Final Report
Designing Biomimetic, Dissipative Material Systems

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Throughout human history, new materials have been the foundation of transformative technologies: from bronze, paper, and ceramics to steel, silicon, and polymers, each material has enabled far-reaching advances. Today, another new class of materials is emerging—one with both the potential to provide radically new functions and to challenge our notion of what constitutes a "material". These materials would harvest, transduce, or dissipate energy to perform autonomous, dynamic functions that mimic the behaviors of living organisms. Herein, we discuss the challenges and benefits of creating "dissipative" materials that can potentially blur the boundaries between living and non-living matter.

"Materials science" as a field has traditionally focused on the creation of "static" materials whose properties are intended to be invariant over the time required for their use. Pressing global needs for effective energy harvesting, conversion and storage, sustainable production, and resource-saving environmentally adaptive systems necessitate new materials with new functionality. Biological systems have evolved to solve such resource-conserving, energy-management problems in order to ensure their survival, doing so by developing unique sensory and adaptive capabilities. The ability of plants to bend or unravel their leaves in the presence of sunlight is a prime example of adaptive behavior in biology that is crucial for survival. Salamanders provide the ultimate biological example of resource conservation and adaption: they can regenerate severed limbs and parts of organs. Materials that exhibit comparable dynamic behavior—autonomously adapting their functionality to changes in the environment, harvesting energy from their surroundings, and undergoing self-repair—could play a crucial role in solving global-scale energy-related problems. Opportunely, biology provides unique and indispensable sets of design rules for creating such responsive and self-regulating synthetic materials.

Borrowing principles and designs from biology does, however, necessitate embracing the notion of dissipation. Dissipation is the physical process associated with the irreversible transformation of energy from one form to another. All living organisms rely on dissipation: they all "eat", taking in nutrients and converting nutrients into chemical energy, which is stored or transduced into mechanical action. All active biological processes rely on this form of dissipation. For instance, it is precisely these dissipative processes that enable biological systems to sense and respond to their environment and to actively perform such vital functions as self-regulation or self-repair. Hence, truly biomimetic materials must be dissipative. A dissipative material requires an in-take and expenditure of energy to sustain its functionality. In contrast, a "static" or non-dissipative material (e.g., a simple coffee cup or a bridge) does not require an input of energy to perform a function.

The field of biomimicry also involves the creation of synthetic materials that display *static* structural motifs found in biology. The key focus in designing biomimetic, dissipative matter, however, is to engineer the functionality of the system (not just morphology) and to do so by mimicking the *dynamic* structures and *dynamic* functional processes found in biology. The ability to carry out time-dependent behaviors necessitates the input and consumption of energy. Thus, the necessary condition for biomimetic, dissipative matter is the ability to perform a life-like function through the utilization of energy.

The deliberate design of biomimetic, dissipative materials remains a major unsolved challenge for contemporary materials science. Namely, we lack well-developed tools to reproduce the exquisite functional design of individual biomolecular components, as well as the modeling capabilities to reliably predict the behavior of dissipative materials. The development of matter that mimics biological behavior using dissipative processes could lead to new materials with new functions, and thus, have the potential for supporting new technologies. Using the appropriate design rules (including, but not limited to the ones below), the materials can be made to harness energy from the environment or internalized compartments, and thereby, work in a relatively autonomous manner, providing self-operating tools. Furthermore, we can envision the development of heretofore non-existent life-like materials that operate at much greater extremes of temperature, pressure, and radiation exposure than natural systems.

It is, in fact, non-trivial to predict the complete set of properties that could be displayed by dissipative biomimetic matter. Indeed, "Life" is the prototypical dissipative system, with characteristics that are unique among physical systems, including: 1) self-replication, 2) memory and adaptability, 3)

responsiveness to threats and autonomous repair of damage, 4) efficient sensing and integration of input from sensors into recognition of patterns, 5) the ability to harvest energy from the environment (for example, by eating or photosynthesis), 6) awareness of itself and of its relationships to its environment, and 7) communication. Understanding what it would mean to embed these characteristics of life in non-living matter is the essence of defining a possible new field.

This new field would also require that we reconsider the traditional definition of what constitutes a "material." Designing biomimetic materials will require the integration of a system of materials and functions, which interact across multiple length and time scales to produce a concerted action. For example, microscopic channels that form an extensive network have been inscribed into polymeric materials as a "synthetic microvasculature", which carries fluids and "nutrients" within the polymer[1]. The entire entity, with the microchannels, the fluid, and the polymeric host, constitute an interactive module that enables self-repair. In essence, the "material" is the sum of interactive (communicating and self-regulating) components, which perform a unified function.

Another critical issue is to create *systems* of biomimetic, dissipative materials, as biological functionality is often achieved by the coordination of multiple interacting components. Designing ensembles of interacting units that communicate and collaborate—without external controllers—to perform complex tasks is one objective of the new science of dissipative materials. An overarching goal is the creation of materials, or systems of materials, that simultaneously provide structure, sensing, and response—all integrated into function.

Finally, it is worth emphasizing the utility of focusing on *dissipative* biomimetic systems rather than just *biomimetic* systems. The idea of biomimetic matter is familiar, and has been explored in many projects. But consider, for example, trying to emulate the ability of bone to repair itself after it breaks. The biological process is effective because it involves the production of new matter and the transport of matter to the damaged site; these processes necessitate the expenditure of energy. Hence, we cannot truly replicate the efficiency of biological repair if we do not devise processes that expend energy to mend the damage.

Another argument for "dissipative, biomimetic matter"—in essence, for a new kind of matter designed to mimic some of the properties of life—rests on the premise that almost every system that is truly interesting (e.g., life itself, energy generation and use) are all dissipative. The ability to define and produce fundamentally new forms of matter—with properties we may not even be able now to define—based on a combination of "dissipative systems" and "matter" would produce properties, behaviors, and almost certainly capabilities that were fundamentally new. Opening the door to dissipative matter will, however, require establishing new "blueprints" for creating these materials.

Requirements for creating new material systems: laying our a blueprint

The directions listed below help layout a blueprint for creating biomimetic, dissipative material systems. While these materials need not encompass all of these features, and the list is not all-inclusive, it nevertheless highlights salient characteristics that will be needed to accomplish life-like functions.

1. Incorporate a metabolism At the most basic level, one of the differences between a living system (whether unicellular organisms or a human being) and a "block" of material is a metabolism, which is the coordinated network of chemical reactions that convert fuel (food) into chemical energy that, in turn, enables sensing, movement, information processing, self-repair, and adaption to changed environmental conditions. There have been essentially no attempts to incorporate a "synthetic metabolism" into man-made materials and very few to design materials that have the ability to autonomously make chemicals[2] (solar cells, batteries, and heterogeneous catalysts are, arguably, exceptions). The development of such synthetic metabolisms is ultimately critical to progress in this field.

2. Introduce a vasculature One requirement for moving the products of reactions among compartments of a biomimetic, energy-harvesting system is a vasculature[1] that could transport nutrients (fuel) and waste around the system. In addition to a built-in circulatory system, biomimicry may require viewing the entire system—the matrix, the vasculature, and the moving fluid (whether liquid, gas, or

suspended solid) as the "material," much as our definition of a "body" encompasses all the biochemical machinery contributing to its functioning. Developing a clear semantics may prove important in redefining concepts and stimulating imagination.

3. Harness energy gradients Dissipative systems consume energy in order to perform their functions. Life, for example, harnesses the free energy available in the combustion of glucose and dioxygen to yield water and carbon dioxide. Unlike their equilibrium counterparts, dissipative systems can spontaneously generate, amplify, and sustain local energy gradients. Living cells use the free energy gradient formed by concentrating potassium inside the compartmentalized cell, and leaving sodium outside, to store energy, and to synthesize ATP. Intentional generation and amplification of gradients and the coupling of the discharge of these gradients to the synthesis, properties, and behavior of materials is, however, not currently a significant part of materials science.

4. Focus on kinetics, not thermodynamics Another important consideration in the generation of materials that mimic living things is that "life" is a manifestation of the kinetics of dissipation through networks of communicating processes (e.g., metabolism) more than the thermodynamics of this dissipation. Considering "materials" as networks of coupled molecular processes rather than structures composed of atoms and molecules is also not a part of the current thinking in materials science. It is useful to recall that cells are networks of reactions. To devise dissipative biomimetic materials, we will need to design materials that encompass and interact through kinetic networks.

5. Harness catalytic networks and non-linearity The development of catalysts with the properties of enzymes—that is, a catalyst with, among its properties, the characteristic that the activity of one catalyst is modulated by the products or reactants of another—has been slow. An important problem is building the kind of cooperative, communicating catalytic networks [3] that are the hallmark of biology. As part of this process, we need to develop "valves" for chemical reactions—loosely analogous to the transistors used to build networks in solid-state circuits. Moreover, we need to understand how to harness non-linearity as an advantage rather than a disadvantage. Notably, auto-amplification is one of the key attributes to achieving meaningful changes in biology over relevant periods of time (e.g., blood clotting, production of insulin, a wide variety of other signaling cascades); this phenomenon is, however, not currently exploited in materials science.

6. Incorporate feedback loops To achieve true biomimetic behavior, we need to design materials that encompass active systems of controls, sensors, and feedback loops. Notably, we do not typically incorporate feedback loops in the design of materials systems. Feedback loops are vital to biomimetic systems since they provide a means of introducing self-regulation[4-7].

7. Create systems of autonomous "machines" Throughout biology, one finds autonomous "machines"—individual entities contributing to a common set of tasks (e.g., ants in colonies, cells cooperating to form tissues, and enzymes in a cascade amplifying a signal). The intriguing challenge is to design such communicating, cooperating "machines" from synthetic materials. While there has been progress in creating programmable microbots,[8] an important goal is to design autonomous micro-machines that do not rely on electronic components[9,10]. Much as in living cells, spatial organization would be useful for such biomimetic microbots. The development of DNA origami[11] allows at least one way to achieve the latter feature. Since DNA can be made to attach to metals, proteins, carbon nanotubes, etc., the origami serves as a breadboard on which different structural and functional units can be assembled. An enabling technology for this area of research would be the development of several different kinds of nano-breadboards so that experimentalists and theorists could design active networks and circuits. Artificial, minimal "protocells"[12-14] could also form the basis of new autonomous machines. Cell-like structures can be engineered to capture physicochemical properties of both the bounding membrane and cytoplasm. The challenge in this context is designing bio-inspired "machinery" that could be incorporated into the protocells to enable biomimetic cell signaling, and hence, allow the protocells to communicate, and consequently, cooperate.

Examples of biomimetic, dissipative material systems

The materials described below exemplify biomimetic, dissipative behavior: they all spend energy to perform a life-like function, such as autonomous motion, self-regulation, self-repair, or communication and collective behavior. The examples also illustrate items from our blueprint.

Self-oscillating polymer gels undergoing the auto-catalytic Belousov-Zhabotinsky (BZ) reaction are prime examples of biomimetic, dissipative materials [7] and simultaneously integrate catalysis, non-linearity and feedback loops **(**items **5** and **6)**. In solution, the BZ reaction produces a cyclic reduction and oxidation of a metal catalyst. When this catalyst is anchored to chains in a polymer network, these BZ gels exhibit autonomous pulsations that are driven by the redox reaction. In particular, the hydrating effect of the oxidized metal catalyst induces an expansion of the gel, which then contracts when the catalyst is in the reduced state. Hence, the feedback loop inherent to the BZ reaction and the feedback between this reaction and responsive polymer network allows the gel to beat autonomously; no external stimuli are needed to drive these regular oscillations. Indeed, in a Petri dish, a sample resembles a beating heart. This stand-alone behavior makes these materials ideal candidates for biomimetic functionality. The materials are clearly dissipative, expending the energy from the chemical reaction to fuel the mechanical oscillations of the gel; millimeter sized samples can beat autonomously for hours and be "resuscitated" by the addition of new BZ reagents into the surrounding solution[15]. This form of energy transduction can broadly be thought of as a "synthetic metabolism" (item **1**). As in biological systems, this synthetic metabolism can power directed motion of macroscopic-sized BZ gels (Fig. 1A). Moreover, the BZ reaction is photosensitive; light can suppress the oscillations in the system[16]. By shining light on just one end of the sample, traveling chemical waves in the gel are propelled along a specific direction, and consequently, narrow centimeter-long gels spontaneously move away from the light[17], resembling the negative photo-taxis exhibited by certain earth worms.

The BZ gels display another vital biomimetic, dissipative activity: auto-chemotaxis, where self-generated chemical gradients lead to the net collective motion of multiple samples[18]. During the course of the pulsations, the BZ gel generates the activator for the reaction, referred to as u , which diffuses into the surrounding solution. The gradients in u affect the pulsations of the neighboring gel pieces, with the portions of gels closest to high concentrations of u beating faster than the other portions. This asymmetry in the dynamic behavior within a gel drives the net motion of the sample toward the higher concentration of u and causes multiple pieces to spontaneously move towards each other. In effect, the BZ gels produce and utilize gradients (item **3**) to communicate and then move in response to that communication, exemplifying item **7**.

The power of utilizing feedback loops (item **6**), as well as interlocking kinetic processes (item **4**), within a synthetic dissipative material was further demonstrated in a device that performs a distinctly biomimetic actively: self-regulation or homeostasis[4]. Specifically, an autonomous thermal regulator was created from a thermo-responsive gel, compliant, microscopic posts (partially embedded in the gel), and a two-layer fluid that flows over this composite in a microfluidic device (Fig. 1B). At the onset, the posts extend into the upper fluid, which contains reactive species that interact with catalysts located on the posts' tips. The resulting chemical reaction generates heat that causes the underlying lower critical solubility temperature (LCST) gel to shrink. The shrinking gel acts as a "muscle" that exerts a force on the posts, causing them to bend and extend away from the top fluid layer. In the absence of the exothermic reaction, the system cools down, and hence, the gel expands. The expansion drives the posts into the upper fluid, thus repeating the inter-conversion of chemical and mechanical energy. In other words, the system encompasses a self-regulated, continuous feedback loop between the exothermic catalytic reactions in the upper fluid and the mechanical action of the thermo-responsive gel. As a result, this "SMARTS"[4]—self-regulated mechanochemical adaptively reconfigurable tunable system—behaves as an autonomous thermal regulator that, within a very narrow range, maintains a local temperature (which is determined by the LCST of the hydrogel). SMARTS itself constitutes a distinct "material" that clearly illustrates item **4** since it harnesses a network of coupled kinetic processes (and interconnected components) to perform a specific, global function: homeostasis.

The two fluid layers in the above system form a primitive microvasculature (item **2**), with the microfluidic pump driving the fluids past the composite, and thereby, delivering the reagents (in the upper fluid), or "nutrients", to the system. Lewis *et al.* have developed a range of direct-write and 3D printing techniques to inscribe fluidic networks into host polymeric materials that closely resemble the microvasculature in biological systems[1] (Fig. 1C). With two interpenetrating networks, each carrying its own fluid and driven by separate pumps, the structures even mimic the presence of arteries and veins[19]. This microvasculature enabled another biologic function: self-repair[19]. When a crack propagates through such a material and breaks the walls of the vasculature, then healing agents leak from these vessels, and thereby, mend the fissure.

A synthetic vasculature could provide an effective means of introducing and regulating chemical reaction networks (CRN) within a host material (items **4** and **5**). Biology performs vital functions through a dynamic cascade of events, or chain of interconnected chemical reactions; this self-organization and self-regulation of reaction networks has proven challenging to produce *in vitro.* One successful example that involved biological components was provided by the "repressilator" network[5], which consists of three genes, where each gene represses the next gene in the loop and is repressed by the previous gene. The repressilator was specifically engineered to exhibit oscillatory dynamics so it could act as an artificial clock that imposed temporal organization within a living cell. Recently, Huck *et al.*[3] developed a strategy for creating programmable chemical reaction networks that exhibit controllable dynamic behavior, including self-sustained oscillations of the reactants. By linking multiple modules together in microfluidic channels, the levels of complexity displayed by the CRNs could be expanded, and thus, begin to mimic the regulatory networks vital to biological functionality. By pumping such programmable CRNs through a vasculature within a responsive gel, one can potentially create synthetic systems showing new forms of biomimetic, autonomous dissipative behavior.

Because it is so readily available, visible light provides an ideal energy source to activate systems encompassing chemical reaction networks. A recent study demonstrated the possibility of developing a supramolecular material designed to integrate all functions for light-driven hydrogen production[2], and thus, form a simple biomimetic material that makes chemicals (item **1**). This system involved a hydrogel scaffold built by the self-assembly of chromophore amphiphiles as light harvesting nanoscale ribbons. The highly charged, self-assembled ribbons attracted an oppositely charged catalyst for hydrogen synthesis from available protons in the aqueous channels. The synthetic capability of this hydrogel for hydrogen fuel was enabled by the two-dimensional crystallization of the chromophores by electrostatic contact with the catalyst, which in turn enhanced their electronic coupling, and thus, their light harvesting ability. Figure 2 depicts the light harvesting assemblies of molecules in electrostatic contact with the catalyst leading to hydrogen production from protons in the wide open aqueous channels of the hydrogel. The material is easily placed on surfaces or in the pores of solid supports and could be utilized for reactions in the domains of solar fuels or environmentally relevant chemical transformations.

Recently, researchers have devised collections of interacting elements that can be viewed as "autonomous machines" (item **7**). For instance, Snezhko and Aranson[9] fabricated millimeter-sized "robots" that are self-assembled from magnetic microparticles (Fig. 3A). Localized at the interface between two immiscible fluids and in the presence of an alternating magnetic field, the particles harness this energy flow to self-organize into "asters". In the presence of a second magnetic field, the now mobile aster robots could grip, transport, and release glass beads. The asters also show a level of self-repair: when a microparticle becomes dislodged, the "robots" can reorganize to resume their functionality. Suspensions of photo-responsive, synthetic colloidal particles display analogous biomimetic self-organization[10]. Activated by light, these colloids spontaneously assemble into two-dimensional "living crystals", which rearrange, exchange particles with other microscopic clusters, break-up, and re-form (Fig. 3B).

A wide range of micron scale constructs referred to as "artificial cells" have been designed to mimic some aspects of living cells. For example, polyelectrolyte microcapsules fabricated in a layer-by-layer (LbL) manner[17] have a cell-like structure, with an outer elastic shell enclosing a spherical, fluid-

filled core. Additionally, the LbL microcapsules can be driven to controllably release encapsulated species in response to local variations in the environment[17]. This responsive behavior proved especially useful when LbL capsules containing corrosion inhibitors[20] were embedded in a film above a metallic layer. Corrosion in the underlying material released byproducts that altered the local pH. The permeability of the polyelectrolyte shells strongly depends on pH; with the local change in pH, the capsules' shells expanded to release the inhibitor. The released inhibitor suppressed the corrosion activity, and the original pH value was restored, causing the capsules' shells to close. The ability of these LbL capsules to sense local environmental changes, display feedback mechanisms (item **6**) and be triggered to release the encapsulated species indicates that these capsules mimic salient features of cell signaling; a remaining experimental challenge is to harness this mode of biomimetic communication to drive the capsules to self-organize into mobile autonomous machines[21] (item **7**).

Protocells are artificial cells specifically designed to mimic the earliest biological cellular structures, and thus, are typically fabricated through the self-assembly of simple lipids and fatty acids. Szostak *et al.* have determined conditions for driving such protocells to perform the ultimate dissipative biological function: self-replication[22]. By adsorbing monomers in solution, the fatty acid vesicles grow into threadlike structures that break-up into smaller spherical daughters, which themselves can grow by taking in fatty acids from solution. These cycles of growth and division can be repeated without the loss of vesicle contents[22].

Researchers[23] have attempted to determine how protocells, which lacked advanced biochemical machinery, might have responded to sudden changes in their surroundings, such as a sudden drop in the concentration of dissolved molecules in the water that bathes the cell. This perturbation could result in a rapid flow of water into the cell through osmosis, causing it to swell, rupture, and die. To avoid this catastrophic death, even single bacterial cells have evolved mechanosensitive channel proteins, which allow them to release excess water from the cell. Recently, Oglęcka *et al.* used giant lipid vesicles, to investigate how a rudimentary cell-like compartment, devoid of proteins and cytosolic components, responds to a sudden drop in the amount of dissolved molecules (i.e., sugar) in water[23]. Using a synthetic, protocell-like system, consisting only of three-component mixtures of lipids, they found that these vesicular compartments respond to the osmotic assault by reorganizing the molecules at the membrane boundary and opening a pore, which allows it to release dissolved molecules and lose excess water from the interior, thus decreasing the pressure of the encapsulated cargo. The action of this "pressure-release valve" is not all-or-nothing. The valve (or hole) opens for less than a second, releases some of the internal sugar several times, producing a pulsating, breathing pattern in the size and molecular texture of the vesicle (Fig. 4A).

This autonomous capability of simple vesicles to manage an external osmotic perturbation by a coordinated and cyclical sequence of physical mechanisms, which allow vesicles to sense (by lateral reorganization of membrane components and by domain formation) and regulate (by solute efflux) their local environment in a negative feedback loop, suggests a primitive form of a dissipative self-assembly in a synthetic material system, i.e., a simple microemulsion produced from just lipids, water, and sugar. From the vantage point of dissipative materials, the findings suggest how chemical energy stored in concentration gradients (item **3**) might be dissipated biomimetically to drive structural reorganizations for advanced functions.

Challenges and New Opportunities

There are tremendous opportunities in the field of biomimetic, dissipative materials simply because there is so much that is not known. Materials science does *not* routinely mimic biology, does *not* develop systems that require dissipation of energy through them to have their intended function, and does *not* build materials out of interacting kinetic networks. Moreover, given the enormous range of functional solutions offered by biology to problems dealing with energy utilization, adapting those solutions to human-centered needs will provide fruitful scientific research for many decades[24].

It is worth emphasizing that this field is based on observing the remarkable functions that characterize living organisms, and trying to abstract and mimic those functions.[24] Hence, we are primarily focused on the challenges and opportunities in creating materials that perform life-like *functions* (rather than simply forming bio-inspired static structures). One of the greatest challenges in this research area is creating materials that can perform not just a single, isolated task (e.g. self-regulation[4] or self-repair[9,19]), but a combination of integrated functions in one hierarchically-organized system. Addressing this challenge will require advances on a number of different fronts (see below), which in themselves provide opportunities for new areas of fundamental research.

1. Design materials far from equilibrium The traditional approaches to materials synthesis have largely relied on uniform, equilibrated phases leading to static "condensed matter" structures, such as, for example, monolithic single crystals. Over the past several decades, these approaches have led to the development of a wide range of technologically useful materials including semiconducting, ferroelectric, nonlinear optical, superconducting, liquid crystalline, elastomeric, and piezoelectric materials. Important as they are, the range of functions in these materials is constrained by their static structure (with the notable exception of piezoelectrics and liquid crystals). Departures from these modes of materials design are pervasive in biology. From the folding of proteins to reorganization of self-regulating cytoskeletal networks, biological materials reflect a major shift in emphasis from thermodynamic to kinetic regimes and hence, as noted in item **4** in our blueprint, it is vital to focus on kinetics, not thermodynamics in designing dissipative biomimetic materials. In the latter systems, equilibrium structures, determined by global free-energy minima, are replaced by highly structured dynamic states that are out-of-equilibrium; here, even the entire concept of thermodynamic energy minimization is not necessarily applicable. Thus, the challenge of creating new materials capable of performing complex, life-like functions provides an impetus and new opportunities towards harnessing out-of-equilibrium processes in the design process. Fundamental challenges to stably design such out-of-equilibrium structures are many: (1) how does one design a material system exhibiting multiple robust dynamic states, e.g., from static to flowing or oscillating, (2) how does one ensure that the accessible dynamic states are controlled by weak external stimuli, (3) how one can tailor dissipative processes to achieve maximum regulation and structure evolution with minimal energy consumption? Such questions are not confined to particular examples found in living systems, but provide a fundamental basis for developing design principles for dynamic, dissipative material systems.

2. Introduce compartmentalization and structural hierarchy Compartmentalization of biomolecules is a characteristic feature of all living systems. Indeed, the emergence of life on Earth itself (and its early prebiological chemical evolution) is thought to be linked to compartmentalization, such as might be produced by self-assembly of prebiotic amphiphiles into compartmental boundaries[25]. Eukaryotic cells employ these compartments of chemically distinct organelles as modules of highly integrated metabolic networks. Far from simply serving as inert vessels, cellular compartmentalization (Fig. 4) plays a plethora of active roles. First, compartmentalization allows physical segregation of certain biomolecules, while promoting crowding of others within an encapsulated volume (typically zepto– (10^{-21}) to femto- (10^{-15}) liters). This in turn allows multiple dissimilar aqueous chemistries (e.g., metabolic reactions) to proceed in parallel[26]. Moreover, the compartments are not hermetically sealed[27]. They communicate and exchange their contents and signals *via* a variety of biophysical mechanisms; the latter include passive permeation, osmoregulation, and active channel-mediated transport, as well as a complex array of membrane deformations (e.g., budding, division, fusion)[28, 29]. Such well-regulated exchanges allow compartmentalized chemical reactions to receive external inputs and become synchronous across their arrays and networks—all in well-defined spatial and temporal cascades of chemical reactions. Second, it is notable that the compartmentalized medium itself is a highly crowded environment within the cell[30]. For instance, the total load of large biomacromolecules inside cells ranges between 5% and 40% (up to 400 grams per liter) of the cellular volume. This molecular crowding directly influences the properties of the encapsulated cargo, including compartmentalization of the aqueous milieu, as well as conformations, diffusion, and transport characteristics of the internal molecules. Together, these factors

influence kinetics and thermodynamics of a variety of physical and chemical processes within the cellular milieu (and sub-cellular organelles)[31, 32], an understanding of which is largely incomplete[30]. Third, it is also notable that multi-component organelles can self-assemble into specific geometries[33] whose functions remain unknown. The vast diversity of lipids and membrane-soluble proteins, which make up a roughly 5 nm thick plasma membrane, are themselves organized into patterns of micro- and nanoscale domains[34], producing a dynamic mosaic of molecules[35]. Like their 3D counterparts, 2D compartments or domains are also not static; dynamic reorganization of lipids (and their micro-domains) provides the membrane with physical mechanisms to generate local physical (e.g., curvatures) and compositional (e.g., signaling proteins) "hotspots" for recognition, sensing, signaling, and regulation—all contributing to a well-orchestrated cellular homeostasis. The above considerations exemplify how mere compartmentalization of chemical cargo enables new functions not yet generally embraced in the design of synthetic materials.[36] Notably, new research in protocells (see below) is addressing how to create life-like cellular structures that encompass hierarchically compartmentalized structures that can harnessed for a range of biomimetic functions. More generally, the creation of interconnecting, multi-chambered, dynamic structures that are capable of recognition, sensing, signaling, and regulation can facilitate the development of self-operating, micron-scale reaction chambers that could autonomously carry out multi-stage chemical reactions in controlled and precise ways.

3. Create synthetic cells. Protocells[37-39] are synthetic biological cells. They can be constructed of either synthetic or natural components, or combinations of these, and are designed to carry forth tasks that cells typically perform, such as secretion, motility, division, or changes of shape. The basic premise is to mimic the hierarchical structure of a cell, but employ components intended to achieve new desirable functions and enable operation under extreme conditions. Furthermore protocells could be assembled into higher order structures analogous to tissues or organs potentially within vascularized networks to enable connectivity and flow of chemical energy and information. A key design feature of cells and protocells is 3D compartmentalization of components (see above discussion). This enables establishment of and operation within potential gradients (chemical, optical, mechanical, and electrical), which are key to energy harvesting, storage, and dissipation to perform desired functions (as noted in item **3** in the blueprint). In terms of new opportunities, recent work has expanded the palette of molecules that can spontaneously make membranes. Now, membranes can be assembled from block copolymers, responsive surfactants, peptides, recombinant proteins, or colloids; each of these affords a novel way to integrate specific functionality into the membrane (Fig. 4B), thereby allowing protocells to be endowed with "new" properties (e.g., responsiveness to light or enzymes) that are not accomplished by real cells. We can also consider new 'intracellular' biomimetic designs of the protocell. Natural cells are extremely crowded[32], where the 3D cytoskeletal network has evolved to organize proteins into local arrangements that are optimized for efficient coupling of chemical reactions. By fusing engineered synthetic membranes onto engineered nano-to macro structured porous particles[40] and cellular replicas[41] (Fig. 4C), we envision a new generation of protocells where the structured and compartmentalized interior recapitulates the natural scaffolding and macromolecular crowding of the intracellular space. Moreover, the exterior surface of porous particles in arbitrary shapes supports the membrane on a 3D surface where the adhesion energy and local curvature stabilize the membrane and direct curvature-dependent fluidity and phase behavior[42] unachievable with nominally spherical liposomes and polymerosomes.

4. Create systems that replace sensors and control loops with the intrinsic properties of the materials Material systems that seamlessly integrate the properties of skin, muscle, and the nervous system would permit new devices that could operate without external sensors and control loops. Today, researchers are attempting to design new "robotic materials"[43] that simultaneously and inherently combine: 1) sensing, 2) actuation, 3) computation, and 4) communication. Although advances in materials science have enabled the fabrication of "smart materials" that are stimuli-responsive or self-healing, few existing smart materials can autonomously perform all the above functions. As a step in this direction, Yashin *et al.* designed a material platform that integrated the self-sustained oscillations of BZ gels (Fig. 1A) with the electro-mechanical properties of piezoelectrics (PZ)[44]. Within each BZ-PZ unit, the

oscillations of the gel cause the deflection of the overlying PZ cantilever, which then generates a voltage. Connected by wires, the voltage generated by one BZ-PZ unit affects the oscillations of the others, and thus, the units can "sense" each other, communicate, and synchronize to perform computational tasks, such as pattern matching and recognition. Notably, the material performs autonomously: both the pulsations of the gel and the voltage generated by the PZ are due to the inherent properties of the material. More generally, robotic materials that could be programmed to autonomously alter their properties in response to changing needs would dramatically enhance the functionality of smart materials and enable sensorial robotics, prosthetics, and even clothing.[2]

5. Establish both temporal and spatial control of material systems Biological functions, such as limb growth[45], involve a series of interlocking temporal events (i.e., item **4** in the blueprint), where each separate event contributes to larger scale phenomena. Moreover, this dynamic cascade requires specific spatial coordination among the interacting components[45] so that the temporal events take place at specific locations or among specific compartments in the organism. Figure 1B illustrates one of the few synthetic material systems that encompass such inherent temporal and spatial coordination of interlocking dissipative events. Another example is provided by a tissue-like printed material composed of tens of thousands of picoliter aqueous droplets joined by single lipid bilayers to form a cohesive network with cooperating compartments[46]. Membrane-bound protein channels, e.g., α-hemolysin, direct electrical communication along specific routes, enabling collective behavior not achievable by synthetic cell mimics like liposomes. Furthermore the droplet networks can be programmed by osmolarity gradients to fold after printing into various designed geometries. Continued development of matter that is programmable on both temporal and spatial scales would be vital to creating biomimetic, dissipative materials with controllable functionality.

6. Devise collaborating material systems (micro-bots) The self-organizing colloidal systems in Fig. 3 exemplify recent advances in creating autonomous machines (item **7** in the blueprint) that do not rely on electronic components to communicate and interact[47-49]. The asters[9] in Fig. 3A are particularly interesting since these objects appear to "collaborate" to surround the particles in solution. There remain, however, few examples of such small scale "robotic" systems (micro-bots) that effectively communicate to perform a collaborative task. Moreover, there are currently no examples of micro-bots that autonomously collaborate to assemble (or even drive the self-assembly) of other micro-bots. DNA origami[50] could provide a useful tool to direct this cooperative behavior, allowing the micro-bots to link together into larger structures. If each micro-bot could produce, store, or harvest energy[47], the assembled "organism" could display emergent properties. Moreover, micro-bots that assemble other micro-bots could provide design rules for creating larger scale robotic systems that interact to cooperate, and thus, perform work in highly efficient ways.

7. Move beyond self-healing to regeneration While there has been significant progress in fabricating self-healing material systems[51], the extent of repair achieved in these systems is still relatively small compared to the remarkable ability of organisms to regrow or regenerate damaged tissue. Creation of such regenerative material systems necessitates radically new composites that encompass not only compartments of stored healing agents[52] and a connected vasculature to transport the healing agents[1, 19] (item **2** in the blueprint) but also an inherent signaling mechanism that alerts the system to initiate regrowth, propagate the growing "tissue", and terminate the regrowth when the material has recovered its initial shape and size. Achieving the latter functionality in a purely synthetic system remains a critical challenge. The creation of regenerative synthetic materials would radically enhance the sustainability of manufactured parts.

8. Develop new theoretical and computational models One of the most significant challenges is developing new predictive theoretical and computational approaches that can provide a springboard for new experiments or yield deeper insight into experimentally observed physical phenomena. As part of this endeavor, we must address a number of fundamental questions. Is it possible to formulate unifying principles for dissipative self-assembly and what are they? What happens when we "sail from the safe haven" of thermodynamics (which is extremely powerful for the describing systems close to thermal

equilibrium)? How do we develop simple (and tractable) discrete or continual models for active materials from simple microscopic interaction rules? For example, many complex interactions between biological filaments such as microtubules and actin can be modeled as binary inelastic collisions. (Attempts have been recently formulated, including models for point-wise self-propelled particles[53] and self-propelled rods[54].) Are there "universality classes" or at least some generic properties shared by active systems? Finally, active materials typically encompass a hierarchical structure that involves many overlapping time and length scales. How do we develop scale-spanning simulations for active materials? Notably, researchers have recently developed minimal models for collective and compartmentalized behavior[55,56], helping to lay the groundwork for addressing these critical questions.

Conclusions

Retrospective and Perspective

Natural biomaterials systems evolved over billions of years to solve some of the most challenging engineering problems needed for their self-preservation and now for the demands of human activity, e.g., energy harvesting, transduction, and storage. These optimized properties and property combinations result from hierarchical designs exhibiting structure and function on multiple scales—with feature sizes prioritized according to the relevant functional length scale (exciton, stress field, van der Waals contact, etc.) For decades, the elegance and functionality of natural materials, along with their aqueous formation under ambient conditions, have inspired scientists in attempts to mimic their designs and construction principles with the goal of imparting 'life-like' qualities to robust synthetic materials. Moreover, by employing the full spectrum of 'non-natural' chemistries, processing conditions, and fabrication tools now available, it has been anticipated that we could improve on Nature's designs and functions. But how far have we come in so-called 'biomimicry' and the development of life-like structures and functionality in manufactured materials? Where are we going?

Arguably biomimetic materials processing began in the 1980s with an emphasis on biomineralization[57]. These studies focused dominantly on understanding the design and biological processing of durable composite materials like bone, shell, and teeth. At that time, it was realized that mimicking the biological process of bone formation (sequential steps of compartmentalized, templated nucleation and growth mediated by an array of ion delivery vehicles or pumps) was not achievable with existing fabrication technologies. But, the realization that structural hierarchy enables mundane materials like calcium carbonate and polymers to have extraordinary mechanical properties led to new successful approaches to control the microstructure, and therefore, toughness of composite materials[58]. Since that time, bioreplication of static structures like the lotus leaf or butterfly wing have led to other useful functions like superhydrophobicity and photonics.

Largely missing in the repertoire of efforts surrounding biomimetic materials is dynamic functionality, which is a hallmark of life. Living systems exist to reproduce. Selection for function has organized the living cell into assemblies of complex biomolecular networks or "interactomes," which operate as dynamical (rather than static) systems with emergent properties[59-61]. Biological systems generate this dynamic responsiveness likely by existing far from equilibrium, harnessing energy from the environment and accessing kinetic states in their free energy landscapes. Structurally, they organize in modular and hierarchical fashions into a network of "interactomes." Different from today's synthetic material systems of interacting components, these networks reconfigure in response to external stimuli through simple insertions, recombinations, and rearrangement of interacting "modules," much like logic circuits of computers[59]. An extraordinary example of an extended module is the versatile case of signal transduction. Here, input from an external signal is sensitively recognized by the cell, even from a noisy and chaotic background, and transduced intra-cellularly to generate a cascade of chemically specific interactions between signaling proteins inside the cell. The initial binding of a signaling molecule allows for the module definition and produces module isolation. The cascade of intracellular catalytic processes serves to amplify and translate the initial input signal to produce a precisely defined outcome. Needless to say, no single biomolecule (nor any single functional module) is responsible for signal transduction, but rather the function arises through interactions between tens or even hundreds of cytoplasmic proteins

acting in concert. This modular organization seems to have proved beneficial to the cell, allowing functions of individual modules to be robust, insensitive to environmental (or genetic) changes, while at once enabling environmentally-sensitive dynamic and even evolutionary changes not by *de novo* synthesis of new proteins but by simply modifying the inter-module networks and connections[62].

Thus, the "decision-making" living systems are intrinsically endowed with the unusual combination of material flexibility (or deformability), adaptability, and evolvability in their structures on the one hand and highly specific, robust, and self-amplifying, and error-correcting on the other. Drawing from these lessons of dynamic structuring, placing function before structure, we envisage new thinking in devising complex materials that embrace modular synthesis and dynamic, adaptive behavior [63] as essential design components.

Moving forward, the next challenge and opportunity in this emerging area is to design materials systems that perform not just a single biomimetic function, but rather carry out multiple life-like functions, such as sensing, actuation, computation, and communication[43], without the need for extensive arrays of embedded electronics. By utilizing the enabling items in our blueprint, these materials systems would harness energy from the environment and transduce this energy to autonomously and seamlessly perform these interlinked functions. Such multi-functional dissipative systems could add unprecedented functionality to everyday objects, such as clothing and furniture, as well as enable sensorial robotics and prosthetics.[43] Creating these autonomously multi-tasking materials requires that we begin to tackle the specific list of challenges articulated above. Addressing these particular issues (such as developing predictive models for systems that operate far from equilibrium) has profound consequences not only for creating new biomimetic materials, but also for making inroads in learning how to control matter to solve a range of our energy needs.[64]

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Figure Captions

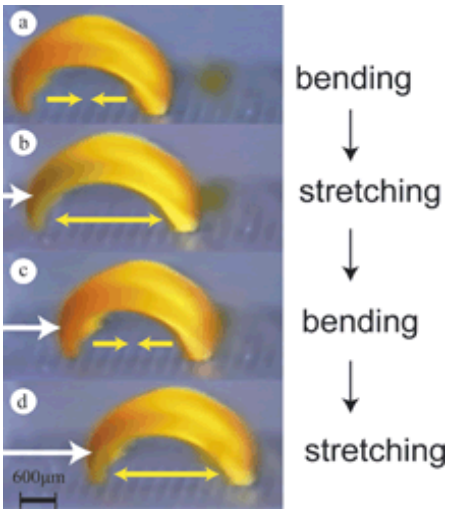
Figure 1 (A) Autonomous motion of BZ gel "walker". Chemical energy from BZ reaction in the gel is transduced into mechanical energy to power the motion. (Reproduced from ref. 7.) (B) Energy transduction in the self-regulated mechano-chemical adaptively reconfigurable tunable system (SMARTS), which encompasses a flowing binary fluid to deliver "nutrients"(reagents) to the catalytic sites at the top of the embedded posts. The resulting exothermic reaction leads to the cascade of energy transduction events. (Reproduced from ref. 4.) (C) Biomimetic microvascular networks created by a direct-write assembly process. By pumping chemicals through a vasculature within a responsive gel, one can potentially create synthetic systems showing new forms of biomimetic, autonomous behavior. (Reproduced from ref. 1 with permission of the Royal Society of Chemistry.)

Figure 2. Molecular graphics representation of the interior of a hydrogel in which an ordered assembly of chromophores that harvests visible light is in electrostatic contact with catalyst (yellow) and generates hydrogen (green) from protons in the aqueous channels of the supramolecular network.

Figure 3. (A) Autonomous micro-robots formed from colloidal particles localized at the interface between immiscible fluids and driven by a magnetic field. The four self-assembled "asters" localized around the target particles (reproduced from ref. 9). (B) A "living crystal' of colloidal particles forms, rearranges, and exchanges pieces with other nearby units (reproduced from ref. 10)

Figure 4. Compartmentalized systems and functions. (A) Dissipation of chemical concentration gradient across vesicular compartment coupling osmotic activity of water (out-of-plane) with the membranes compositional degrees of freedom (in-plane) results in oscillatory pore formation and domain dynamics (reproduced from ref. 23). (B) Protocell designs: Membranes and components can be assembled from novel surfactants with designer functionality, to respond to light or enzyme activity and to engineer shape changes and responsiveness. The interactions may propagate many cell diameters, leading to collective behavior. (C) Protocells formed by fusion of lipid bilayers or native membranes on silica cell replicas that recapitulate the local curvature of the cytoskeleton surface and crowded intracellular environment

(A)


a
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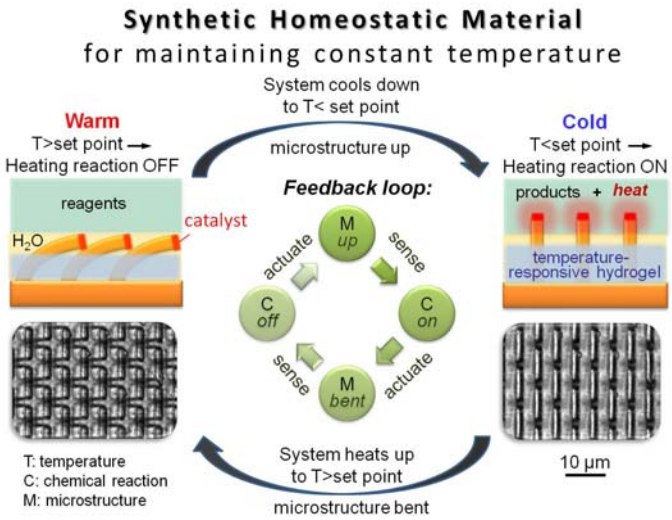
bending
stretching

(B)


Synthetic Homeostatic Material
for maintaining constant temperature
System cools down
to T< set point
Warm
T>set point
Heating reaction OFF
microstructure up
Cold
T<set point
Heating reaction ON
Feedback loop:
reagents
catalyst
H_2O
products + heat
temperature-responsive hydrogel
M up
sense
C on
actuate
M bent
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microstructure bent
10 μm

(C)

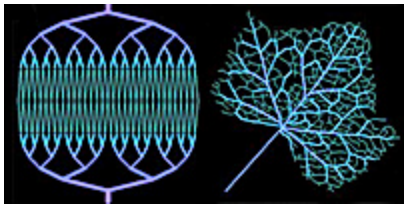


Figure 1

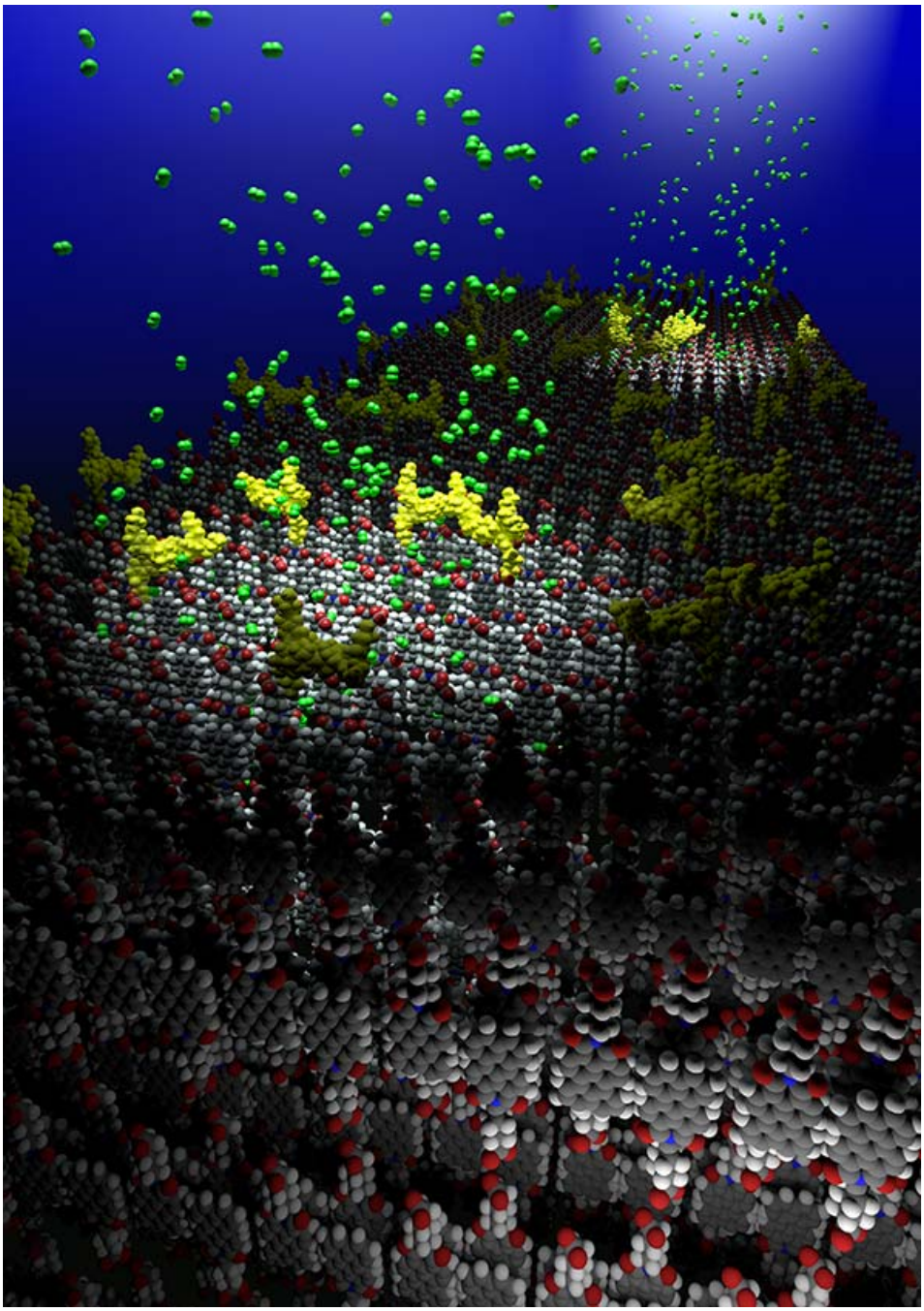
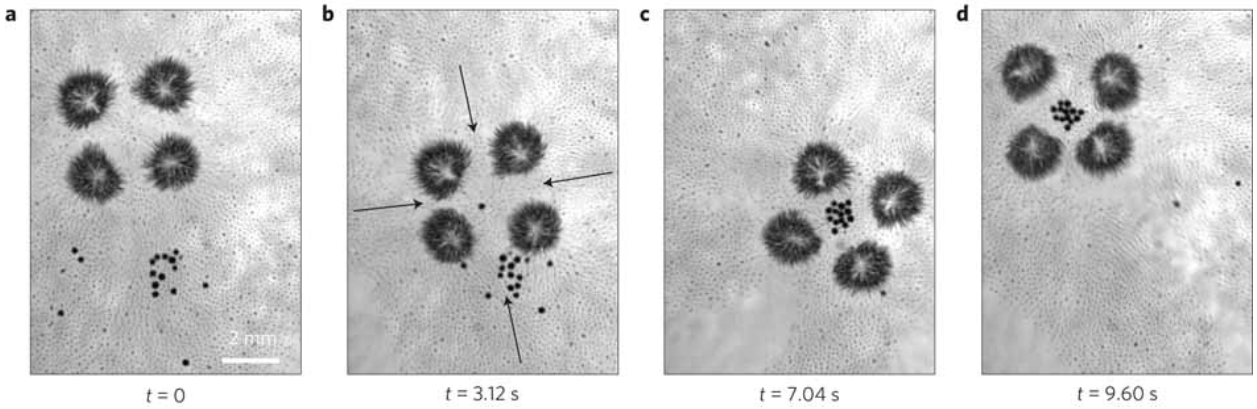


Figure 2

(A)



(B)

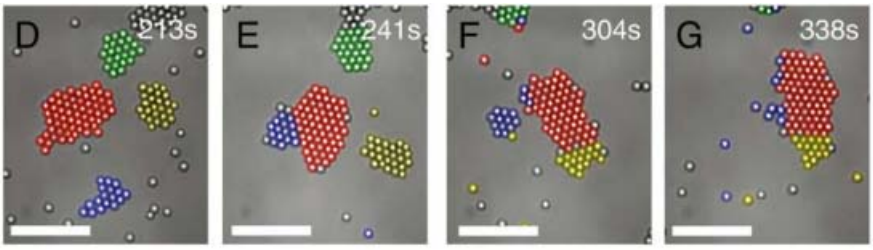


Figure 3

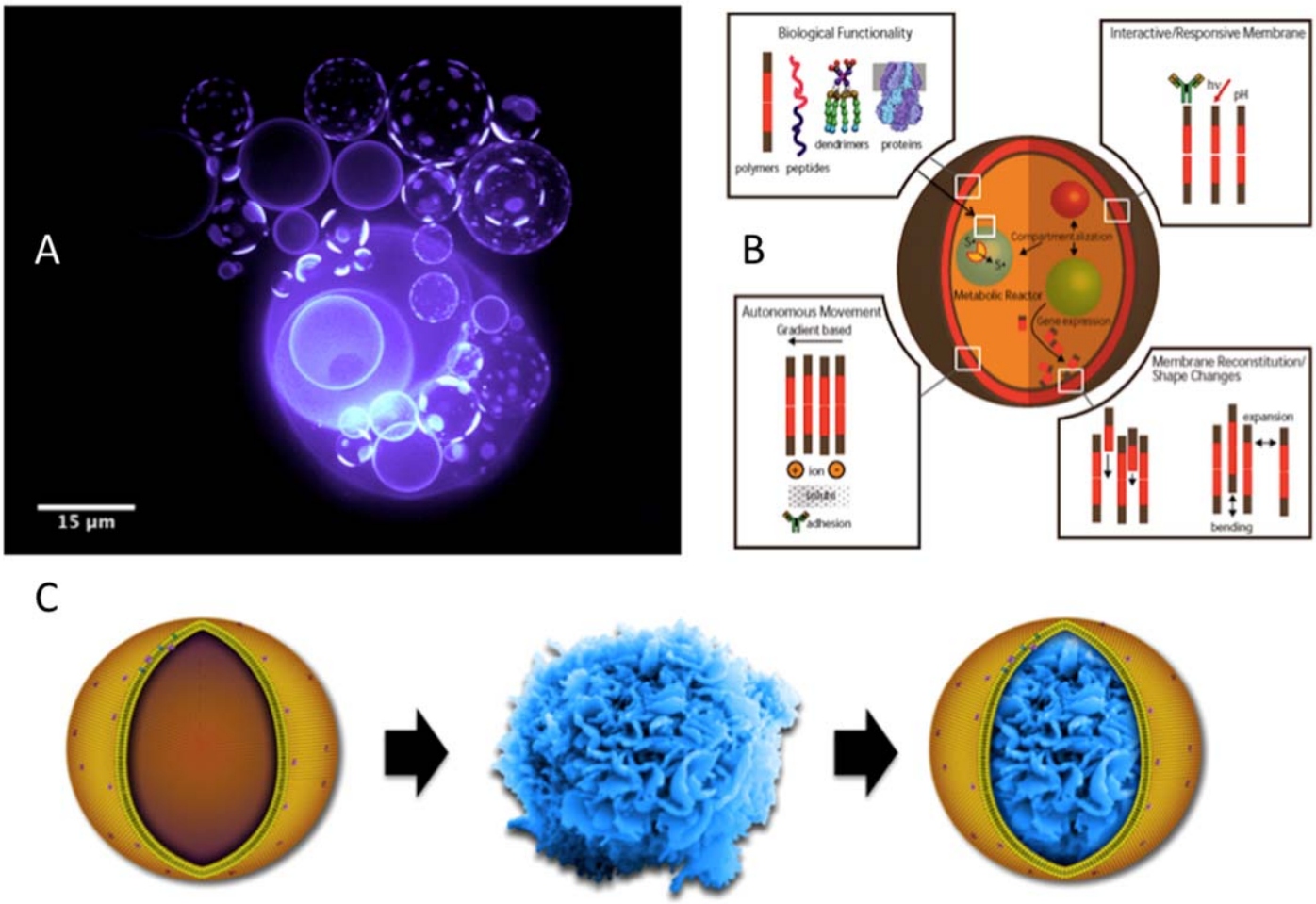

A
15 µm
B
Biological Functionality
polymers
peptides
dendrimers
proteins
Interactive/Responsive Membrane
hν
pH
Compartmentalization
Metabolic Reactor
Gene expression
Autonomous Movement
Gradient based
ion
adhesion
Membrane Reconstitution/
Shape Changes
expansion
bending
C

Figure 4