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Using Lessons from Cellular and Molecular Structures for Future Materials**

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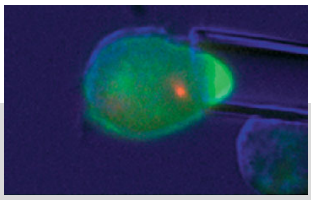

Cells and molecules exhibit robust and efficient characteristics that occur as a result of highly organized and hierarchical structures within these small scale living systems. These structures have the ability to adapt themselves to a wide variety of stimuli, including mechanical and chemical environmental changes, which ultimately affect behavior including cell life and death. The characteristics of these structures can be utilized as they provide unique advantages for building a future generation of material science technologies. In this article, we provide an overview of the similarities between materials and living cells, and discuss specific types of biological materials including cytoskeletal elements, DNA, and molecular motors that have already been leveraged to build unique functional materials. The future challenge will be to continue to use the scientific discoveries of today with upcoming discoveries in cellular and molecular science, and apply these principles to develop as yet unknown technologies and materials.

1. Introduction

The ability to use biology as an inspiration for developing the framework for future innovations has been successful on many levels. This emulation of biological systems has created explosions of research in fields such as biomimetics where biology-oriented lessons have enabled the development of new directions of research. One needs only to look at recent successes with research in areas such as gecko-inspired adhesive systems[1–3] and high strength-to-weight ratio materials based on silkworm and spider fibers[4–6] to see enterprising examples of this. One common factor that many of these biomimetic systems share is the size-scale of the phenomenon that is enabling a particular function, as this is often at the micrometer or nanometer scale. With gecko-feet, for example, their characteristic of adhesion is a combination of factors, including surface interactions and structural architectures of the hair on the foot. While biological inspiration has been utilized more regularly at the organism level, the next generation of discoveries may be parsed out of biology from different perspectives, such as those that may be generated from molecular and cellular biology. Many lessons can be learned from dissecting biological systems, such as living cells, to uncover how they integrate small-scale components at the molecular level into large-scale ensemble systems with complex functional abilities. These principles then can be used to create high impact advances. When viewing cells from a generalized systems perspective, it becomes rapidly apparent that the robustness and efficiency of cells are a direct result of highly complex interactions with billions of heterogeneous molecules functioning synchronously to accomplish a multitude of intertwined tasks. Using the lessons from these evolved biology-based systems may provide a multitude of new ideas for building future material-based technologies.

Cells and molecules already have specific interesting analogies to current material science topics that have been explored over the past decades. One important area that has generated excitement in material science is the field of "smart materials". Smart materials have a number of definitions, but one overall principle of smart materials, which is interesting from an adaptability perspective, is that these materials can undergo significant alterations in a controlled manner when exposed to external stimulation. Smart materials include a wide range of general types that are advantageous in various applications including piezoelectric materials, shape memory al-

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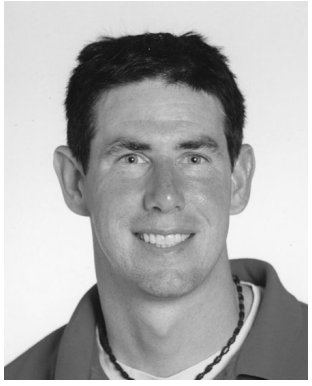
loys/polymers, pH-sensitive polymers, and chromogenic systems.[7–10] This is not an exhaustive list, but it does present a range of materials and associated stimuli that can be leveraged for a variety of purposes. For example, piezoelectric materials can be used to both sense and impose changes in voltage, which allows them to respond as well as control their environment through inputs such as force.[7,11] Shape memory alloys and polymers have the ability to change their structure and form based on thermal differences, which have resulted in applications such as self-tightening sutures.[8] pH sensitive polymers can respond to a change in an aqueous environment through shrinking or swelling and include materials such as hydrogels.[9,12] Chromogenic systems can visually adapt to a wide variety of stimulants including heat, optics, and voltage depending on the particular application.[13] One common theme for these materials is their ability to significantly change in response to external stimulation and in specific cases also to alter their environment in return. This principle is absolutely present in cells and molecules as these biological systems actively change in response to external stimulation. Cells and molecules also work in concert not only to respond, but also to radically change their environment when necessary as they adjust to external stimulation. In cellular and molecular behaviors, there are a number of smart-material-like responses with respect to stimulation; some examples are described below. This is prefaced by a discussion of the generalized framework for cellular and molecular responses to external stimuli, as this is a central tenet for this paradigm.

Cells respond to a variety of stimulants; each induces a signaling cascade that can lead to cell fates, such as apoptosis (i.e., cell death). This stimulation can include chemical, mechanical, electrical, optical, scaffolding, and thermal environmental changes. Due to the aqueous environment of living cells, chemical stimulation is typically considered the primary parameter that affects cellular responses. However, the mechanical responses of living cells are considerably important since the physiology of cells and organisms inherently experience mechanical stimulation. The mechanically induced cellular responses result in behavioral changes that parallel chemical stimulation; the field of mechanotransduction explores this interplay between mechanics and biochemistry.[14–18] Optical, thermal, electrical, and scaffolding alterations are also important and have affected a wide variety of cellular responses including cell differentiation, structure, and chemotaxis.[19–25] Although these stimulation parameters have important implications in terms of material similarities due to responses, in this article, we focus on the intersection of the mechanical and chemical aspects.

Cells have the ability to respond to stimulation by internally altering their function as well as actively adapting their extracellular environment. In comparison with materials, which are often designed to respond to one particular stimulation parameter (carbon nanofibers are often designed for adapting to mechanical stimulation), cells have evolved to respond to a variety of inputs, including mechanical and chemical stimulation in a coordinated manner. For example, cells can move to-



Philip LeDuc was born in Columbia, Missouri in 1970. He attended Vanderbilt University, North Carolina State University and then received his Ph.D. from Johns Hopkins University in 1999 working with Gang Bao. He then was a post-doctoral fellow at Children's Hospital and Harvard Medical School with Donald Ingber. He is currently an Associate Professor in the Mechanical Engineering Department at Carnegie Mellon University with courtesy appointments in Biomedical Engineering and Biological Sciences. His research interests are linking mechanics to biochemistry at the cellular and molecular levels through examining structural regulation. Also, through focusing on nature inspired design principles at the molecular and cellular levels, novel approaches to technology development will be enabled. He pursues these goals through developing and utilizing nanotechnology, microtechnology, computational biology, and controls theory. He has also been involved with many philanthropic organizations including mission trips to Africa and Armenia and with raising money for non-profit organizations.

Born in 1969, Douglas Robinson grew up in Columbus, Indiana. After completing his undergraduate training at Purdue University, he did his Ph.D. thesis in developmental genetics with Professor Lynn Cooley at Yale University School of Medicine. He then did postdoctoral research in biochemistry with Professor James Spudich at Stanford University School of Medicine. He started as an Assistant Professor at Johns Hopkins School of Medicine in the fall of 2001. He holds appointments in the Department of Cell Biology and the Department of Pharmacology and Molecular Sciences. Robinson participates in the Biochemistry, Molecular and Cell Biology (BCMB), the Anti-Cancer Drug Development (ACDD), and the NanoBioMed (NBMed) training programs at Johns Hopkins. His research focuses on the molecular basis of cell division mechanics and regulation, and his group utilizes genetic, biochemical, chemical, quantitative cell imaging, microengineering and mathematical approaches in their research.

ward favorable conditions through chemotaxis, such as in wound healing, by adapting their structure to a change in scaffolding or mechanics (i.e., cells are presented with injury areas where cells are absent, which induces their subsequent movement into these altered areas as a direct response to the physical change in the extracellular environment). The mechanics and scaffolding are separate variables, but they can be intertwined as the mechanics that cells and molecules experience can be affected by the scaffolding environment. For example, if a cell is only attached to a planar scaffold versus a three-dimensional scaffold, the mechanical stimulation would create a different response. This cell movement has direct correlations with the local chemical environment as well. One example is that cells can directly influence their surrounding environment so that they are not only adapting, but are actively changing their external environments. For example in motility, cells can secrete extracellular matrix molecules, such as fibronectin, to alter the scaffolding on which they move.[26] This allows them to control motility through biochemical means. One of the essential structural components in the cell that directly changes under mechanical and chemical external stimulation is the cytoskeleton. The cytoskeleton not only is adaptable but is also one of the main structural and organization units within a living cell. While the cell has internal structures that affect its response, materials can also have structures that respond to stimulation such as mechanics through its integration within the material (e.g., fiber-reinforced composites) as shown in Figure 1.

It is important to note that cells and molecules reflect many of the material science-based principles common to smart materials, but beyond this, there is great potential for learning how to apply lessons learned by studying cellular and molecular function in a cross-disciplinary manner with material science. By dissecting and re-synthesizing these interactions and principles, we can consider high-impact ideas when hypothesizing new approaches for future material science-based technologies. One of these salient features to consider from a biological perspective is assembly. The concept of assembly is essential in many fields, including nanotechnology, where it can be used for the scaling-up of systems from the nanometer size to create larger organized systems; this involves both organizational and hierarchical issues. The field of assembly, in terms of molecular systems, has been examined by polymer scientists in the past since there are advantages in inducing and controlling self-assembly that enable unique properties for large-scale systems. For example, self-tightening sutures[8] are polymers that control small-scale interactions to create large-scale deformation. They rely on assembled polymers to form systems that are responsive to thermal stimulation creating a mechanical response.

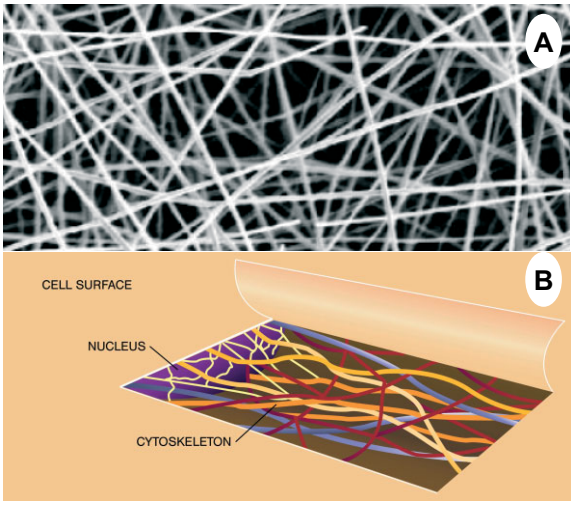


Figure 1. Cells and molecules have inherent structures that share characteristics with inorganic materials. Understanding these types of biological structures provide lessons gleaned from the small-scale biological world, which could potentially lead to future developments in the fields of materials science. A) Carbon nanofibers. Reproduced with permission from [27]. Copyright 2004 American Association for the Advancement of Science. B) Filamentous cytoskeleton elements within a cell. Reproduced with permission from [28]. Copyright 1998 Scientific American Inc.

2. Using DNA Structure for New Technologies

The areas of assembly and scale-up are essential in cell functioning and these behaviors can provide fundamental advantages in new technology development. The cell has a number of essential components that are self-assembly-based, including DNA and cytoskeletal elements. DNA has intriguing properties and potential with respect to material technologies based on its repeatable yet robust structure. DNA encodes the genetic information of the cell, yet has a tantalizing simple structure with the units being comprised of just four nucleotide bases (adenine, cytosine, guanine, and thymine). The DNA is organized into chromatin, which contains an extreme amount of information arranged into a highly compact structure. The entire diameter for packing the chromatin within an individual cell is measurable in single micrometers, yet if the DNA of one cell was to be stretched into a linear strand, it would be over a meter in length.[29] From an organizational point of view, the chromatin is fascinating, but, when exploring its response characteristics, the dynamics reveal efficiencies that are challenging to be matched by man-made systems. This highly organized molecular system is dynamic by nature and is often in flux in terms of being structurally altered by enzymes, such as acetylases and deacetylases that modify the scaffolding network and enzymes, and polymerases, helicases and methylases that modify the DNA directly. Furthermore, DNA is so highly organized that the copying process is tightly regulated temporally and spatially, as has been well demonstrated for *Caulobacter crescentus*.[30]

While DNA is a fascinating system from a biological perspective, the characteristics and lessons learned from DNA can be used to produce future technologies from a material science standpoint. Some specific recent examples are the use

of nucleic acids for building nanoscale structures and for templating approaches in chemical synthesis.[31–35] For nanoscale structures, one approach that has yielded results is the use of DNA for self-assembly technology to create complex structures. Nanometer-sized octahedrons have been assembled through the folding of single-stranded DNA (Fig. 2).[31] The key to this work was that the researchers utilized specific biological, but material-like, properties of self-assembly and self-organization. Since there was specific bonding between DNA base pairs, they directed assembly at small scales by controlling the DNA sequences. The combination of specific single-stranded DNA along with a shorter synthetic oligodeoxynucleotide enabled the structure of an octahedron to be realized. The final product had 12 edges that intersected at four-way junctions to form a 22-nanometer octahedron. This demonstrated that, by leveraging direct biological principles such as self-assembly, small-scale material structures can be controllably produced. Another approach that has been successful is to use DNA as a templating system. Specific chemicals were linked to DNA, which then organized the chemicals, creating favorable conditions for reactions to proceed. While chemical reactions are typically completed through homogeneously mixing chemicals in aqueous solutions, the ability to induce non-favorable reactions to occur provides a framework for creating novel reactions. By decreasing the spatial separation between the individual chemical components, the efficiency of the reaction increased (Fig. 3).[32,33] Thus, the reaction probability increased multi-fold, which is especially useful when the amounts of reactants are limited. The approach yielded a wide variety of reactions such as an efficient carbon-carbon bond forming reaction for creating an enone from an alkyne, using palladium as a catalyst. Compartmentalization is a well known behavior in the cellular world, which biology has utilized. Some specific examples of advantages that are observed when using compartmentalization include increasing reaction efficiencies, sequestering molecules for fast dynamic responses, and exclusion of molecules from sub-cellular locations. In summary, the concept of implementing molecularly inspired materials (e.g., DNA) to provide advances in controlling chemical reactions reveals the strength in using lessons from the molecular and cellular worlds. Using these assembly and scaling effects for chemical reactions also has applications in other fields, such as the potential development of biological nanofactories to modify chemicals within the body using a biologically inspired material based approach (Fig. 4).[36] This semi-solid-state design principle is common-place in living cells and thus might only be the beginning of directions to pursue in using assembly based biologically inspired approaches.

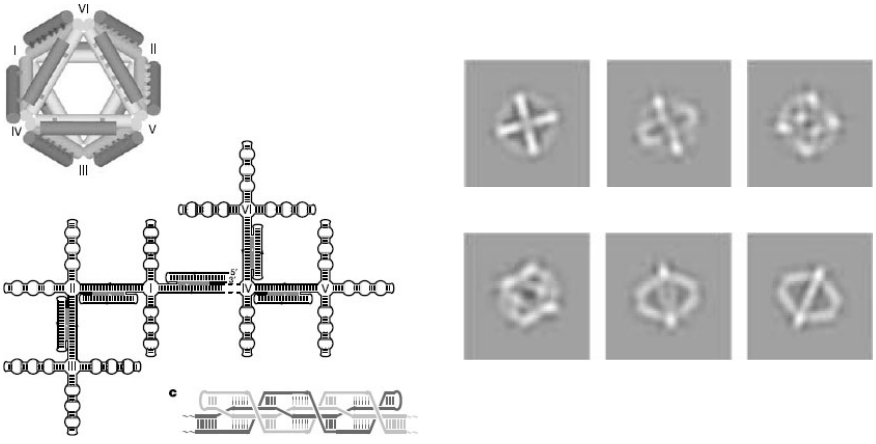


Figure 2. Single-stranded DNA folded into an octahedron shape. This three-dimensional configuration has twelve struts and six joints. Using cryo-electron microscopy, projections of the three-dimensional maps for this system were made. Reproduced with permission from [31]. Copyright 2004 MacMillan.

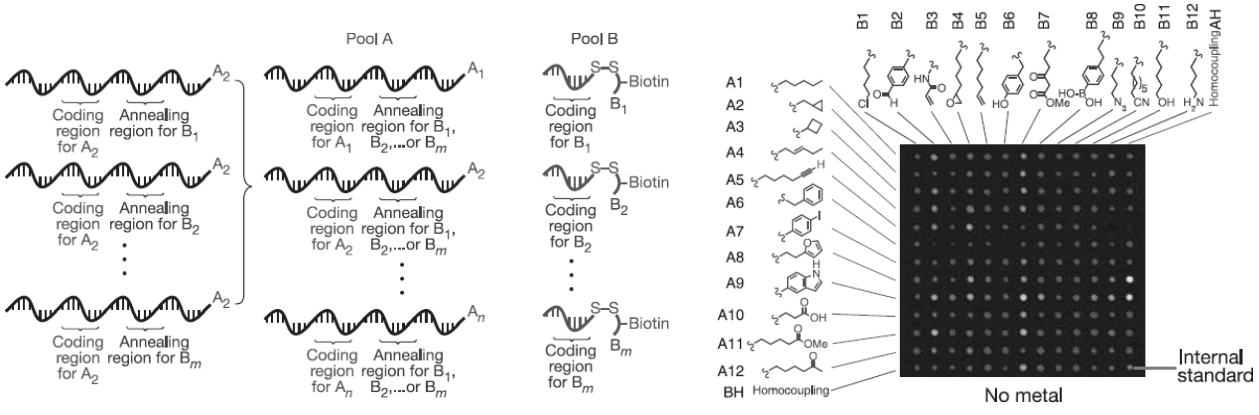


Figure 3. An approach for pursuing novel reaction discovery methods using DNA-linked organic functional groups, which enables the creation of unique sequences. The results show different discovery selections through utilizing controlled reaction conditions based on the nucleic acid sequences and functional groups. Reproduced with permission from [33]. Copyright 2004 MacMillan.

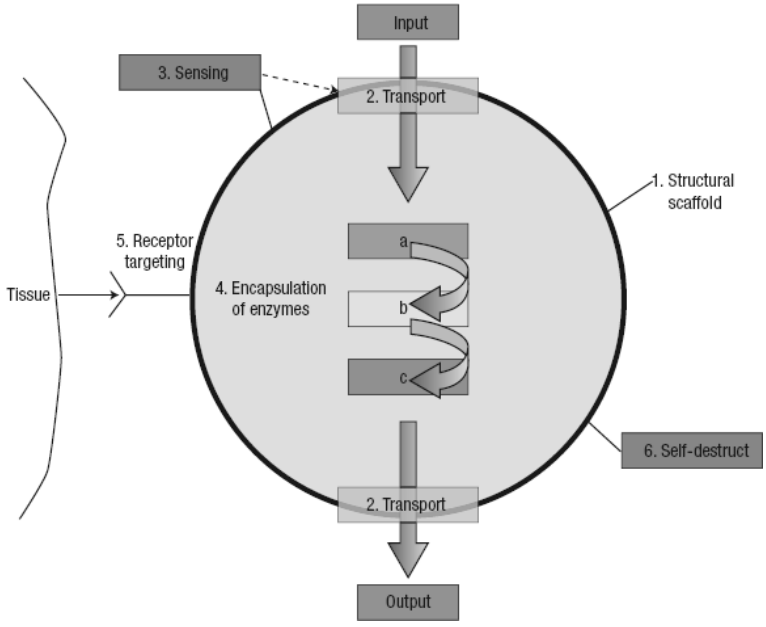


Figure 4. A proposed framework for a biological nanofactory inside the body. The principles for building this system are biologically inspired, but lead to the creation of a material science-based device. Instead of traditional drug discovery, this proposed factory could reside in the body modifying chemicals and creating products that are physiologically beneficial [36]. Reproduced with permission from [36]. Copyright 2007 MacMillan.

3. The Cytoskeleton as an Adaptable, Robust, and Responsive Material

While DNA and chromatin are self-assembly systems that constitute the genetic material, the cytoskeleton is a self-assembly system that provides structure across the cell for organizing hierarchical and complex interactions. Often interactions within a cell require the completion of a complicated set of tasks while the cell accomplishes these efficiently and demand that some seemingly opposing jobs be accomplished simultaneously. The earliest cells undoubtedly had to deal with chemical, thermal, and mechanical perturbations, and some of these stimuli act positively to direct the cell while other inputs are better avoided. Consequently, cells developed the ability to respond to specific signals while having the ability to reject unwanted disturbances. For example, cells can avoid deleterious mechanical deformations, which could lead to cell injury, while maintaining the ability to be purposefully deformed and reshaped during processes such as cell division or cell motility.[14,37] All of these dichotomous functions are largely carried out by the cytoskeletal polymer network and its associated proteins and motors.

From a mechanics perspective in biology, the cytoskeleton is a remarkable material. Constructed from genetically encoded proteins that assemble into dynamic polymers, the cytoskeleton provides a number of functions for cells. The majority of the material properties of living cells are derived from intermediate filaments and actin filaments.[38,39] Microtubules do contribute to cell mechanics, but their primary roles are to organize cell activity, mark the cell center, set up cell polarity, and provide tracks for long distance transport through the cytoplasm. Intermediate filaments (IFs) are nonpolar fibers constructed from dimeric coiled-coil subunits. IF-family filaments are found underlying the nuclear envelope (e.g., nuclear lamins) as well in the cytoplasm (e.g., keratins, and vimentin) in a wide range of tissue types. This family of proteins appears to be a late arrival from an evolutionary perspective, as it is primarily metazoan genomes that contain both nuclear and cytoplasmic members. The IFs give many cell-types of higher metazoans their characteristic mechanical properties, particularly in the case of the epithelia that make up skin. Skin has the fantastic properties of being elastic, water repellent, self-renewing, and healable in one material. The outer cornified layer of the skin is comprised of largely dead cells whose predominant (up to 80 %) cellular protein is filamentous IF keratin. The IFs have the property of being able to withstand large strains without rupturing, a feature that undoubtedly makes them well suited to provide mechanical support to tissues like skin.

Actin filaments, while constituting only ~1 % of the mass of humans, are particularly important cellular polymers that provide diverse functions in the cell. Classically, actin is well appreciated for forming the basis of the stable paracrystalline structure of the muscle sarcomere where the actin filaments provide the ropes that the muscle myosin-II pulls on to shorten the sarcomere.[40] However, in non-muscle cells, actin filaments are much more highly dynamic; they polymerize and depolymerize in response to a number of intrinsic and extrinsic signals, and allow for enormous reorganization of the architecture and shape of cells. Polymerization leads to force generation, and is central to processes, including whole cell motility, immune cell recognition, contractile belt assembly during cell division, and motility of endosomes and many types of pathogens. Mechanically, actin filaments are semi-flexible fibers with an elastic modulus of ~2.3 GPa (approximately the same as polymethyl methacrylate); in the cell, they typically exist at ≤10 % (≤1 μm in length) of their persistence length (~10 μm).[38,41] In a sense, one could say that the human body is constructed, in part, from a network of tiny, plastic-like fibers. While the size of a typical cell ranges from 10–30 μm in diameter, the actin filaments are much shorter. Pure actin filaments generate relatively poor mechanical resistance and instead derive much of their mechanical properties from cross-linking proteins.[42–45] These cross-linking proteins result in the actin filaments being arranged in a complex network of isotropically cross-linked actin filaments, parallel arrays of actin filaments (bundles), and networks with intermediate levels of filament ordering. A typical genome contains on the order of 100 different actin cross-linking proteins. A generalized material example of this might be a wire (an actin filament as a biological parallel) that

is bundled together with a multitude of additional wires to make a thick cable such as in the Golden Gate Bridge. This is compared to wires that are linked together in a chain-link fence; these would result in a different mechanical and structural response. For the cable, the thin wires are gathered together in tightly packed bundles, which results in a mechanically strong structural element. These cross-linkers can typically link two or more actin filaments, but there are also tethering proteins that link one or more actin filaments to other structures such as integral plasma membranes or microtubules.

These cross-linkers also confer the mechanical properties of pure actin networks. By stabilizing the lifetimes of actin polymer entanglements, cross-linkers define the structure and time-scale dependent properties of the network (Fig. 5).[47] A wide range of cross-linker effects on actin networks has been observed in purified systems outside of living cells. During extension, cross-linkers (e.g., filamin) cause actin networks to strain-stiffen over a range of strains but at high strains the networks soften.[44] Under compression, the cross-linked networks show a similar strain-stiffening with a non-hysteretic softening at high stresses due to actin filament collapse, presumably because the two strands of the actin filaments become dissociated.[48] Because actin filaments are semi-flexible and respond differently to extension when compared to compression, cross-linked semi-flexible polymer networks produce negative normal stresses during shear-thinning, as opposed to the typical positive normal stresses observed for flexible polymer materials. These normal stresses can be almost as large as the shear stresses, which may have significant consequences for how the active living cytoskeleton responds to deformations, either purposeful or imposed.[49] The strain-stiffening behavior arises in cross-linked networks due to the cross-linkers' stabilization of the interactions between the semi-flexible filaments. As the filaments are extended, the undulations in the filaments between cross-links are extended, resulting in the creation of a more rigid network. This is exciting as cells have evolved interconnecting systems to produce a wide range of networked structural responses in living cells through building blocks.

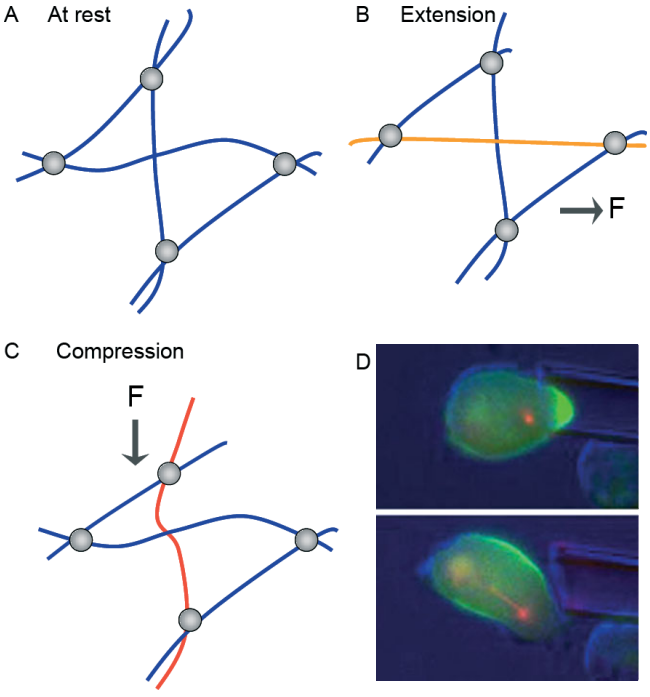


Figure 5. Cross-linked semi-flexible polymers and the mechanosensory network of cells. A) An illustration of cross-linked (gray spheres) semi-flexible polymers (actin, blue ropes) at rest. B) The network in extension due to an applied force (F). The networks strain-stiffen as a result of pulling the undulations from the filaments (orange). C) The network under compression. The network also strain-stiffens due to the induced undulations. At extreme compression, the actin filaments buckle, causing stress softening. D) A dividing cell expressing a fluorescently labeled actin-cross-linking protein. Reproduced with permission from [46]. Copyright 2006 Elsevier. The mechanical load brought about by micropipette aspiration triggers the accumulation of the cross-linkers at the micropipette tip. The cell then contracts from the load and reorients the green fluorescent protein cross-linker to the equator. The red signal (red fluorescent protein tubulin) identifies the mitotic spindle.

Within living cells, much less is understood about how cross-linkers control cell mechanics though. While it is tempting to treat cross-linkers as synonymous, data from genetic, sub-cellular localization, structural, and kinetic studies all portray a more complex picture. This is not surprising when one considers what cells have to accomplish. Cells have to be simultaneously mechanically resistant to external mechanical perturbation yet able to reorganize and restructure themselves to perform essential tasks such as cell division and crawling. To provide mechanical resistance to externally applied forces, it is advantageous for the cross-linked network to strain-stiffen to protect the cell. The cross-linker filamin most likely plays a significant role in strain-stiffening mechanics. Cells deficient in filamin form numerous membrane blebs, regions where the plasma membrane has separated from the cortical actin network, indicating a defect in the membrane-cortex attachment.[50] Interestingly, the *filamin* gene is mutated in a large percentage of human tumors, probably because its inhibition promotes cell motility and furthers the ability of the tumor cell to penetrate tissue layers, promoting metastasis, which can lead to a higher mortality rate.[51] Mechanical perturbation can also activate signaling pathways that lead to cytoskeletal remodeling and reinforcement.[14,52] Furthermore, many types of cells sense externally applied forces and convert the disturbance into signaling inputs that can alter gene expression and even cell fate.

During cell division, an even more complicated response is found. Failure of cell division due to mechanical disturbances is deleterious for the cell and for multi-cellular organisms.[37] However, the cell in a similar mode, must be able to reshape itself purposefully in the desired manner to produce two cells.[53] To accomplish this, spatially enriched (equatorial) actin cross-linkers, in concert with myosin-II (a mechanoenzyme) and globally distributed actin cross-linkers, must orchestrate this elegant process of division. These two pathways (global versus equatorial) provide the molecular basis for a

force-balance system that stabilizes the dividing cell as it goes through its shape evolution.[54] In isotropic networks, strain causes a network to stiffen. Yet, cells create strain to purposely change shape, thus constricting the equator. At first blush, one would think that this is a self-defeating process. However, one plausible explanation is that this is where the different pathways (global versus equatorial) of actin cross-linkers become significant.[53] By organizing the networks with different cross-linkers, the different regions of the network can be structured uniquely with cross-linkers that release on different time-scales and with a unique response to specific mechanical strain parameters.

Intriguingly, mechanosensory responses are also altered during cell division. Mitotic *Dictyostelium* cells respond to applied mechanical disturbances by reorganizing their contractile apparatus to the site of the disturbance, which allows the cell to contract away from the applied load (Fig. 5).[46] During interphase, the cell does not respond to an applied load by readily redirecting its contractile machinery; instead, the cell presumably strain-stiffens with its existing network. Dividing cells are already primed for contractility so that they seem poised to respond in this manner; this mechanosensory response is likely to be part of the mechanism that the cell uses to achieve and ensure symmetry before undergoing division.

Cells also have a fascinating ability for self-repair, which can occur on many size scales. Tissues and cell mono-layers can heal by activating cells to crawl into the opening (e.g., during wound healing after an incision). At the sub-cellular level, tears in the plasma membrane are also healed to prevent cell death.[55] Higher levels of free extracellular calcium trigger the recruitment of cytoplasmic vesicles to the site of the membrane tear. The vesicles work together, fusing to each other before ultimately fusing with the plasma membrane. Similarly, the cortical cytoskeleton must be repaired during this process. Within 15–20 s of wounding, signaling proteins are activated locally. These signals recruit actin filaments and myosin-II, which accumulate at the site of the tear within 60 s. Concomitantly, microtubules are assembled and oriented perpendicularly to the membrane. Although this coordinated response can heal the cell, the manner by which this rapid wound-healing network is regulated, assembled, and organized is still poorly understood.

The characteristics of the cytoskeletal elements in cellular behavior suggest numerous areas where future design principles in the material science realm can be developed. The cross-linked actin network can strain-stiffen, offering an integrated mechanical network. By stiffening the network, strain can be transmitted to specific proteins, leading to local unfolding and the creation of new binding sites. This offers fresh possibilities for enzyme activation that, in turn, leads to chemical signal transduction. In contrast, the same network can be remodeled in a spatially and kinetically controlled manner to produce two daughter cells. This contractile network is now sensitized to mechanical perturbation, allowing external cues to direct its localization, and is responsive to direct cues from the environment that may lead to healing of damage. In sum, the cell can distinguish between unwanted shape deformations and yet purposefully deform for specific functions. These highly opposed yet efficient processes all occur employing the same cytoskeletal backbone, demonstrating the tremendous efficiencies of these fundamental structural building blocks in cells. The most strategically relevant lesson here is to extract principles from the analysis of this robust network to build multifunctional adaptive structures for material technology in the future.

4. Applying Lessons from Materials Science to Small Scale Biology for Future Materials

Understanding the science behind the response of biologically based systems such as cells is essential, but translating these unique characteristics into advantages in the material science world will enable many future technologies and discoveries. This has already been accomplished in examples such as DNA templating, with a multitude of potential application areas. To more fully exploit the possibilities, one approach is to understand the essentials of the small-scale interactions in cellular and molecular studies and then use these concepts to develop a future generation of technology. This approach of studying small-scale interactions in order to forge new and useful directions in technology has been used in material science in the past. As an example, in the field of plasticity, the science of dislocations has provided exciting new avenues over the past several decades for understanding the principle of yielding in metals.[56–58] As is well known in the field of plasticity, steel was used for a long time prior to dislocations being understood or even discovered. This was possible because of the empirical nature of the characteristics. The relationship between stress and strain for steel was mostly known during the time of using it for building structures. While this was useful and applicable knowledge, the exact mechanism for plasticity from an atomic standpoint remained unclear; however, the pursuit of the scientific reason for this response continued. Over time, the development of theoretical approaches along with advances in electron microscopy revealed the mechanism through which atomic dislocations were responsible for the plasticity response in numerous types of metal.[59–62] This discovery allowed for novel approaches to be pursued as the scientific basis for this response was used as the building block for reconsidering materials and how to improve their properties.[63–65]

Just as material science has been spurred by discoveries of small scale behavior such as dislocations, cell mechanics is similarly poised to be the genesis of novel and exciting work. Currently, the field is just beginning to appreciate the links between mechanical stresses and chemical responses (i.e., mechanotransduction). These mechanically activated cellular responses though have greater variability than the known mechanical response in the case of metals. Some of the interactions in mechanotransduction are just now being elucidated although there is still much debate on the precise mechanism.

The small-scale interactions responsible for these responses in both cells and metals require us to decipher the governing rules and apply them to large-scale systems through addressing organization and hierarchical issues. For the mechanical response of metals, the increasing size-scales can include atomic dislocations, grain boundaries, homogeneity, and composites. In cells, the size-scales can include atomic interactions, protein domains, single proteins, multi-protein complexes, cells, tissues, organs, and whole body. Though simplified, these general hierarchies for scaling small-size principles into aggregate behavior can provide directions for future technology development. The biological world has already begun to provide some of these scaling and hierarchical insights,[66,67] yet there are numerous directions that will likely produce high impact results.

By using principles of organization in the biological world and interfacing them with material science, one can promote the possibilities of combinatorial work that would employ unique characteristics of both systems. One of the more fascinating technology intersections is centered on biological systems and their ability to convert chemical energy into mechanical work with extraordinary efficiency. In biology, cells have evolved molecular motor proteins that couple the energy released by hydrolyzing an ATP into conformational changes that lead to mechanical work.[40] These motors are extraordinarily efficient, achieving 50–90 % efficiency with the ability to generate 3–10 pN of mechanical force per motor.[38] In muscle, these motor-based ensembles are further organized into large paracrystalline arrays that allow entire tissues to contract, moving entire limbs of the animal body through a multitude of organized nanometer-scale motors. The combination of remarkable efficiency, the large forces involved, the clearly hierarchical organization, and the ability of arrays to self-assemble into useful machines have captured the fascination of innovators who would aim to imitate such elegance to design devices inspired from these principles.[68] When contemplating this direction, an ideal biological nanomachine should have the ability to generate a considerable amount of work with high efficiency using a biological energy source such as ATP. Such a machine must also have an interface that can link the biological component with synthetic components so that the motors can be functionalized for specific applications.[69,70] A few systems that use either microtubule-based motors or the mitochondrial F1/F0 ATPase have already been developed.[69,71–73] On larger-length scales, gliding bacteria have been harnessed to drive a rotary motor (Fig. 6).[74] This feat required that the appropriate geometry of a rotor and a track be created to allow bacteria to enter the system, attach to the rotor arms, and swim in a circular fashion, turning the rotor. For completely non-biological systems, but using principles of molecular systems, nanorotary motors and linear synthetic molecular muscles have been developed.[75–77] The nanorotary motor (Fig. 7) is based on a chiral helical alkene that undergoes a directional rotation in response to two photo-induced cis–trans isomerizations, mimicking the rotational movement of the mitochondrial F1/F0 ATPase. The

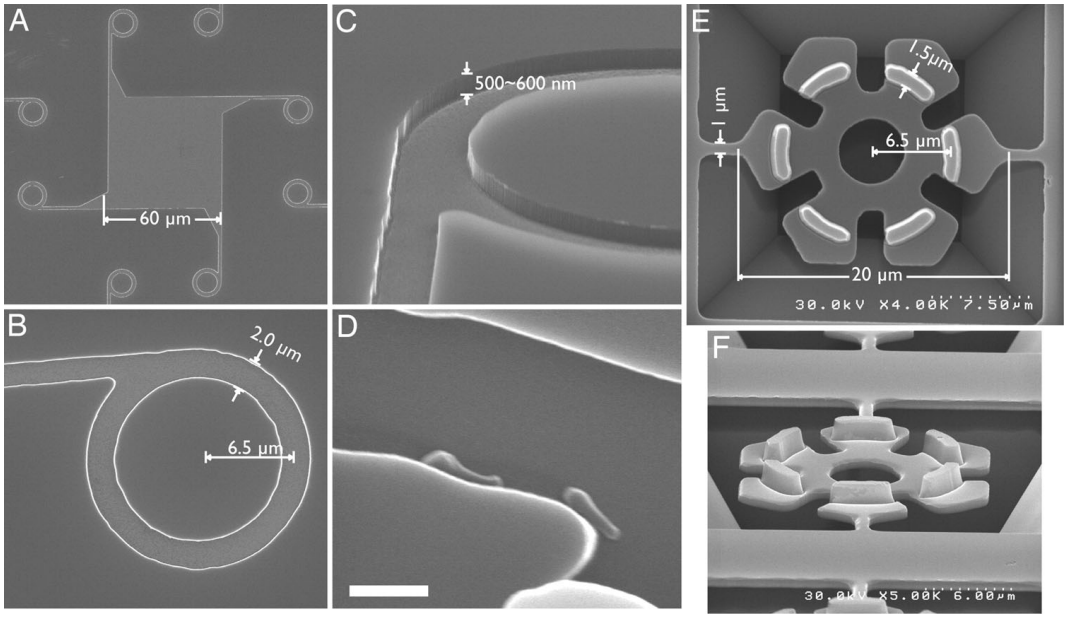


Figure 6. A bacteria-powered microrotary motor. A–D are scanning electron micrographs (SEMs) of the Si track and E and F are SEMs of the rotor. Panel A is an overview of the track with B and C highlighting the dimensions of the rotary track. The protrusion on the rotors (E and F) fit into the track. The gliding bacteria *M. mobile* are added to the square chamber in panel A and they swim along the wall into the straight passageways until they engage the rotor. In panel D, two bacteria can be seen swimming, turning the rotor. The chamber is coated with a sialic acid-containing protein (fetuin), which is required for the bacteria to glide along surfaces. To facilitate engagement with the rotor, the rotor was coated with streptavidin, and the cell-surface proteins of the bacteria were biotinylated. Figure and legend were adapted with permission from [74]. Copyright 2006, National Academy of Sciences.

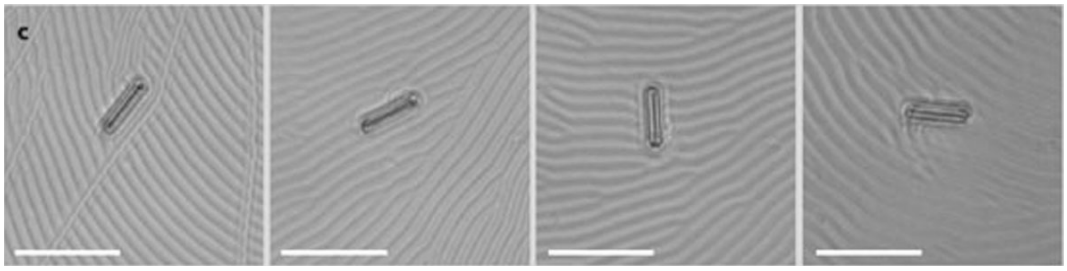


Figure 7. A nanorotary motor based on a chiral helical alkene that undergoes a directional rotation. A glass rod rotates on a liquid crystal in response to UV irradiation using this motor. Frames taken every 15 s. Figure and legend adapted with permission from [77]. Copyright 2006 Macmillan.

molecular muscle draws upon a synthetic bistable rotaxane in which a tetracationic cyclophane ring moves between two redox-sensitive, thermodynamically stable positions, allowing the movement of the ring to be controlled.[75] The rotaxanes could bend reversibly flexible microcantilevers by alternately exposing the molecules to oxidants and reductants. From these examples, it is clear that a wide range of strategies are being conceived and tested for their potential to develop nanomachines inspired by biological systems. Some strategies draw upon biological design principles while others directly incorporate biological materials into the nanomachine. Both directions focus on the fundamental strategy of pursuing the interface of cellular/molecular research with material science and will lead to exciting new discoveries in the future.

5. Conclusion and the Future

Cells and molecules within a cell are organized in directed ways that enable these biological systems to be highly robust and efficient. This organization, crafted by the cytoskeleton, DNA, and other associated molecules, provides numerous excellent examples of biological technology that can be leveraged by the material science community. The characteristics of DNA are useful in building novel technologies that can be used to control chemical reactions and form new geometrically defined materials of nanoscale dimensions. The elements of the cytoskeleton (polymers, motors and cross-linkers) work in concert to enable a range of functions, including intracellular communication and mechanical responses. This amazingly efficient network of molecules will provide novel insights for future technologies if by no other means than by stimulating the imagination for the possibilities of future materials and devices.

Cultivating new hybrid technologies by understanding the complexity and elegance of biological systems and merging them with established principles of material science will empower the development of unimagined advances. Biology at the scale of cells and molecules is a tremendously fertile area where scientific discoveries frequently occur and unique characteristics are continually uncovered. Because these behaviors have been optimized through evolution, cells and molecules have developed robust and efficient functions often beyond current ability of research to understand and much less to mimic. The immediate challenge, however, is to determine which biological discoveries will be the most useful and then translate them into novel technology. We must dissect the insights garnered at the cellular and molecular scale and select those most appropriate for application in material science to engender high-impact discoveries for the future. By continuing to follow these multidisciplinary paths and by bringing together material scientists, biologists, chemists, physicists, and engineers, the potential for high impact innovation and development will be enabled for many decades to come.

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