Polymer science and biology: structure and dynamics at multiple scales

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I give a brief, biased survey of some recent problems in molecular and cell biology from the perspective of physical science, with a few answers, but a great many questions, challenges and opportunities.

1 Introduction

A quantitative physicochemical analysis of biological systems is the natural desideratum of our increased knowledge of living organisms at the molecular and cellular level. Broadly, this raises questions about the mechanisms associated with interconversion of matter into different structured forms, the transduction of energy into various forms as well as interplay with matter, and the processing of information at multiple scales, from the genome to the organism itself. Of course, these three domains are closely intertwined with each other; indeed it is the natural richness of phenomena that arises at these interfaces that draws so many of us into thinking about biology. I will review some of the recent advances in this field, from a personal and, therefore, somewhat narrow perspective.

A natural starting place in thinking about biological systems starts with the observation, at the molecular and cellular scale, of a preponderance of filamentous and membranous structures. These low dimensional objects have a large surface to volume ratio and thus serve as substrates for chemical reactions associated with the dynamical processes underlying life while having the ability to encode function in complex dynamic structures. In Section 2 I will, therefore, discuss some of the simpler aspects of the morphology and dynamics of filamentous and membranous structures. In Section 3 I will discuss how one might build on our understanding of the filamentous and membraneous structures to quantify some simple aspects of cell dynamics. Finally, in Section 4 I will close with some remarks on the challenges ahead.

2 Physics of filamentous aggregates

Long polymeric molecules can aggregate into either ordered bundles or disordered networks and indeed can switch from one form to another. A partial list of examples include actin bundles and cytoskeletal networks, axonemal structures and other microtubular organelles, misfolded proteins that form amyloid fibrils and networks, beneficial aggregates such as blood clots and a variety of extracellular structural arrangements made of keratin, collagen, elastin *etc.* associated with tissues such as skin and hair. The slender geometry of these molecules allows them to bend and twist much more easily than they can stretch, independent of their chemical composition.[1]

When a number of these single molecules aggregate into an ordered bundle of filaments, they can also shear or slide relative to each other, either passively (in

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examples such as actin hair bundles in the inner ear) or actively (in motor-driven microtubule flagellar axonemes). In disordered aggregates, one has in addition to account for the variable connectivity of the filaments that often form a heterogeneous network and can lead to collective behaviors that one cannot deduce from the mechanics of individual filaments. Although the specific interactions that form these bundles or networks are clearly important at the molecular level, at the mesoscopic nanometer range or larger, these interactions can be coarse-grained into a few simple concepts that help us to classify and quantify the morphology and mechanochemistry of supramolecular structures. In the following, I review some minimal models that sharpen the questions that these systems pose.

2.1 Morphology of ordered bundles

Unlike single polymer molecules that are constantly buffeted by the thermal sea they inhabit, bundles are usually very stiff by virtue of their thicker radius, so that the persistence length of these objects is large enough that thermal effects may be neglected at the cellular level. In an ordered bundle of filaments, there are a number of interactions associated with filament bending and twisting, inter-filament adhesion, and finally bundle bending and twisting. For filaments of diameter d made of a material of Young's modulus E with bending stiffness $B \sim Ed^4$, and inter-filament adhesion energy per unit length γ, a natural length scale is the characteristic adhesion length $L_a \sim (B/\gamma)^{1/2}$.[2] A simple explanation for how this length arises can be seen by considering the geometry of a curved two-filament planar bundle shown in Fig. 1a. As the filament on the outside has to traverse a longer length it must stretch relative to the inner filament to prevent the filament crosslinks from becoming deregistered (for strongly adherent filaments), or slip relative to the inner filament (when adhesion is very weak). For a bundle that starts out from a straight nucleus, there is no reason to form bends or kinks. However, if the bundle nucleus enforces a natural curvature to the bundle, then the previous argument suggests that if the curvature is very large, the bundle will favor the formation of a series of periodic kinks wherein an extra monomer is inserted after a characteristic spacing proportional to the adhesion length L_a. The spatial extent of the kink $L_{kink} \sim \left(\frac{B}{\gamma}\right)^{1/2} f(L/D)$, where L/D is the aspect ratio of an individual monomer of length L and diameter D (see Fig. 1 a). In fact, geometrical considerations imply that $f(x) \sim x$ so that $L_{kink} \sim \left(\frac{B}{\gamma}\right)^{1/2} L/D$.[2]

This characteristic scale may explain why bundles of actin, sickle cell haemoglobin fibres and even amyloid fibrils form kinks. In three-dimensional bundles, we also need to account for the role of three-dimensional curvature and twist of the bundles which arises in tertiary structures of biological polymers such as coiled coils and other helical motifs. Since this twist is uniform for a filament with a circular cross-section, we may ignore it for free bundles since this twist can always "escape" from the free boundaries. To understand the role of the third dimension qualitatively, we will restrict ourselves to the simple case of two filaments wound around each other along a helix of pitch p and radius r. Then the energy per unit length of the aggregate $U/L \sim \frac{B}{r^2(1+P^2)^2} - \gamma\left(1+\frac{1}{P^2}\right)^{1/2}$, where $P = p/2\pi r$. The first term arises from bending a filament into a helix,[3] and the second characterizes the adhesion of the two filaments. Minimizing U leads to an expression for the pitch written in a general dimensionless form as $P \sim f\left(\frac{B}{\gamma r^2}\right)$. When three filaments wind around each other helically, energy minimization leads to braided rope-like structures.[8] However, when four filaments adhere to each other, another new

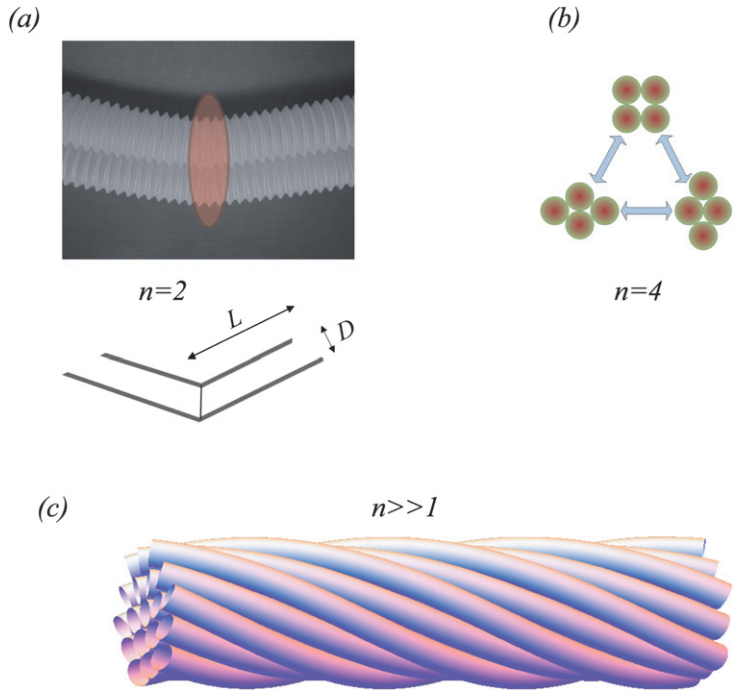

Fig. 1 Morphology of ordered fibrils. (a) A physical model and a schematic of a two-fibril adherent bundle. Any inherent curvature in the bundle leads to a mismatch in the strains experienced by the two filaments which have different path lengths. This leads to a set of periodic kinks, such as that highlighted in red. The schematic shows that the kink size depends on a characteristic ratio of the length of a subunit and its diameter, L/D. In bundles that are non-planar, the filaments can twist relative to each other and this allows them to further increase their adhesion. (b) In a bundle with 4 filaments which can twist relative to each other, the symmetry of packing leads to three possible states, so that the bundle can switch from one to another even if its central axis is straight. This can lead to a periodic pattern of defects as the filaments switch their relative positions at a cross-section. (c) In a bundle with many filaments, so that $n \gg 1$, one may be able to use a continuum theory that accounts for the shear, stretch, twist and bending.

characteristic in the bundle arises naturally, since the individual filaments are no longer equivalent. Indeed, looking at a bundle of circular filaments in cross section as shown in Fig. 1b shows that there are three possible packings: a square array or two symmetry-related triangular arrays between which the bundle may switch giving rise to a structure with periodic defects. This geometric feature might explain the amyloid structures of different morphologies that arise as a function of the number n of fibres in a bundle. When $n \gg 1$, we may use a continuum theory similar to that used in describing liquid crystals, but including penalties associated with both stretching and shearing filaments.[4–7] These bundles can exhibit dynamical transitions; for example, prokaryotic flagella are well known to undergo polymorphic transitions when subject to flow or pH changes,[9] in *Vorticella* there is an order-disorder transition in a polyelectrolyte gel mediated by binding to calcium ions,[10] while in the *Limulus polyphemus* sperm, a dynamic actin bundle can be extruded when an order–order transition changes a twisted kinked super-helical actin bundle into a straight one.[11] These transitions propagate through the bundles at rates that are dependent both on the underlying mechanochemistry as well as the macroscopic constraints associated with moving organelles through the ambient liquid.

There remain a number of questions associated with the morphology of these bundles, of which I will highlight just two. (i) A theory for the maximum diameter of these bundles. A simple physical picture associated with the fact that the outer

filaments of the bundle must be stretched to register with the filaments on the inside, immediately leads to a thermodynamic limit on the radius: when the energy of binding becomes comparable to the enthalpic energy required to stretch bonds, it is no longer preferable for the bundle to grow radially, and therefore it only grows axially. (ii) A theory for the dynamical transitions between different morphological states of a bundle. While experiments are suggestive of simple transition dynamics, a complete quantitative understanding remains elusive, and requires many concepts from polymer physics. From an evolutionary perspective, these designs are examples of convergence dictated by geometry, chemistry and physics. From the perspective of a polymer scientist, since these transitions occur in fairly simple systems, perhaps this is a case of biomimetic opportunism waiting to be exploited.

2.2 Mechanics of disordered filamentous aggregates

Cross-linked networks arise inside a cell as the cytoskeleton, but also are a crucial part of the extracellular matrix in organs, in collagenous networks that are common in skin, in blood clots, *etc.* As material systems, these networks are characterized by topologically complex connectivity and are often made of polymers with very different chemical and mechanical properties. The effects of thermal fluctuations are not always negligible in these polymeric systems, which have in addition an inherent structural disorder. When combined with enthalpic effects these determine the mechanics of the networks. In addition, the cross links themselves may be active (as in the case of motors that consume energy) and/or have their own kinetics. Recent theories and experiments have shown that a characteristic of biopolymeric networks is their strain stiffening ability as a function of the applied pre-stress, so that the material resists deformations strongly.[12,13] The underlying mechanisms for the strain stiffening behaviour fall into two categories: (i) those that rely only on microscopic nonlinearities associated with the deformation of the filaments and/or cross linkers that arise, say, from ironing out shorter and shorter wavelength thermal wrinkles as the applied deformations become larger (ii) those that arise from the collective non-affine deformations associated with the inability of mesoscopic regions to follow the macroscopically imposed deformations. However, despite much theoretical and experimental effort, it is still not clear which of the above mechanisms is relevant even in passive *in vitro* networks.

Here, I will highlight the role of connectivity in determining how non-affine deformations in heterogeneous networks of harmonic springs can lead to strongly nonlinear force-displacement characteristics. It was Clerk-Maxwell who first considered the conditions for rigidity of a network of bars with hinged joints; for a system with N nodes in d dimensions, with N_c constraints (springs) connecting them, the number of internal degrees of freedom of the system is given by $Nd - N_c$. When the number of internal degrees of freedom just vanishes on average, so that $Nd = N_c$ and the average coordination number $z = 2N_c/N = 2d = z_c$ (here the factor of 2 arises because each spring is shared between 2 nodes), we have a marginal state known as a marginal or isostatic state. In a network where $z < z_c$, applied boundary displacements lead to heterogeneous strains without stresses. Understanding this requires knowledge of the zero-energy modes of the system (see Fig. 2). These modes are associated with rotational degrees of freedom that allow the network to deform on multiple scales and are directly controlled by the average coordination number of the cross links. As $z - z_c$ sweeps through zero, the critical strain at which the spring network becomes stiff vanishes.[14] Shown in Fig. 2 are simulations of a filamentous network that is gradually strained.[15] We see that below a critical strain, the system deforms without offering any resistance, and then rather suddenly starts to stiffen under the influence of an externally imposed strain. This simple example suffices to emphasize that multiple microscopic mechanisms can lead to macroscopic strain stiffening behaviour, including (i) microscopic nonlinearity associated with the competition between entropy and enthalpy, (ii) quenched disorder and variable

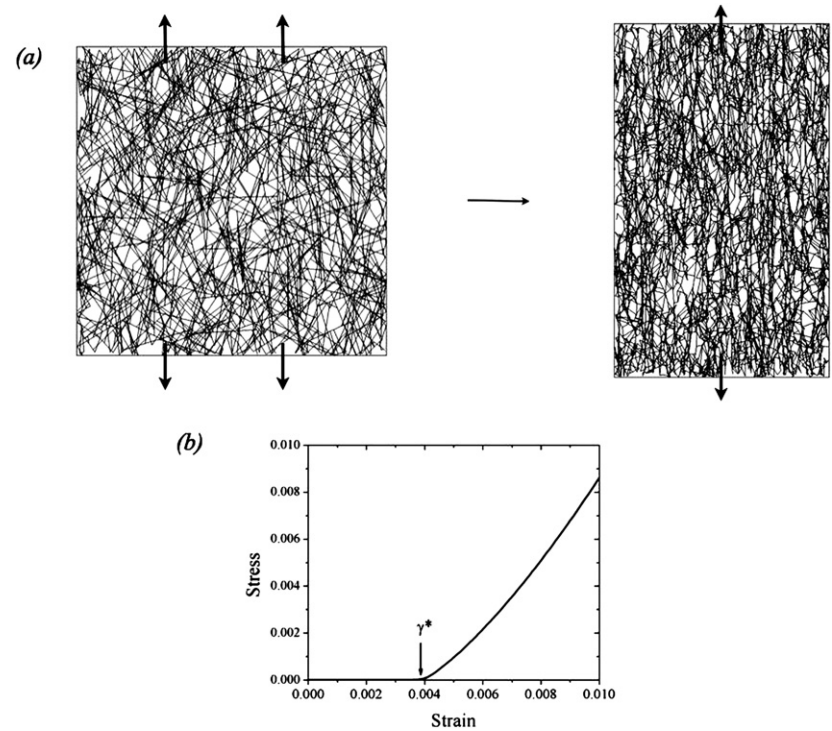

Fig. 2 Mechanics of disordered networks. (a) A two-dimensional network of fibres, with the average coordination number (see text) $z < z_c$, so that the network is floppy, is subject to a strain at the boundaries. As seen, this leads to the shrinking of the network in one direction and an extension in the direction of the applied strain, coupled to an orientational ordering of the filaments. (b) A plot of the nominal stress (using arbitrary units) as a function of the nominal strain shows that the collective response of the network leads to no stress until the strain reaches a critical value γ^*. This is because of the presence of floppy modes that allow for the rotation of parts of the network to accommodate the boundary strains up to a critical threshold. Only beyond this critical threshold does the network deform with a finite resistance. The springs are all assumed to be harmonic, *i.e.* they are linear, with a spring constant inversely proportional to their rest length. The simulations were carried out using a damped molecular dynamics method.

connectivity, and (iii) soft modes associated with rotational motions, as briefly discussed here.

Deciphering the relative importance of these effects will set the stage to uncover how biological networks respond to mechanical stimuli. Interestingly, the study of amorphous systems such as the cytoskeleton links aspects at the frontiers of physics to those at the frontiers of biology. Indeed just as the origins of life are shrouded in mystery,[16] so is the difference between the living and the non-living. For example, dessicated and frozen cells seem to be nearly ametabolic and in suspended animation while nevertheless remaining structurally intact.[17] Just as glasses strike at a number of questions at the heart of polymer physics, so too do dessicated and frozen cells that form living glasses, structured out-of-equilibrium systems that are nearly, but perhaps not completely ametabolic.

3 Simple aspects of cell dynamics

A cell is the minimal self sustaining unit in biology and consists of a heterogenous, yet structured assembly of filamentous and membranous polymers bathed in water. It can replicate, repair itself, move, respond to stimuli, and communicate with its

neighbors in a multicellular organism. Here I consider three questions. How can one describe the microstructured water-laden cytoplasm? How can one model the fundamental process by which a cell adheres to a substrate or to another cell? How might one study the physics of a molecular disease?

3.1 A micro-structural model for the cytoplasm

The cytoplasm of the typical animal cell shown in Fig. 3a shows that the heterogeneities in its structure range from a scale of between $l_p \sim 5$–50 nm corresponding to the pore or network size that varies from the cell lamellopodium to the nucleus, all the way to the system size which ranges from between $L \sim 10$–30 μm. A natural question at this scale is: what is the appropriate mechanical description of the cytoplasm? Recent experiments[18] on understanding the flow of water through the cytoplasm suggests a new description that is in stark contrast with classical theories that treat the cell as a visco-elastic or visco-plastic material. The cytoplasm is inherently a complex material as it is made up of water, ions, metabolites, soluble proteins, large protein aggregates and organelles, such as the cytoskeletal and membrane network, all of which are changing. Thus, even at the simplest level, one must account for the fact that the cytoplasm has two distinct phases, a solid phase consisting of a network, membranes and particulates, and a fluid phase consisting of water, ions, metabolites and soluble proteins, that interpenetrate each other. Poroelasticity, the theory that describes the mechanics of a fluid infiltrated solid such as water-laden soil, crosslinked gels in a solvent, colloidal networks, *etc.* provides a natural framework for this multiphase material that allows for the relative dilatational movement between the fluid and solid phases.

To understand this in a minimal setting, we consider the thought experiment in which a load is applied to laterally confined, hydrated, soft, porous gel *via* a porous membrane (Fig. 3b). In a cellular situation, the porous membrane might, for example, represent the plasma membrane which is driven by a contractile force. When the membrane is depressed rapidly, the network dilates locally to accommodate the incompressible fluid but barely moves further away. Eventually, as water exits the system through the porous membrane and progressively more of the load is borne by the gel, the network dilatation at all positions reaches the same value, and the gel relaxes until it reaches an equilibrium where the applied load is everywhere balanced by the elastic stresses in the network.[21] This experiment and its variants have been well studied in simple physical gels,[19] as well as in biogels such as

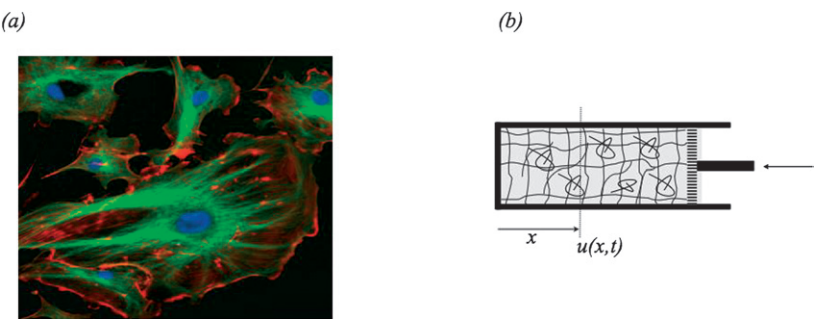

Fig. 3 (a) A plan view of an animal cell (Wikipedia) stained to show some of the cytoskeletal proteins such as microtubules (green), and actin (red). The characteristic size of the cell is about 10 μm, and clearly shows that it is made of a heterogeneous network similar to that shown in Fig. 2. Water makes up as much as 70–80% of a cell's volume. (b) A minimal model of the cell that accounts for the fluid and solid phases of the cytoplasm is that of a soft, fluid-infiltrated sponge. Here, to understand the response of such a system, we assume that the cytoplasmic gel is confined to a rigid chamber and compressed by a porous piston, with $u(x, t)$ the displacement of a cross-section at a location x at time t.

cartilage and collagen networks.[20] They demonstrate that in certain circumstances, the local dilatational strain and the stress in the network, as well as the pressure, are all functions of space and time in a fluid-infiltrated soft network. A brief description of the underlying theory and scaling ideas are outlined below.

If the displacement field of the gel (assumed to be made of incompressible constituent materials) is given by $u(x, t)$, the stress in it at a given cross-section is $K\partial_x u$, where K is the drained bulk (compressibility) modulus that characterizes the resistance of the porous network to volume changes in the absence of a fluid. Balancing the change in stress from one cross-section to another with the fluid pressure gradients yields $K\partial_{xx}u = \partial_x p$. The relative swelling or shrinkage of the gel is driven by fluid flow, which in a porous medium has a velocity v proportional to the local pressure gradient, *i.e.* $v = -k\partial_x p$ where k is the hydraulic permeability of the network ($k \sim l_p^2/\eta$, where η is the viscosity of the infiltrating fluid and l_p is the mesh size of the gel). Since the fluid can flow only because the gel network moves relative to it (given that the fluid and the solid of which the network is made are effectively incompressible), we also have the relation $\partial_t u = -v$. Combining the above equations, we find that $K\partial_{xx}u = -v/k = \partial_t u/k$, so that the displacement satisfies the diffusion equation $D\partial_{xx}u = u_t$ with diffusion constant $D = Kk$. For a suddenly applied load that is held constant, at a boundary of a gel of finite length L, we find that the largest characteristic time scale for relaxation is L^2/D, i.e. the larger the system, the longer it takes for the displacements and pressure to equilibrate. Similarly, the smaller the diffusion constant (corresponding to a small, very stiff mesh infiltrated by a very viscous fluid), the longer it takes for the pressure to equilibrate. This suggests that just as different parts of the cell are chemically unequilibrated, they may also be mechanically unequilibrated and lead to random uncoordinated blebbing in a cell in the absence of any external stimulus.[18] However, when a cell gets polarized in the presence of an external stimulus, it preferentially blebs along the axis of polarization. A simple mechanism by which this happens might just reflect the physical synchronization of different blebbing domains that have approximately equal frequencies (reflecting the cortical myosin driven contractions) but random phases that gradually align themselves temporally in response to the diffusive pressure or volumetric strain signal that naturally couples different cortical regions.

The movement of water in and through the cytoplasm must be eventually coordinated with the movement of water into and out of the cell through various membraneous routes. Given the importance of water as a solvent at the molecular level, this leads to a natural set of questions at the mesoscale: how does water content vary from one cell to another? How is water homeostasis achieved in cells? What is the role of water in cell motility and cell division?

3.2 A model of cell adhesion

Multicellular organisms consist of many cells that are adherent, at least most of the time. The mechanisms by which cells adhere to form cohesive tissues, organs and organisms are complex and involve a delicate dance that combines chemical signalling cascades, geometrical contact and mechanical interactions through focal adhesions, desmosomes, *etc.* The dynamic interface that the cell presents to the environment is a bilayer embedded with a number of channels, receptors and other proteins that exchange matter, information and energy with the exterior. Avoiding all but the simplest questions, one might ask how a cell responds when it starts to spread on a substrate. Since there are a variety of cell types, substrates and proteins that mediate these interactions, one might expect to see a variety of responses.

Ignoring these differences for a moment, if we assume that during the early stages of adhesion there is no actively directed mechanism that enhances/reduces adhesion, we may use a physical argument to characterize the dynamics of this process. On the time scale of the experiments ranging from a few seconds to a few minutes, the cell and its actin cortex are similar to a viscous shell that encloses a liquid cytoplasm

(Fig. 3). During spreading, the increase in cell contact with the surface is driven by the adhesion associated with the formation of both specific bonds and non-specific interactions, leading to cell deformation and flattening, which is accompanied by the dissipation of energy. The dynamical balance between these processes determines the temporal evolution of adhesive contact. Then, for a rate of change of the contact area $R\mathrm{d}R/\mathrm{d}t$ (assuming a disk-like shape for the contact zone), the adhesive power is $JR\mathrm{d}R/\mathrm{d}t$, where J, the adhesion energy per unit area is the product of the areal density of adhesive bonds and the energy per bond. To accommodate adhesion, the viscous cortical shell has to flatten and flow during spreading with a characteristic strain rate of order $\mathrm{d}R/w\mathrm{d}t$, where w is the thickness of the cortical shell. Since flow in the thin dense cortex dominates that in the rest of the cytoplasm, the characteristic volume over which dissipation occurs is of order R^2w. If η is the cortical shell viscosity, the energy dissipation rate due to the viscous flow in the cortical shell scales as $\eta(\mathrm{d}R/w\mathrm{d}t)^2R^2w$. Balancing this with the adhesive power leads to a simple scaling law for the contact radius at short times $R \sim (Jwt/\eta)^{1/2}$. Recent experiments[22] show that the initial dynamics of cell spreading are consistent with the simple picture outlined above. In particular, the area of contact is seen to grow linearly with time, independent of cell and substrate type. Furthermore, the theory also predicts its own demise: if the cortex is destroyed (using actin depolymerizing drugs), the dynamics of cell spreading should change qualitatively. This is seen in the experiments consistent with a modified theory.[22]

On the one hand, this is hardly surprising, since all the molecular details are not necessary to answer the relatively rough macroscopic question: how does a cell spread? On the other hand, this raises more questions than it answers: for example, what controls the adhesion energy J and the rheology/viscosity η of the cortex–membrane composite at the microscopic scale? Why does the active nature of the cell never play a role in determining its adhesive dynamics? Perhaps it is useful to emphasize the role of theory in biology in this context: it is not as important to answer a question in a nascent field in biology *via* this example which is primarily to sharpen questions. The success of our theory of cell spreading is only temporary; eventually the detailed facts will get the better of it, and the theory will be proven wrong, but out of the ashes will be born a new one that is still sharper. And so on.

3.3 Cellular flows and jamming

As the last example, I would like to consider the physics of a disease. Sickle cell anemia, the first molecular disease identified more than a half century ago by Linus Pauling and his colleagues, has been studied extensively at the molecular, cellular, and organismal level. Much is known separately about the molecular details of sickle haemoglobin polymerization,[23] sickle cell deformability and its effects on flow, and the clinical heterogeneity of sickle cell disease.[24] At the molecular level, the polymerization of haemoglobin S (HbS) occurs *via* a double-stranded nucleation mechanism and leads to explosive cooperative growth[23] that is critically dependent on the ambient partial pressure of oxygen. Polymerization leads to the formation of HbS fibers that change the morphology and stiffness of the red blood cell (Fig. 4) and this leads to an inability of the cells to flow through the narrowest vessels. In vascular tissue that absorbs oxygen, polymerization thus causes the cells to slow down and deliver more oxygen, so that the local oxygen concentration falls even more, leading to further sickling through a positive feedback mechanism, and eventually jamming of the capillary. The symptoms of the disease arise due to this jamming which leads to hypoxia, inflammation, thrombosis, strokes, *etc*.

The above phenomena involve two collective processes at different length and time scales: that of sub-second polymerization and morphological and rheological change at the level of an individual cell; and that of collective hydrodynamic flow of a soft suspension of cells which change their stiffness in a confining vessel and

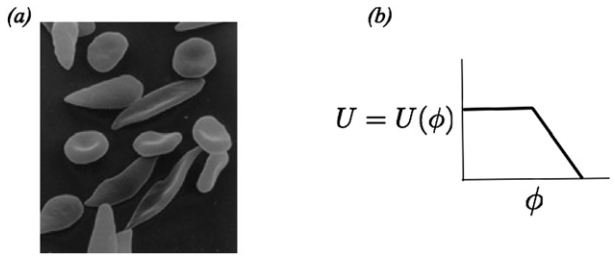

Fig. 4 (a) A view of normal (disc-shaped) and sickled (elongated) red blood cells (Wikipedia). The diameter of normal red blood cells is 8 μm, while the length of the sickled cells can be more than twice as large. As a consequence, sickled cells cannot flow through narrow capillaries. This vaso-occlusive process leads to hypoxia in downstream tissues, triggering the main symptoms of the disease. (b) A simple view of the jamming process can be characterized in terms of relation between the flow velocity of the red blood suspension U as a function of the cell volume fraction ϕ. At low volume fractions the velocity is a constant that is determined by the balance between the driving pressure gradient and the viscous resistance, while as the volume fraction approaches an effective close-packing fraction ϕ_m, the suspension viscosity increases dramatically and its velocity vanishes. This leads to a jam not unlike those observed in traffic flows.

slow down over the course of minutes. Our recent work[25] has shown that it is possible to evoke, revoke, control and inhibit the collective vaso-occlusive or jamming event in sickle cell disease using a microfluidic device that serves as an artificial vasculature with an ambiently controlled oxygen concentration. This allows us to use a combination of geometric, physical, chemical and biological means to quantify the phase space for the onset of a jamming event as well as its dissolution, thus opening the way to a quantitative integrative description of the processes that lead to vaso-occlusion. Here I will focus on just one aspect of the problem, namely the jamming process itself. For a population of sickled cells moving through a confined capillary, conservation of mass implies that $\partial_t\phi + \partial_x(U\phi) = 0$, where ϕ is the volume fraction of cells in the blood, and U their mean velocity. This equation is incomplete until we specify the relation between the velocity U and parameters such as the pressure gradient $\partial_x p$, the suspension viscosity $\eta(\phi)$, the radius of the capillary R, the oxygen concentration C_O and the local volume fraction ϕ, so that $U = U(\partial_x p, \eta, R, C_O, \phi)$. At a simple level, since the suspension viscosity $\eta(\phi)$ diverges as the volume fraction of the cells reaches some critical fraction ϕ_m (akin to the close-packing limit), we model this relation by specifying $U = U(\phi)$, represented schematically in Fig. 4(b). On approximating the dependence of the velocity on the volume fraction close to the critical fraction *via* the linear law $U = U_0(1 - \phi/\phi_m)$, and switching to a moving frame traveling at speed U_0, we obtain the well-known Burgers equation $\partial_t\phi - (U_0/\phi_m)\phi\partial_x\phi = 0$, whose solutions include shock waves that correspond to jammed states. Of course, reality is more complex, and an important aspect that remains to be addressed is a systematic derivation of a mesoscopic law that replaces the crude approximation used above.

Sickle cell disease provides one of the simplest examples of how a physicochemical process at the molecular level leads to a diseased state at the organismal level. Integrating these processes presents a challenge at the intersection of medicine, biology, chemistry and physics. Here, we are even able to see a potential path towards amelioration of the symptoms. Reducing the potential for sickling requires that we decrease the effective concentration of hemoglobin in the cells, or decrease the relative time that the cells spend in the low concentration environments associated with the narrowest capillaries in the body. Two possibilities suggest themselves: partial swelling of the cells so that the haemoglobin concentration drops sufficiently to prevent the cooperative polymerization even when the oxygen vapour pressure falls, but still allowing the cells to squeeze through the narrowest capillaries rapidly enough, or the use of dynamical drugs that bind to HbS transiently

with much the same effect: microfluidic mimics of the vasculature allow us to search for potential ways to achieve this.

The jamming of moving particles in a confined environment is also important in other pathophysiological situations that involve a hyperviscosity syndrome seen in leukaemia, thrombocytosis and multiple myeloma. It is also seen in a number of physical processes such as the flow of grains, colloids, and traffic in confined environments.[26] Once again, we see the similarity between a problem in the physics of amorphous materials and that of organized biopolymers that involves a range of spatial and temporal scales.

4 Prospects

In the study of problems that range from the origins of life to the pathophysiology of disease, polymer science naturally complements biology, since both ultimately involve the study of soft, warm, wet systems that are out of equilibrium. The examples that I have discussed have in common the connections across scales, in space and time. Looking more broadly at the intersection between these fields, one obvious nexus concerns the origins of life itself. A practical definition of life includes systems that can autonomously replicate, repair themselves and evolve *via* natural selection. This process requires both molecular templates (polymers) and complex organelles such as vesicles (also polymers) that are flexible enough to enable these processes,[16] but the main obstacle seems to be the difficulty of packaging and unpackaging macromolecular assemblies, a question in polymer science. A second obvious question is that of the limits to life. We know that extremophiles, organisms that live on the edges of what is now considered an ideal environment for life, are an excellent testbed to study this question. A particular example of relevance is that of anhydrobiosis, *i.e.* life in the near absence of water that has repeatedly evolved in a variety of single-celled and multi-cellular organisms.[17] A third example at this nexus of polymers and biology is that of infection mechanisms. Ultimately, any infection requires the physical crossing of an organismal or cellular barrier by another organism or macromolecular assembly. How this happens in the variety of life might shed light on evolution from a physical perspective and again may have implications for disease prevention.

I have focused on the simplest systems at the boundary between polymer science and biology, at the risk of studying "minced meat" rather than living forms. There is now a growing interest, and some understanding of how to generalize statistical and continuum field theories to look at phenomena that are far from equilibrium, as life is. This leads to a theme that has arisen repeatedly in biology: how are structures organized or self-organized in space and time in an organism, from simple macromolecules to complex architectures, and how do collections of organisms evolve over many generational times? The challenges are as great as the opportunities in these problems. The intellectual ideas go both ways; biology throws up new questions that traditional polymer science has not seen, while polymer science brings new tools that serve as useful starting points to look at problems in biology.

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