol. **86**(5), 1445 (1999).
[70]R. D. Astumian, Phys. Rev. E **76**(2 Pt 1), 020102 (2007); S. Leibler and D. A. Huse, C. R. Acad. Sci. **313**(1), 27 (1991).
[71]S. Highsmith, Biochemistry **29**(47), 10690 (1990).
[72]G. S. Manning, Biopolymers **105**(12), 887 (2016).
[73]C. Battle, C. P. Broedersz, N. Fakhri, V. F. Geyer, J. Howard, C. F. Schmidt, and F. C. MacKintosh, Science **352**(6285), 604 (2016).
[74]T. E. Angelini, E. Hannezo, X. Trepat, J. J. Fredberg, and D. A. Weitz, Phys. Rev. Lett. **104**(16), 168104 (2010); J. A. Park, J. H. Kim, D. Bi, J. A. Mitchel, N. T. Qazvini, K. Tantisira, C. Y. Park, M. McGill, S. H. Kim, B. Gweon, J. Notbohm, R. Steward, Jr., S. Burger, S. H. Randell, A. T. Kho, D. T. Tambe, C. Hardin, S. A. Shore, E. Israel, D. A. Weitz, D. J. Tschumperlin, E. P. Henske, S. T. Weiss, M. L. Manning, J. P. Butler, J. M. Drazen, and J. J. Fredberg, Nat. Mater. **14**(10), 1040 (2015).
[75]C. P. Brangwynne, G. H. Koenderink, F. C. MacKintosh, and D. A. Weitz, J. Cell. Biol. **183**(4), 583 (2008).
[76]A. E. Patteson, A. Gopinath, and P. E. Arratia, Nat. Commun. **9**(1), 5373 (2018); N. C. Darnton, L. Turner, S. Rojevsky, and H. C. Berg, Biophys. J. **98**(10), 2082 (2010).
[77]H. T. Nia, M. Datta, G. Seano, S. Zhang, W. W. Ho, S. Roberge, P. Huang, L. L. Munn, and R. K. Jain, Nat. Protoc. **15**(8), 2321 (2020).
[78]T. E. Woolley, E. A. Gaffney, J. M. Oliver, S. L. Waters, R. E. Baker, and A. Goriely, J. Theor. Biol. **380**, 83 (2015).
[79]R. J. Petrie, H. Koo, and K. M. Yamada, Science **345**(6200), 1062 (2014).
[80]T. Karlsson, A. Bolshakova, M. A. Magalhaes, V. M. Loitto, and K. E. Magnusson, PLoS One **8**(4), e59901 (2013).
[81]V. M. Loitto, T. Karlsson, and K. E. Magnusson, Cell Motil. Cytoskeleton **66**(5), 237 (2009).
[82]D. D. Thomson, S. Wehmeier, F. J. Byfield, P. A. Janmey, D. Caballero-Lima, A. Crossley, and A. C. Brand, Cell Microbiol. **17**(3), 342 (2015).
[83]N. Minc, A. Boudaoud, and F. Chang, Curr. Biol. **24**(12), 1436 (2014).
[84]R. J. Howard, M. A. Ferrari, D. H. Roach, and N. P. Money, Proc. Natl. Acad. Sci. U. S. A. **88**(24), 11281 (1991).
[85]A. Goriely and M. Tabor, Phys. Rev. Lett. **90**(10), 108101 (2003).
[86]P. Durand-Smet, E. Gauquelin, N. Chastrette, A. Boudaoud, and A. Asnacios, Phys. Biol. **14**(5), 055002 (2017).
[87]E. M. Purcell, Am. J. Phys. **45**(1), 3 (1977).
[88]M. Miyata, R. C. Robinson, T. Q. Uyeda, Y. Fukumori, S. i. Fukushima, S. Haruta, M. Homma, K. Inaba, M. Ito, and C. Kaito, Genes Cells **25**(1), 6 (2020).
[89]H. C. Berg and R. A. Anderson, Nature **245**(5425), 380 (1973).

[90]N. C. Darnton, L. Turner, S. Rojevsky, and H. C. Berg, J. Bacteriol. **189**(5), 1756 (2007).
[91]R. M. Berry and H. C. Berg, Proc. Natl. Acad. Sci. **94**(26), 14433 (1997).
[92]R. M. Donlan and J. W. Costerton, Clin. Microbiol. Rev. **15**(2), 167 (2002).
[93]D. McDougald, S. A. Rice, N. Barraud, P. D. Steinberg, and S. Kjelleberg, Nat. Rev. Microbiol. **10**(1), 39 (2012).
[94]L. Craig, K. T. Forest, and B. Maier, Nat. Rev. Microbiol. **17**(7), 429 (2019).
[95]J. M. Skerker and H. C. Berg, Proc. Natl. Acad. Sci. **98**(12), 6901 (2001).
[96]P. Stoodley, R. Cargo, C. J. Rupp, S. Wilson, and I. Klapper, J. Ind. Microbiol. Biotechnol. **29**(6), 361 (2002).
[97]P. S. Stewart and J. William Costerton, Lancet **358**(9276), 135 (2001).
[98]R. Vasudevan, J. Microbiol. Exp. **1**(3), 00014 (2014).
[99]G. O'Toole, H. B. Kaplan, and R. Kolter, Annu. Rev. Microbiol. **54**(1), 49 (2000).
[100]K. Kovach, M. Davis-Fields, Y. Irie, K. Jain, S. Doorwar, K. Vuong, N. Dhamani, K. Mohanty, A. Touhami, and V. D. Gordon, NPJ Biofilms Microbiomes **3**(1), 1 (2017).
[101]L. Karygianni, Z. Ren, H. Koo, and T. Thurnheer, Trends Microbiol. **28**(8), 668 (2020); M. Tallawi, M. Opitz, and O. Lieleg, Biomater. Sci. **5**(5), 887 (2017).
[102]R. Hartmann, P. K. Singh, P. Pearce, R. Mok, B. Song, F. Díaz-Pascual, J. Dunkel, and K. Drescher, Nat. Phys. **15**(3), 251 (2019).
[103]A. M. Vinogradov, M. Winston, C. J. Rupp, and P. Stoodley, Biofilms **1**(1), 49 (2004).
[104]J. N. Wilking, V. Zaburdaev, M. De Volder, R. Losick, M. P. Brenner, and D. A. Weitz, Proc. Natl. Acad. Sci. **110**(3), 848 (2013).
[105]M. Trejo, C. Douarche, V. Bailleux, C. Poulard, S. Mariot, C. Regeard, and E. Raspaud, Proc. Natl. Acad. Sci. U. S. A. **110**(6), 2011 (2013).
[106]J. Yan, C. Fei, S. Mao, A. Moreau, N. S. Wingreen, A. Košmrlj, H. A. Stone, and B. L. Bassler, eLife **8**, e43920 (2019).
[107]A. Seminara, T. E. Angelini, J. N. Wilking, H. Vlamakis, S. Ebrahim, R. Kolter, D. A. Weitz, and M. P. Brenner, Proc. Natl. Acad. Sci. **109**(4), 1116 (2012).
[108]M.-C. Duvernoy, T. Mora, M. Ardré, V. Croquette, D. Bensimon, C. Quilliet, J.-M. Ghigo, M. Balland, C. Beloin, S. Lecuyer, and N. Desprat, Nat. Commun. **9**(1), 1120 (2018); F. Beroz, J. Yan, Y. Meir, B. Sabass, H. A. Stone, B. L. Bassler, and N. S. Wingreen, Nat. Phys. **14**(9), 954 (2018).
[109]M. Asally, M. Kittisopikul, P. Rué, Y. Du, Z. Hu, T. Çağatay, A. B. Robinson, H. Lu, J. Garcia-Ojalvo, and G. M. Süel, Proc. Natl. Acad. Sci. **109**(46), 18891 (2012).
[110]A. Cont, T. Rossy, Z. Al-Mayyah, and A. Persat, Elife **9**, e56533 (2020).
[111]K. Little, J. Austerman, J. Zheng, K. A. Gibbs, and G. O'Toole, J. Bacteriol. **201**(11), e00726 (2019).
[112]F. Julicher, A. Ajdari, and J. Prost, Rev. Mod. Phys. **69**(4), 1269 (1997).
[113]M. Aepfelbacher, M. Essler, E. Huber, A. Czech, and P. C. Weber, J. Immunol. **157**(11), 5070 (1996); S. J. Henry, C. S. Chen, J. C. Crocker, and D. A. Hammer, Biophys. J. **109**(4), 699 (2015).
[114]M. Prass, K. Jacobson, A. Mogilner, and M. Radmacher, J. Cell Biol. **174**(6), 767 (2006).
[115]M. Dogterom, M. E. Janson, C. Faivre-Moskalenko, A. Van der Horst, J. W. J. Kerssemakers, C. Tanase, and B. M. Mulder, Appl. Phys. A **75**(2), 331 (2002).
[116]D. W. DeSimone and A. R. Horwitz, Science **345**(6200), 1002 (2014).
[117]K. M. Stroka, H. Jiang, S. H. Chen, Z. Tong, D. Wirtz, S. X. Sun, and K. Konstantopoulos, Cell **157**(3), 611 (2014).
[118]R. Levayer, Semin. Cancer Biol. **63**, 69 (2020); G. Page, M. Tardieu, J. L. Gennisson, L. Besret, P. Garteiser, and B. E. Van Beers, Cancers (Basel) **13**(8), 1891 (2021).
[119]Z. Teff, Z. Priel, and L. A. Gheber, Biophys. J. **92**(5), 1813 (2007).
[120]L. Ping, Y. Wu, B. G. Hosu, J. X. Tang, and H. C. Berg, Biophys. J. **107**(4), 871 (2014).
[121]Z. Peng, A. Resnick, and Y. N. Young, Math. Biosci. Eng. **18**(2), 1215 (2021).
[122]M. Szczot, A. R. Nickolls, R. M. Lam, and A. T. Chesler, Annu. Rev. Biochem. **90**, 507 (2021).
[123]I. Radin, R. A. Richardson, J. H. Coomey, E. R. Weiner, C. S. Bascom, T. Li, M. Bezanilla, and E. S. Haswell, Science **373**(6554), 586 (2021).
[124]G. B. Monshausen, T. N. Bibikova, M. H. Weisenseel, and S. Gilroy, Plant Cell **21**(8), 2341 (2009).
[125]T. Rasmussen and A. Rasmussen, Subcell Biochem. **87**, 83 (2018).
[126]R. Peyronnet, D. Tran, T. Girault, and J. M. Frachisse, Front. Plant Sci. **5**, 558 (2014).
[127]I. Andreu, B. Falcones, S. Hurst, N. Chahare, X. Quiroga, A. L. Le Roux, Z. Kechagia, A. E. M. Beedle, A. Elosegui-Artola, X. Trepat, R. Farre, T. Betz, I. Almendros, and P. Roca-Cusachs, Nat. Commun. **12**(1), 4229 (2021); P. Niethammer, Annu. Rev. Cell Dev. Biol. **12**, 4229 (2021).
[128]H. G. Coster, Plant Physiol. **58**(5), 636 (1976).
[129]P. F. Davies, J. A. Spaan, and R. Krams, Ann. Biomed. Eng. **33**(12), 1714 (2005); M. E. McCormick, E. Manduchi, W. R. T. Witschey, R. C. Gorman, J. H. Gorman, 3rd, Y. Z. Jiang, C. J. Stoeckert, Jr., A. J. Barker, S. Yoon, M. Markl, and P. F. Davies, J. Biomech. **50**, 11 (2017).
[130]X. Sheng, Y. Sheng, S. Gao, F. Fan, and J. Wang, Histochem. Cell Biol. **154**(6), 639 (2020).
[131]R. R. Ferreira, H. Fukui, R. Chow, A. Vilfan, and J. Vermot, J. Cell Sci. **132**(14), jcs213496 (2019).
[132]D. L. Huang, N. A. Bax, C. D. Buckley, W. I. Weis, and A. R. Dunn, Science **357**(6352), 703 (2017).
[133]S. Liu, J. Jiao, T. J. Lu, F. Xu, B. G. Pickard, and G. M. Genin, Biophys. J. **113**(9), 2068 (2017).
[134]W. Zheng and J. R. Holt, Annu. Rev. Biophys. **50**, 31 (2021).
[135]S. Liu, R. Tao, M. Wang, J. Tian, G. M. Genin, T. J. Lu, and F. Xu, Appl. Mech. Rev. **71**(4), 0408031 (2019).
[136]S. A. Belteton, W. Li, M. Yanagisawa, F. A. Hatam, M. I. Quinn, M. K. Szymanski, M. W. Marley, J. A. Turner, and D. B. Szymanski, Nat. Plants **7**(6), 826 (2021).
[137]G. Zhen, Q. Guo, Y. Li, C. Wu, S. Zhu, R. Wang, X. E. Guo, B. C. Kim, J. Huang, Y. Hu, Y. Dan, M. Wan, T. Ha, S. An, and X. Cao, Nat. Commun. **12**(1), 1706 (2021).
[138]P. Vakiel, M. Shekarforoush, C. R. Dennison, M. Scott, C. B. Frank, D. A. Hart, and N. G. Shrive, Ann. Biomed. Eng. **48**(12), 2836 (2020).
[139]W. E. Thomas, E. Trintchina, M. Forero, V. Vogel, and E. V. Sokurenko, Cell **109**(7), 913 (2002).
[140]B. Martinac, M. Buechner, A. H. Delcour, J. Adler, and C. Kung, Proc. Natl. Acad. Sci. **84**(8), 2297 (1987).
[141]A. Persat, Y. F. Inclan, J. N. Engel, H. A. Stone, and Z. Gitai, Proc. Natl. Acad. Sci. **112**(24), 7563 (2015).
[142]Y. Fichman and R. Mittler, Plant J. **107**(1), 7 (2021); L. Zhang, L. Du, and B. W. Poovaiah, Plant Signal. Behav. **9**(11), e973818 (2014).
[143]P. A. Janmey and R. T. Miller, J. Cell Sci. **124**(Pt 1), 9 (2011); P. A. Janmey, R. G. Wells, R. K. Assoian, and C. A. McCulloch, Differentiation **86**(3), 112 (2013); A. Kindberg, J. K. Hu, and J. O. Bush, Curr. Opin. Cell Biol. **66**, 59 (2020); A. Krajnik, J. A. Brazzo, 3rd, K. Vaidyanathan, T. Das, J. Redondo-Munoz, and Y. Bae, Front. Cell Dev. Biol. **8**, 595849 (2020); A. E. Miller, P. Hu, and T. H. Barker, Adv. Healthc. Mater. **9**(8), e1901445 (2020).
[144]E. Lauga, Annu. Rev. Fluid Mech. **48**, 105 (2016); H. C. Berg, Annu. Rev. Biochem. **72**(1), 19 (2003).
[145]R. Chawla, R. Gupta, T. P. Lele, and P. P. Lele, J. Mol. Biol. **432**(2), 523 (2020).
[146]M. C. Leake, J. H. Chandler, G. H. Wadhams, F. Bai, R. M. Berry, and J. P. Armitage, Nature **443**(7109), 355 (2006).
[147]M. J. Tipping, N. J. Delalez, R. Lim, R. M. Berry, and J. P. Armitage, MBio **4**(4), e00551 (2013).
[148]A. L. Nord, E. Gachon, R. Perez-Carrasco, J. A. Nirody, A. Barducci, R. M. Berry, and F. Pedaci, Proc. Natl. Acad. Sci. **114**(49), 12952 (2017).
[149]A. Del Rio, R. Perez-Jimenez, R. Liu, P. Roca-Cusachs, J. M. Fernandez, and M. P. Sheetz, Science **323**(5914), 638 (2009).
[150]A. K. Rai, A. Rai, A. J. Ramaiya, R. Jha, and R. Mallik, Cell **152**(1–2), 172 (2013).
[151]H. C. Berg and L. Turner, Nature **278**(5702), 349 (1979).
[152]A. Patteson, A. Gopinath, M. Goulian, and P. Arratia, Sci. Rep. **5**(1), 15761 (2015).
[153]V. A. Martinez, J. Schwarz-Linek, M. Reufer, L. G. Wilson, A. N. Morozov, and W. C. Poon, Proc. Natl. Acad. Sci. **111**(50), 17771 (2014).
[154]C. Prigent-Combaret, O. Vidal, C. Dorel, and P. Lejeune, J. Bacteriol. **181**(19), 5993 (1999); F. Song, H. Wang, K. Sauer, and D. Ren, Front. Microbiol. **9**, 110 (2018).

[155]E. Lauga, W. R. DiLuzio, G. M. Whitesides, and H. A. Stone, Biophys. J. **90**(2), 400 (2006); G. Li and J. X. Tang, Phys. Rev. Lett. **103**(7), 078101 (2009).
[156]G. Li, P. J. Brown, J. X. Tang, J. Xu, E. M. Quardokus, C. Fuqua, and Y. V. Brun, Mol. Microbiol. **83**(1), 41 (2012).
[157]K. M. Blair, L. Turner, J. T. Winkelman, H. C. Berg, and D. B. Kearns, Science **320**(5883), 1636 (2008).
[158]A. Siryaporn, S. L. Kuchma, G. A. O'Toole, and Z. Gitai, Proc. Natl. Acad. Sci. **111**(47), 16860 (2014).
[159]S. Kuchma, A. Ballok, J. Merritt, J. Hammond, W. Lu, J. D. Rabinowitz, and G. A. O'Toole, J. Bacteriol. **192**, 2950–2964 (2010).
[160]R. Hengge, Nat. Rev. Microbiol. **7**(4), 263 (2009).
[161]C. A. Rodesney, B. Roman, N. Dhamani, B. J. Cooley, P. Katira, A. Touhami, and V. D. Gordon, Proc. Natl. Acad. Sci. **114**(23), 5906 (2017).
[162]M. C. Wolfgang, V. T. Lee, M. E. Gilmore, and S. Lory, Dev. Cell **4**(2), 253 (2003).
[163]S. T. Rutherford and B. L. Bassler, Cold Spring Harbor Perspect. Med. **2**(11), a012427 (2012).
[164]N. Biais, D. L. Higashi, J. Brujić, M. So, and M. P. Sheetz, Proc. Natl. Acad. Sci. **107**(25), 11358 (2010).
[165]M. Forero, O. Yakovenko, E. V. Sokurenko, W. E. Thomas, and V. Vogel, PLoS Biol. **4**(9), e298 (2006).
[166]P. de Almeida, M. Jaspers, S. Vaessen, O. Tagit, G. Portale, A. E. Rowan, and P. H. J. Kouwer, Nat. Commun. **10**(1), 609 (2019).
[167]W. Chen and P. H. J. Kouwer, Adv. Funct. Mater. **31**, 2105713 (2021).
[168]I. Filipova, I. Irbe, M. Spade, M. Skute, I. Dabolina, I. Baltina, and L. Vecbiskena, Materials (Basel) **14**(1), 136 (2020).
[169]J. Maximino C. Ongpeng, E. Inciong, V. Sendo, C. Soliman, and A. Siggaoat, Appl. Sci. **10**(15), 5303 (2020).
[170]C. Yu, W. Zhu, B. Sun, D. Mei, M. Gou, and S. Chen, Appl. Phys. Rev. **5**(4), 041107 (2018).
[171]N. Noskovicova, R. Schuster, S. van Putten, M. Ezzo, A. Koehler, S. Boo, N. M. Coelho, D. Griggs, P. Ruminski, C. A. McCulloch, and B. Hinz, Nat. Biomed. Eng. **5**, 1437–1456 (2021).
[172]See https://biorender.com/ for figure template "Myofibril Structure" (Last accessed 12/21/2021).