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Chemically Powered Synthetic "Living" Systems

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SUMMARY

Synthetic chemically powered active matter aims to reproduce many of the salient features of out-of-equilibrium living systems. These include exhibiting emergent properties and complex functions based on interactions with each other and the environment. In this perspective, we focus on some of the principal achievements to date, their significance, and their possible applications. We also outline several future challenges, such as designing memory and evolution into active systems and engineering "living" chimeras, which are hybrid systems involving communication and interaction between living and synthetic active matter.

INTRODUCTION

Research in chemistry focuses primarily on systems that approach equilibrium. Chemical synthesis typically involves reagents that react to form products that are at the bottom of the free-energy landscape. In contrast, biology encompasses dynamical systems that operate away from equilibrium by constant energy input (e.g., by catalytic conversion of ATP to ADP + Pi). The living world, thus, is special in that it is made from building blocks that are "active" and that transduce energy from catalytic reactions, in contrast to many chemical and physical systems that only contain "static" structures. Emulating the behavior of living matter in synthetic active systems is a rapidly burgeoning field of research that involves the design of micro- and nanostructures that can harvest energy to move autonomously and self-organize to perform complex tasks.[1–4] Recent work has shown that groups of simple catalytically active particles (from molecules to colloids) show surprising emergent behavior, ranging from directional chemotactic motility in response to chemical gradients to dynamic assembly driven by phoretic and hydrodynamic effects. The resultant organization and collective behavior of interacting active particles show remarkable similarities with the biological world.[5–7] The seemingly complex phenomena such as the flocking of birds or the directed movement of biological cells, thus, share common principles with inanimate but "active" micro- and nanoparticles.

Self-powered chemically driven active systems have, thus, emerged from a scientific curiosity to powerful models for the study of non-equilibrium phenomena. An overarching theme is the design of synthetic systems exhibiting emergent properties and complex functions based on interactions with each other and the environment. The potential applications of such synthetic interacting nano- and micromachines would be almost limitless. Rationally designed dynamic materials made from non-equilibrium building blocks would be capable of remodeling themselves and transforming their environment. These active materials could self-organize and evolve their structures and functions to adapt and improve their performance and accomplish tasks collectively and emergently (like a colony of ants) that a single building block cannot.

The Bigger Picture

Challenges and opportunities:

- Memory needs to be built into synthetic active systems for them to autonomously reconfigure their motion and function in response to varying environmental cues. Memory requires the ability to store past information in a way that influences future decision making.
- Evolution of function in response to externally imposed conditions remains a challenge for synthetic systems. Critical to evolution is the ability to explore many different options (adaptation) and select suitable solutions. A system with many dynamic components could adapt and evolve by reconfiguring in response to changing external conditions.
- Synthetic active systems are truly biomimetic when they become functionally indistinguishable from their living counterparts. A particularly intriguing challenge is to engineer "living" hybrid systems, or chimeras, in which communication and interaction between living and synthetic active matter lead to complex organization akin to, but extending beyond, what is observed in morphogenesis.

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Self-powered dynamic materials can also act as active sensors that explore and respond to their environment without being tethered to a single power source or location.

Despite significant progress to date, current synthetic active systems do not yet reach the autonomy and sophistication of their biological counterparts. More integrated functionalities and a "division of labor" between specialized components are two key elements that need to be addressed in the future design of synthetic active systems. The ultimate research objective is to create a new paradigm for the design of active functional materials and systems by leveraging (1) precise molecular-level control to create functional "active" building blocks, (2) mobility resulting from energy harvested from the local environment, (3) rapid and reversible non-equilibrium self-assembly, (4) intelligence and communication, as in interacting microorganisms, and (5) the ability to perform specific tasks in response to signals from each other and the environment.

From a fundamental standpoint, there remain many questions that need to be addressed going forward: (1) What are the possible mechanisms for transducing locally available chemical energy into motion from the micron to the molecular length scale in different environments? (2) How can the motion be directed, e.g., by chemical gradients? (3) How do inter-particle interactions arise in chemically driven systems? (4) What common principles underlie the self-organization of complex structures? (5) How do the ensemble dynamics of active particles evolve in space and time? (6) Most intriguingly, how can synthetic active systems be effectively integrated into the biological world?

What follows is an entirely subjective perspective of the field, encompassing some of the significant achievements to date and some of the most important challenges going forward. Chemically powered synthetic active matter can be fabricated from catalysts ranging from inorganic particles to enzymes. Although we have chosen to focus primarily on enzyme-based systems, much of the discussion also applies to active systems derived from other forms of catalysis. The emphasis is on uncovering new science that serves to bring synthetic systems closer to their living counterparts. Only then can the promised novel applications of synthetic active systems be realized.

CATALYTIC TRANSDUCTION OF CHEMICAL ENERGY INTO MECHANICAL FORCE

It is now clear that catalysts, from molecules to larger micron size particles, are able to generate motive force during substrate turnover.[8–10] In the presence of a substrate gradient, they display directional movement (chemotaxis).[11] When attached to a surface, the motive force is transferred to the surrounding fluid, resulting in active fluid flow and directed transport of entrained particles.[12] A variety of mechanisms have been suggested for the chemical to mechanical energy transduction step. These vary according to the scale and the nature of the catalytic species. The mechanisms include self-electrophoresis and self-diffusiophoresis arising from ionic and neutral solute gradients, thermophoresis and solutal buoyancy effects, and, for single molecules, conformational changes.[13,14]

Chemotaxis: How Information Arises from Chemical Gradients

One of the most fascinating phenomena uncovered in the study of synthetic active matter is chemotaxis. This is defined as the ability of catalytically active species to

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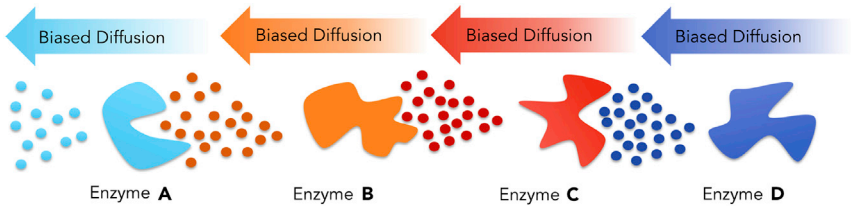

Figure 1. Schematic of Chemotaxis in an Enzyme Cascade

Enzymes along a metabolic pathway, in which the product of one is the substrate for the next, associate through a process of sequential, directed chemotactic movement. The extent of enzyme migration is proportional to the exposure time to the substrate gradient.[11]

move directionally up (positive chemotaxis) or down (negative chemotaxis) the substrate gradient.[3] Positive chemotaxis has been observed for many different systems ranging from inorganic particles[15,16] to single enzyme molecules[3,8,9,17] and enzyme-attached hard and soft particles.[18–22] The behavior has been exploited for targeted delivery; specific examples include the crossing of the blood-brain barrier by enzyme-encapsulated synthetic vesicles[22] and the chemotactic migration of enzyme-attached polymer particles to inflammation sites.[21]

Other practical applications for the positive chemotactic behavior of enzymes have also been reported. One particular study used chemotaxis to separate a mixture of active and inactive enzymes.[23] In microfluidic systems, active enzymes migrated further toward the substrate-containing channels than inactive enzymes, which allows for simple separation of the active enzymes from their inactive counterparts. A paper-based device for chemotactic separation of enzymes has also been reported, allowing for a more facile separation.[24] Unlike other label-free techniques, chemotactic separation is activity based and does not depend on physical properties, such as molecular size and surface charge.

The sequential positive chemotaxis of reaction-linked enzymes may be the basis for the organization of metabolic networks in the cytosol of living cells.[25] Enzymes that participate in reaction cascades have been shown to assemble into metabolons in the presence of the first enzyme's substrate.[11] We applied microfluidic techniques to study the coordinated movement of the first four enzymes of the glycolysis cascade: hexokinase, phosphoglucose isomerase, phosphofructokinase, and aldolase. Each of these enzymes independently follows its own specific substrate gradient, which is produced by the preceding enzymatic reaction (Figure 1). The extent of enzyme migration is proportional to the time the enzyme is exposed to the substrate gradient. Significantly, the chemotactic migration of enzymes is fairly rapid even under conditions that mimic cytosolic crowding. The observed rate was also very similar to the reported rate of enzyme diffusion in living cells. As in living systems, the enzyme cascade-assisted spatiotemporal assemblies described above are dynamic and fully reversible; when the substrate for the first enzyme is fully consumed, the chemical gradient disappears, and the enzymes disperse.

A model was proposed to describe the positive chemotactic behavior of active enzymes, based on the reversible binding of the substrate.[11,26] According to this model, chemotactic drift arises from a thermodynamic driving force that lowers the chemical potential of the system due to favorable substrate binding. The substrate gradient-induced enzyme chemotaxis by cross diffusion is in the opposite direction of enzyme Fickian diffusion, transferring enzymes toward regions of higher

substrate concentration. The diffusive flow for the concentration c_e of enzyme, *e*, in the presence of its substrate, *s*, can be written as:

$$J_e = -D\nabla c_e - D_{XD}\nabla c_s$$

where D is the Brownian diffusion coefficient of the enzyme, D_{XD} is the "cross-diffusion" coefficient, and ∇c_e and ∇c_s are gradients in enzyme and substrate concentrations, respectively. The cross-diffusion coefficient, D_{XD}, is a function of the local substrate concentration, c_s, the diffusion coefficient, D, and the equilibrium constant, K, for substrate binding to the enzyme:

$$D_{XD} = -Dc_e\frac{K}{1+Kc_s}$$

Combining these two equations gives:

$$J_e = -D\left(\nabla c_e - c_e\frac{K}{1+Kc_s}\nabla c_s\right)$$

This equation highlights the factors that drive cross-diffusion flux. The first term inside the parentheses is the traditional diffusive flux toward lower concentrations of enzyme. The second term is the chemotactic flux of the enzyme, which has the opposite sign, showing that this flux is toward higher concentrations of substrate. In addition to the substrate gradient, this term's magnitude is determined by the diffusion coefficient D and the enzyme concentration.

Note that for a generic enzyme catalysis,

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \overset{k_{cat}}{\rightarrow} E + P$$

K_D (k_{-1}/k_1) is a measure of the enzyme-substrate affinity and is the inverse of the binding constant, K. High K_D indicates weak binding of the enzyme to the substrate, and low K_D indicates strong binding. If k_{-1} is much greater than k_{cat}, $K_M \approx K_D$. This condition is met for most enzymatic reactions. Chemotaxis depends on (1) the strength of the enzyme-substrate binding and (2) the fraction of the enzyme available for chemotaxis—only unbound enzyme molecules will chemotax. Low K_D results in a high chemotactic flux of free substrate molecules, and high K_M implies that a larger fraction of the enzyme is in the free form and available for active chemotaxis. Thus, too strong a binding interaction prevents chemotaxis since the fraction of free proteins quickly drops to near zero. On the other hand, catalysis enhances chemotaxis of an enzyme by providing an additional pathway for the reformation of free (unbound) enzyme available for chemotaxis.

As the above analysis suggests, all molecules will chemotax up a gradient of an attractant, depending on the interaction strength and the concentration gradient.[27] The chemotaxis often gives transport rates several times that of diffusion. This fact, combined with its directionality, can make chemotaxis a valuable strategy for transport over longer distances. Chemotaxis is of direct relevance to numerous binding events occurring in biological systems. In sensing and detection applications, chemotaxis can significantly speed up the migration of the analyte to the detector. While most of the mechanistic studies on chemotaxis have focused on soluble molecular systems, the phenomenon of chemotaxis has also been observed in colloidal systems; however, the mechanism remains uncertain in these systems.

The sequential chemotaxis in catalyst cascades allows for time-dependent, self-assembly of specific catalyst particles participating in the cascade (Figure 1).[11] This

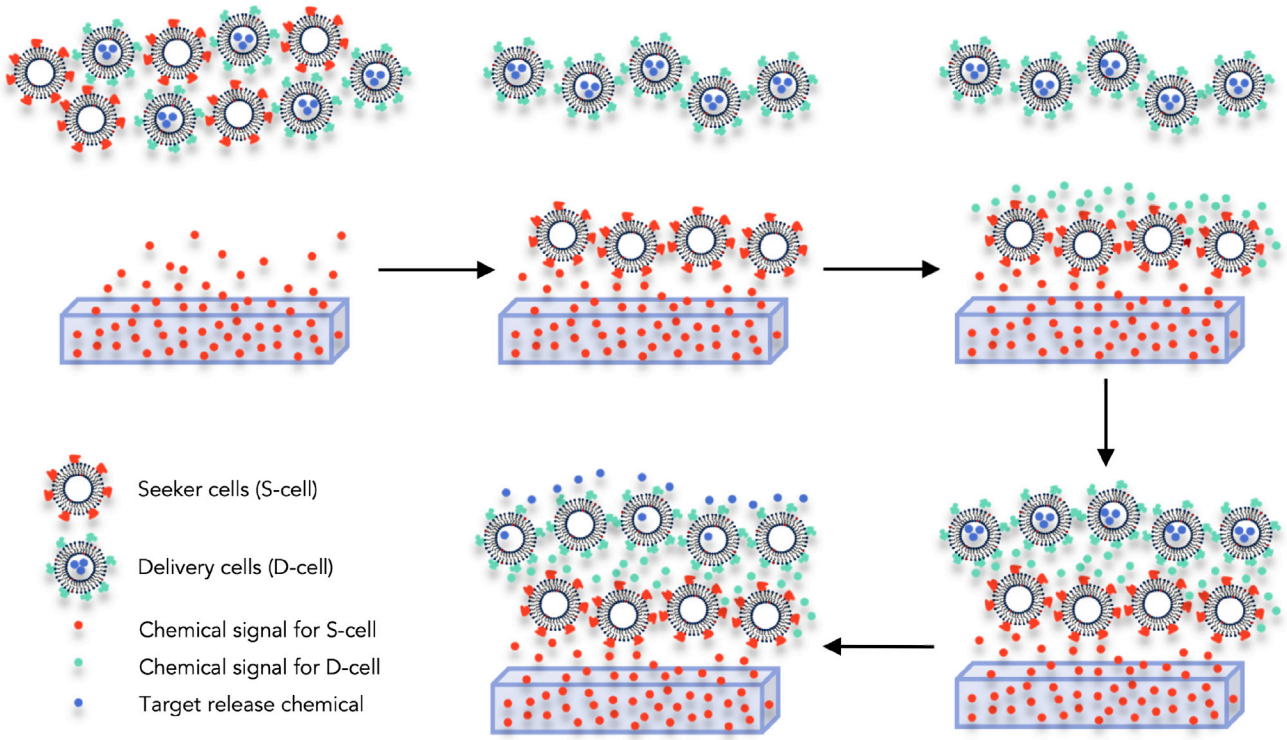

Figure 2. Schematic of a Multi-enzyme Cascade-Based Autonomous Protocell System that Detects a Chemical Source and Collectively Delivers a Response Chemical to It

S-cells seek out the source, attract D-cells, which deliver response chemicals, and indicate the location of the source.

is an example of how information can arise from chemical gradients and, because of the generality of the phenomenon, it is tempting to suggest that similar mechanisms underlie the organization of primitive living systems. Interestingly, both motility and communication arise from the same chemical gradients, a critical observation that should be taken into account in any realistic theoretical modeling effort.[13,17]

Finally, chemotaxis allows for the coordinated movement of dissimilar particles that are not attached to each other, making it easier to transport and deliver cargo to a designated area. In addition, particles with different functions can act collectively, greatly simplifying the design of intelligent functional assemblies. As an example, consider two populations of particles. Through a sequence of chemotactic steps, the "seeker" particles locate a target, summon "delivery" units, which in turn deliver a payload and indicate the location of the target (Figure 2).

Catalytic Pumps: A Novel Platform Combining Sensing and Response

When immobilized onto a surface, catalysts can transfer the reaction-generated force to the surrounding fluid and induce movement of the fluid and entrained particles.[28] While the reported catalytic pumps are derived from many different active materials,[28–30] the most studied are micropumps involving immobilized enzymes.[12,31] Enzymes are typically attached to a gold patch via a thiol monolayer attachment or biotin-streptavidin linkage (Figure 3).[3]

When the substrate is introduced, pumping is induced, and the fluid velocity tracks the overall reaction rate. Additionally, flow direction can be changed

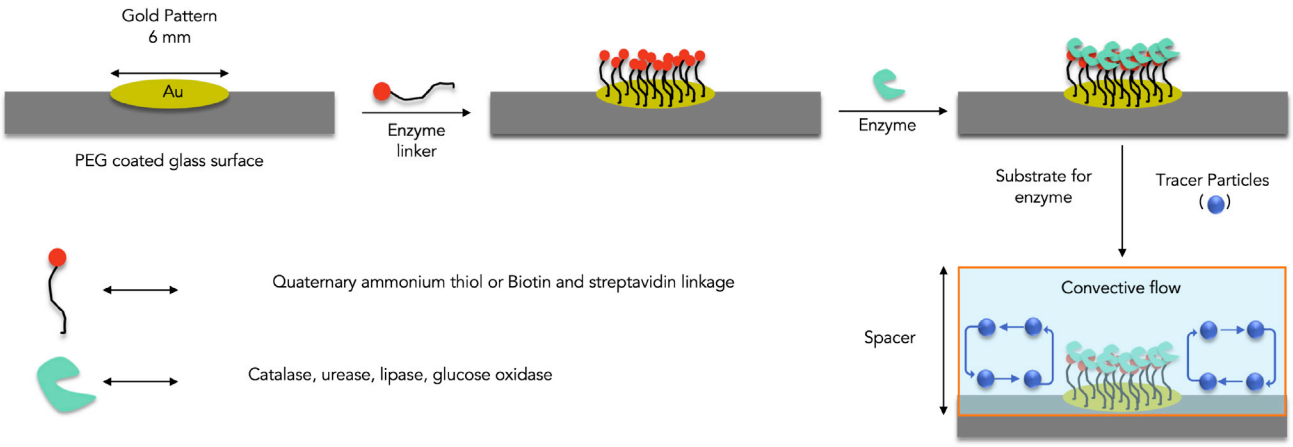

Figure 3. Schematic of the Design of Enzyme Micropumps

Experimental setup for the enzyme powered micropumps. Glass slides are coated with PEG (polyethylene glycol) and gold is patterned. The gold patch is functionalized with a linker, and the enzyme is attached to the linker via electrostatic attractions or through a biotin-streptavidin linkage. Fluid flow initiates when the enzyme's substrate is added.[3]

depending on the enzyme used. In all cases studied, when the pumps are inverted, the direction of fluid flow is reversed, confirming that the flow is density driven and eliminating other possible mechanisms such as diffusiophoresis or diffusioosmosis. Since enzymes typically catalyze exothermic reactions, the role of thermal gradients was investigated, and it was concluded that the heat produced from the enzymatic reaction was not sufficient to account for the experimental pumping speeds.[12,32] Rather, the predominant factor that governs the direction and speed of fluid pumping is the density differences between reactant and product molecules. When the products are denser than the reactants, the fluid settles and slides down and away from the micropump. Conversely, when the products are less dense than the reactants, the fluid rises up and away from the pump (Figure 4).[3]

The enzyme pumps constitute a novel platform that combines sensing and microfluidic pumping into a self-powered microdevice. Several potential applications have been demonstrated. This includes (1) the release of insulin from a gel with anchored glucose oxidase at a rate that depends on the concentration of glucose in the ambient solution[12] and (2) the concomitant hydrolysis of nerve agents and release of an antidote by gel-anchored phosphatases (L. Valdez and A. Sen, unpublished data). The dependence of the flow speed on the reaction rate also allows for the detection of substances that inhibit the enzymatic reaction. Using this principle, sensors for toxic substances, such as mercury, cadmium, and cyanide, were designed using urease or catalase-powered pumps, with limits of detection well below the concentrations permitted by the U.S. Environmental Protection Agency.[33] Finally, enzyme pumps have been harnessed for the directional delivery of microparticles in microchambers.[34]

FUTURE CHALLENGES: DESIGNING MEMORY AND EVOLUTION INTO ACTIVE SYSTEMS; ENGINEERING "Living" CHIMERAS

There are several key attributes of biology that are missing from synthetic active systems. We believe that their incorporation into the latter is essential for the design of truly biomimetic synthetic systems. We introduce three of the concepts here in the expectation that researchers in the field will bring these to fruition.

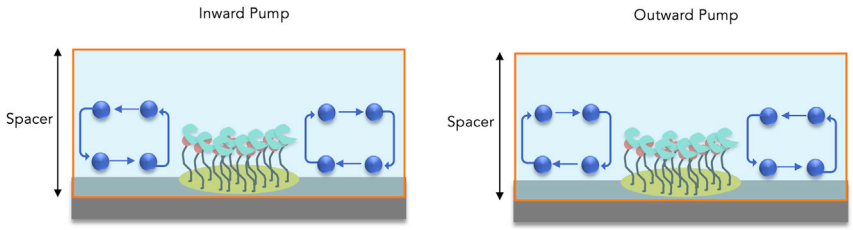

Figure 4. Schematic of Solutal Buoyancy Mechanism for Enzymatic Pumping

Demonstration of the solutal buoyancy mechanism. In the inward pump, the products are less dense than the reactants, so the local fluid rises and then due to convective flows, falls back down and moves toward the patch on the glass slide. In the outward pump, the enzyme products are denser than the reactants, causing the fluid to locally become denser and slide down and away from the patch.[3]

Memory

Memory is essential for learning. Memory needs to be built into synthetic active systems for them to autonomously reconfigure their motion and function in response to varying environmental cues. A particularly useful form of memory is the persistent ability to move toward or away from a signal or space, even when the causation agent is no longer present. Thus, memory requires the ability to store past information in a way that influences future decision making.

It is not difficult to enable a chemical entity with storage capability, by means of chemical deposition or alteration via reactions, and to have the stored information have a certain impact on the entity's current behavior. For example, the chemical deposition from the environment changes the surface potential of a chemically powered motor, the movement of which will be altered due to this change if the propelling mechanism involves surface potential (e.g., electrophoresis). A biological counterpart involves ants following chemical trails laid down by fellow ants; however, this behavior ceases if the trail evaporates. It is debatable, however, whether these behavioral patterns can be considered "intelligent" since the past experience affects the current behavior but not the future anticipation process (or planning). An example to clarify the difference is presented as follows (Figure 5): a motor with surface functionalities passes through a region of positive ions at location X and some positive ions attach to the surface by electrostatic interaction and render the surface of the motor positive. The motor keeps on roving around and avoids the positive region because of same-charge repulsion. This is a simple rigid control lacking intelligence because all that the motor senses is a repulsive force. However, if the motor somehow remembers that X is a region to avoid even if the positive ions have been relocated to location Y, then this implies intelligence since the motor builds up an indirect connection between the physical location and the repulsive charge interaction, the two of which are otherwise unrelated. The second scenario involves memory (motor encountered repulsive charges at location X), reasoning based on the memory (location X is to be avoided because there may be repulsive charges there), and planning of actions (motor will continue to avoid location X while moving). For a chemical system to do that at least two separate but related elements need to be implemented. Elements A and B each records a set of information and the two sets of information interact (e.g., the status of A is represented by the change of surface charge while B records location information, neither would mean anything unless the location information is associated with the charge information) to influence the movement.

A somewhat different form of memory is involved in bacterial chemotaxis. Bacteria are able to sense a change in concentration, rather than the absolute concentration, of a given chemo-attractant or repellant. This requires temporal memory of how the

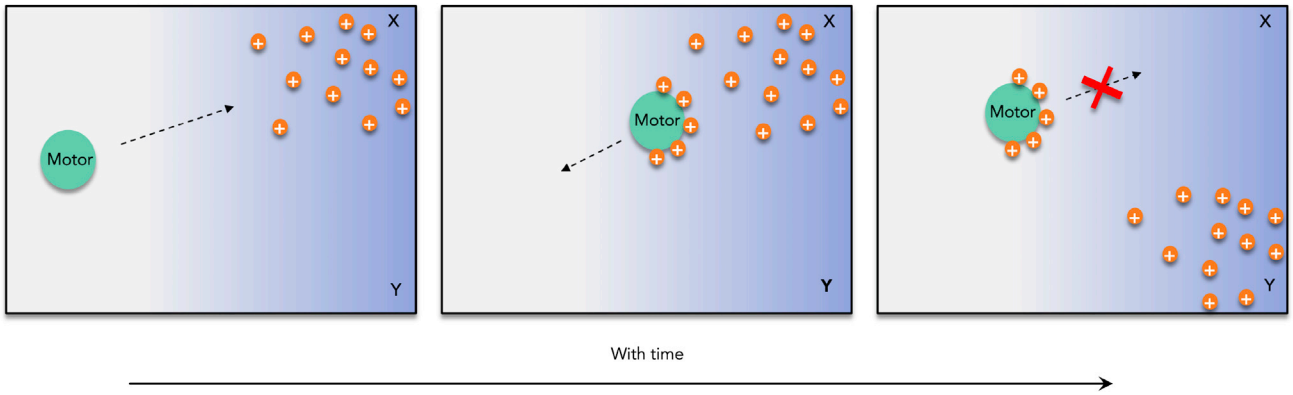

Figure 5. Schematic of a Motor that Exhibits Memory

The motor picks up positive charge when it encounters positive charges at position X. The motor is then repelled from position X. Even after the positive charges relocate to a different position Y, the motor remembers to avoid position X. Thus, the motor can be said to have memory.

concentration of the chemical changes as the bacteria moves. A minimal system for achieving this kind of functionality was proposed by Koshland before the detailed mechanism of bacterial chemotaxis was understood (Figure 6).[35] Again, to compare the concentration values at different times, a two-element response is required. In the Koshland model, the fast response element reflects the current concentration, while the slow response element reflects the past value.

Evolution

The evolution of function in response to externally imposed conditions is the hallmark of biology but remains a challenge for synthetic systems. The design of systems that can evolve their function in response to specific demands would be revolutionary. Living systems are essentially catalysts that promote thermodynamically favorable processes. In this light, evolution is the progression toward structures with successively better catalyst function (i.e., better ability to utilize the available resource, substrates) under a given set of externally imposed conditions. Clearly, the identity of the optimal catalyst depends critically on the reaction conditions, which are externally imposed. As a trivial example, an organometallic catalyst with monodentate ligands may be optimal at ambient temperature but may undergo degradation at higher temperatures. In contrast, one with chelating ligands, while perhaps exhibiting lower overall activity, may confer higher stability and be the superior catalyst at higher temperatures.

How Catalysts May Evolve

For synthetic active matter to remain functional under changing environmental conditions, the system must evolve to better utilize the resources (e.g., the substrate) at hand. As an example, the extent of chemotactic response to a substrate gradient is related to substrate binding and turnover by the catalyst.[26] Clearly, this important functional behavior of the active system will be lost if it fails to adapt to new conditions, including the utilization of new substrates that can power its motion and collective response. Accordingly, we provide one scenario for directed evolution, based on catalysis by homogeneous organometallic species. Consider the metal species, M, in presence of a ligand set, L^1, L^2, L^3 ….

$$L^1M \underset{-L^1}{\overset{L^2}{\rightleftharpoons}} L^2M \underset{-L^2}{\overset{L^3}{\rightleftharpoons}} L^3M$$

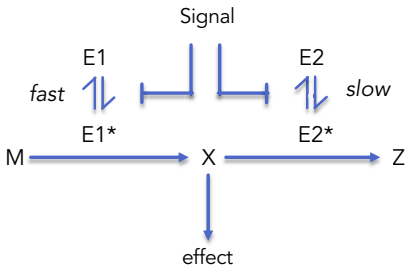

Figure 6. Reaction Scheme Proposed by Koshland as a Possible Kinetic Model for Bacterial Chemotaxis

The signal molecule regulates the activation of enzymes 1 and 2 with fast and slow kinetics, respectively. Activated enzyme E1* catalyzes the formation of actuator molecule X, which is depleted by the action of activated enzyme E2*. In this scheme, temporal memory is achieved through the timescales of activation and deactivation of E1 and E2.[36]

If L^3M is the optimal catalyst with respect to a specific substrate, it will preferentially chemotax toward regions of higher substrate concentration, leaving the rest of the species to re-equilibrate. This will occur even if L^3M is not the most favorable species in the equilibrium. Thus, over time, the concentration of L^3M will increase at the expense of the others in the substrate milieu. On the other hand, for a different substrate, L^2M may be the optimal catalyst and it will be preferably enriched in this substrate mixture. In effect, the substrate (environment) is responsible for the selection and evolution of the catalyst. Note that the above scenario requires that the equilibration rate between the different catalyst species be slower than the substrate binding and release rates that govern chemotaxis.

Note that evolution is about functional adaptation in response to a given set of conditions. Changes in structure is subordinate and occur only as needed for functional adaptation. Darwin's finches have different beak shapes and sizes, but only to better utilize the resources in a given niche (= functional response). Evolution also does not necessarily require replication. For example, a system with many dynamic components can adapt and evolve by reconfiguring in response to changing externally imposed conditions. This is clearly one of the important challenges in the design of synthetic active systems.

What is critical to evolution is the ability to explore many different options (adaptation) and select suitable solutions. A major challenge is to design "self-evolving" systems and materials that exploit the principles of evolution as encountered in biology. In this context, it is instructive to compare how materials are fabricated naturally versus synthetically. In living systems, materials are "grown" in a process that involves constant turnover of building blocks, while they interact with their environment. Thus, adaptation (e.g., of composition, and function) takes place during the lifetime of the material itself. This is in contrast to synthetic materials that are typically fabricated according to predesigned parameters and then put in place.

It has been suggested that constant turnover of building blocks while maintaining the integrity of the overall assembly is the hallmark of out-of-equilibrium kinetic structures—a phenomenon known as the dynamic kinetic stability (DKS).[36,37] Examples range from the persistent structural integrity of waterfalls even though individual water molecules are being constantly replaced, to the contents of our memory, which persist despite the ongoing replacement of our brain cells. To paraphrase Richard Feynman, the potatoes that we ate last week can now remember what was

going on in our minds a year ago! This is in stark contrast to equilibrium thermodynamic structures in which the building blocks persist in a given assembly.

A persistent problem with physico-chemical descriptions of nature is that they address structures rather than functions. By contrast, biological evolution and the drive toward complexity cannot be understood without understanding the central role of function. Thus, the emergence of function is key to the transition from chemistry to biology and remains one of the greatest challenges in science.

"Living" Chimeras: Interacting Living and Synthetic Active Matter

Synthetic active systems are truly biomimetic when they become functionally indistinguishable from their living counterparts. A particularly intriguing challenge is to engineer "living" hybrid systems, or chimeras, in which communication and interaction between living and synthetic active matter (e.g., living and synthetic protocells) lead to complex organization akin to but extending beyond what is observed in morphogenesis. Protocells are model structures primarily composed of spherical assemblies of lipids, polymers, and/or proteins that mimic aspects of living cells. Motility can be built into protocells by incorporating catalysts, typically enzymes, into them.[18] Synthetic protocells may also communicate with distant living cells, secrete attractants, or repellants, leading to long-range cell organization and response. In addition, the protocells may mediate cellular communication between different types of living cells which is not possible *in vivo*.[38] Thus, the protocells could initiate complex multicellular interactions across multiple length scales leading to functions and dynamics that are not observed physiologically. As an example, imagine the following sequence of events: (1) protocells chemotax toward cancer cells in response to chemical cues released by cancer cells; (2) upon reaching the cancer cells protocells release chemokine in response (e.g., due to lower local pH[39]); (3) immune cells respond by migrating to the cancer cell-protocell assembly. In essence, the protocells serve to modulate and enhance the immune response.

In an important first step, synthetic protocells that are able to sense and synthesize quorum signaling molecules have been shown to perform two-way communication with different types of bacterial cells.[40] In deceiving the bacterial cells, the synthetic cells pass the Turing intelligence test which quantifies how lifelike the artificial cells are in comparison with the target living cells.

CONCLUSION

Chemically powered micro and nanoscale active systems offer immense potential toward mimicking living systems—promising a myriad of novel technological innovations. However, the fabrication of tiny, autonomous systems is inherently challenging due to the stochastic nature of particle dynamics, the limitations of experimental and modeling techniques in characterizing non-equilibrium systems,[41] and the need for a multidisciplinary approach. Most importantly, it is critical to understand the underlying physico-chemical principles that govern living systems. Only then would it be possible to design synthetic systems that truly mimic life. Molecular chemotaxis may well be one such unanticipated principle, and its discovery has allowed the targeted active delivery of particles both *in vitro* and *in vivo*. Most likely, there are other principles that remain to be discovered.

An important goal is to use these synthetic active systems as micro and nano machines to accomplish tasks that our current tools cannot. While there have been many proof-of-concept demonstrations in recent publications, we have yet to find a niche where

such systems are indispensable or the tools of choice for a given application.[1,42–45] As an example, consider targeted drug delivery to a specific disease site. Currently, the delivery of drugs relies on the circulatory system, and the drug carriers are only "passively" conveyed toward the targets. A drug delivery system that can manipulate the local flow and actively deliver drugs to a specific site through chemotaxis would (1) greatly diminish the therapeutic dosage and (2) reduce collateral cytotoxicity. Several hurdles remain before such a scenario can become a reality. First, it is important to design self-powered systems that can use fuels that are biocompatible, especially fuel sources present in the body. Ideally, the nano- or micro-transporters should employ enzymes as catalysts and fuels (e.g., glucose) present in living systems. Second, the transporters need to be powerful enough to move against fluid flows, such as blood flow. In the latter context, the demonstration of rheotaxis by synthetic active matter enabling them to move against imposed fluid near walls is a useful development.[46–48]

The most "futuristic" scenario involves active systems that can independently carry out operations such as sensing, reporting, and delivery, with different populations of interacting particles performing different tasks. The discovery of particle assemblies that exhibit chemotaxis and predator-prey behavior is a step in this direction.

Freed of the usual biological constraints, we now have the unprecedented opportunity to probe the limits of self-organization in these chemically powered synthetic systems that operate far from equilibrium. Thus, it is possible to imagine a day when intelligent machines navigate through the body and perform critical tasks, realizing the function of Asimov's *Proteus* in *Fantastic Voyage*.

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AUTHOR CONTRIBUTIONS

A. Sen conceived and outlined the article. All authors participated in discussions and the writing of the article.

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