The Future of Molecular Machines

Ivan Aprahamian*

ABSTRACT: Artificial molecular machines have captured the imagination of scientists and nonscientists alike for decades now, given their clear potential to transform and enhance all aspects of human life. In this Outlook, I use a bicycle as an analogy to explain what a molecular machine is, in my opinion, and work through a representative selection of case studies to specify the significant accomplishments made to date, and the obstacles that currently stand between these and the field’s fulfillment of its great potential. The hope of this intentionally sober account is to sketch a path toward a rich and exciting research trajectory that might challenge current practitioners and attract junior scientists into its fold. Considering the progress we have witnessed in the past decade, I am positive that the future of the field is a rosy one.

INTRODUCTION

The blueprint of what can be accomplished with artificial molecular switches and machines is already available to us, thanks to biology.1,2 As to how we might attain the same level of exquisite control over molecular motion and function such that they could be harnessed in performing useful work, now that is the real question/challenge.3 What seems evident to me is that a well-orchestrated symphony of molecular interactions is required to translate molecular-level motion, which is usually induced on the sub-nanometer level into effects that can be measured and used on the micro and macro levels. For this goal to be attained—based on biological examples—alignment, order, directionality, tracks, signaling, communication, compartmentalization, amplification, fuel, regeneration, replication, waste management, temporal and spatial control, and feedback loops (the list goes on and on) are required. We have merely scratched the surface, and much more needs to be achieved before we reach the level of competence/sophistication required to overcome the obstacles in our path toward engineering useful artificial machines, i.e., molecular systems that transduce or interconvert nonequilibrium free energy without dissipating it (solely) as heat. The prize when and if—as we do not have the time scale that was available for biology—the end of the tunnel is reached will be revolutionary, reconfiguring every aspect of life and heralding a nanotechnological revolution.4–6 This transformation is the goal that has been, and is, fueling practitioners in the field, and stimulating the progress, development, and inroads that have appeared recently. I believe it crucial to try and define, from the outset, precisely what makes a system an artificial molecular machine. A machine, based on the Cambridge dictionary, is “a piece of equipment with several moving parts that uses power13 to do a particular type of work”.

This outlook is my personal view of where the field is going and what challenges need to be addressed before we get there. It is informed and inspired by my group’s research12 and input from others in the field. Because of space limitations, I will only use select examples chosen to convey my line of argument. For more in-depth analysis of recent advances and examples in the field, I will refer the reader to numerous excellent reviews4–11 that have appeared recently.
conformational, configurational, translational, or circumrotational movement) could be externally controlled using a stimulus. With time, the sense of machine changed to denote molecular systems whose controlled movement can be used to perform work, while systems that cannot do so became distinguished as switches. This last distinction has become tacitly accepted by some in the field, while others, and to be consistent with definitions in physics and biology, call all such systems machines, with a distinction between ones that can produce work, called motors, and those that cannot, called switches. Arguably, the former definition of machine is too restrictive, while the latter is too lax. Blurring the lines of demarcation even further, some researchers choose the term machinery to refer to switchable systems, except that the Cambridge dictionary defines machinery as “a group of large machines or parts of a machine that make it work,” according to which there is no machinery without a machine. Confused yet? Well, my head is spinning! I will try to clear up this conceptual mess by proposing the bicycle as an analogy to pinpoint what I take a molecular machine to actually be.

A bicycle can easily be a part of an Ai Weiwei installation (Figure 1), but this by itself does not make it a machine. While

![Figure 1. Forever Bicycles installation by Ai Weiwei as part of the 2011 “Ai Weiwei Absent” exhibition held at the Taipei Fine Arts Museum. The piling of the bicycles strips away any freedom associated with cycling by rendering them immobile, and hence useless. Reprinted with permission from the ©Taipei Fine Arts Museum.](https://dx.doi.org/10.1021/acscentsci.0c00064)

A more precise, working definition of a machine can be derived by extrapolating from the discussion of the bicycle above to the molecular level. I should note that we will have a machine as long as the pedal is attached to a chain; otherwise, we have a motor, i.e., while there is directionality in the movement and energy is consumed, the molecule is decoupled from environment, and so no useful work is produced because there is no load, i.e., the free energy is transferred into thermal energy. Time to duck for cover!

As in every analogy, I am taking some liberties here, and I must clarify that in the molecular world Brownian motion and low Reynolds numbers dominate, while friction, inertia, and gravity play no important role. Moreover, I should note that with careful design and engineering (e.g., using ratcheting and building tension) it is possible to design molecular machines using only switches. In the context of a bicycle, this movement is like asymmetrical forward and backward pedal strokes, resulting in a change in the bicycle’s position. Finally, this analogy might not necessarily encompass all possible examples in the literature; nevertheless, it is a useful way of thinking about molecular machines.

So now that we settled on what a molecular machine is, how do we go about making one? First, it usually entails a lot of synthesis, something that is rarely elaborated and talked about. In certain cases, it is the synthesis that is the actual bottleneck toward progress. Once the molecules show that the designed function/motion is attainable, it needs to be interfaced with the external world. The most straightforward manner of achieving this goal is by attaching them to surfaces, or integrating them into bulk materials such as polymers, liquid crystals, or crystals. This “bulk” approach works because it takes advantage of the inherent order and/or alignment found/propagated in such materials to induce cooperative, hierarchical, and/or synchronized interactions that can be tapped into, amplifying the molecular motion across different length scales. On another hand, if the machines are to produce useful work in solution, then, in my opinion, a systems chemistry approach than that derived by extrapolating from the discussion of the bicycle above to the molecular level. I should note that we will have a machine as long as the pedal is attached to a chain; otherwise, we have a motor, i.e., while there is directionality in the movement and energy is consumed, the molecule is decoupled from environment, and so no useful work is produced because there is no load, i.e., the free energy is transferred into thermal energy. Time to duck for cover!

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reversibility making its use more complicated and demanding. I will not go into much detail here trying to explain out-of-equilibrium systems and what a fuel is, although I think, and loosely using a term from the investment world, a "market correction" is overdue. In short, metastable states are trivial out-of-equilibrium systems; i.e., all thermodynamically driven reactions are out-of-equilibrium (with downhill energy trajectories) until they reach equilibrium. Such systems are in general not going to be useful in our context. As for using chemicals as fuel, it necessitates the use of the energy released from a reaction in producing work/driving a system out-of-equilibrium; otherwise, it is just a reactant. In this outlook, I will focus on the use of light and chemical inputs in designing molecular machines and will refer the readers to a recent review by Credi and co-workers on redox-driven systems. The Outlook is organized such that we will progress from organized to less organized environments, using examples that carry the message I want to convey, while highlighting the benefits of the specific cases and pointing out the issues that need to be addressed to push things forward. I must point out that I am focusing here on the production of work as the option for molecular machines, as this goal has been identified as a "gold standard" of sorts in the field. But there is another option that I will not discuss, and that is using molecular machines as clocks, i.e., information production. This alternative is something that will be elaborated on another occasion.

**CRystalline Machines**

Crystals, with their well-defined, ordered, and periodic structures are perfect vehicles for the transmission of controlled molecular motion across different length scales. One way of taking advantage of this medium is by designing systems that show correlated motion, which is a focal point in the research on amphidynamic (and to a certain extent thermosalenant) crystals. While much progress has been made on this front since the days of Mislow, we still have some way to go to be able to use this strategy in designing useful molecular machines. An alternative approach is to use molecular motion to impart stress on a crystal such that it will bend and, hence, can be used as an actuator. A prerequisite for this approach is switching in neat solid state, which until recently has been limited in scope to diarylenes (DAs). These switches undergo very fast (picosecond scale) cyclization/cycloreversion reactions when exposed to ultraviolet (UV) and visible lights, and the associated structural changes are small and anisotropic, which is ideal for switching in confined spaces. Irie and co-workers have shown that a multicomponent crystal made of two different DAs can be made to bend reversibly toward and away from the light sources more than 1000 times without showing signs of damage to the crystal; this mechanical movement is akin to cycling back and forth in our analogy. The actuation occurs because the light isomerizes only the switches at the surface of the crystal resulting in stress from the uneven mixing of structurally different ring-open and -closed molecules. More intriguing and relevant is the use of the light-induced back and forth bending of the crystal in the rotation of a millimeter-sized gearwheel (Figure 2), i.e., using actual ratcheting to convert a molecular switch into a machine. This example is a beautiful illustration of how straightforward interfacing can be used to convert molecular level motion into a macroscopic event.

There are some general drawbacks associated with the use of crystals as molecular machines: they are brittle and limited in size, and there is a narrow structural space that can be tapped into. Another consideration is the limited penetration depth of light, i.e., optical density and filter effects, which limits the thickness of the crystal (and any substrate as a matter of fact) that can be actuated, and hence the amount of useful work that can eventually be produced. Engineering solutions to this problem, especially in the context of crystals, is not on the immediate horizon as far as I can see. Nonetheless, and as we have seen, surface effects can still be tapped into for producing useful work, and new photochromic compounds that exhibit solid-state switching are coming online. More promising is the recent drive to incorporate molecular switches, rotors, and motors into metal—organic frameworks (MOFs), which should allow for the diversification of systems that can be used as switchable crystals. The main reason for this advance is the inherent free volume in MOFs that allows for the switching to occur in the solid state, especially if they are used as side groups, but less so if they are used as part of the framework. Hence, more careful crystal engineering is required to allow for the framework to breathe in cases where switching results in large geometrical changes. This requirement will be an important step toward using such systems in actuation for example, which is yet to be demonstrated in switchable MOFs. On the other hand, large amplitude motion can be accessed when using mechanically interlocked struts (e.g., rotaxanes) in the framework as the translational motion of the rings does not alter the geometry of the framework itself. This motion is also possible because of the voids in the MOF, which work as a double-edged sword; while the switches/motors are well organized in the MOF, the voids separate them, and hence any correlated/cooperative/coherent motion can be discounted unless these systems are somehow mediated by other means. Therefore, interswitch/motor communication needs to be built into the MOFs to amplify the molecular motion across length scales; such communication might be accomplished by filling the voids with active materials, for example: a daunting challenge that will keep practitioners busy for a while. A "simpler" way to address this issue might be the use of surface-attached MOFs

![Figure 2](https://dx.doi.org/10.1021/acssensci.0c00064)
(SURMOFs)\(^{47,48}\) and use the operation of the switch/motor to change the properties of the surface (e.g., tension, electrical properties, etc.) while bringing the benefits of porosity to the mix. On the one hand, this approach will address the issue of interfacing the crystal with the outside world; on the other hand, it will necessitate the development of MOFs that are externally decorated with switchable units that can interact with the surfaces in a meaningful way. Finally, and now this idea is a fantasy at this stage more than anything, imagine MOFs with molecular motors as side groups.\(^{50,51}\) If these all can be made to rotate in the same direction such that a flow is established, then one can think of using such a device in separating targeted compounds (e.g., polycyclic aromatic hydrocarbons) based on size,\(^{19}\) for example, while moving them from one point to another, i.e., active filtration.

### SURFACE MOUNTED MACHINES

Anchoring/depositing switches and motors on surfaces and studying the effect on the molecule’s function and the surface’s properties is a vibrant area of research because of the plethora of nanotechnological applications that it can enable.\(^{20}\) The surface limits the degrees of freedom available to the molecules, imparts a certain amount of order on them, and is a convenient way for interfacing and scaling molecular events with/to the macroscopic world. One way of taking advantage of surface bound molecular switches in the context of performing work is by using their motion in producing stress on the surface, thus making them bend, which is what Stoddart and co-workers\(^{50,51}\) did with the help of surface-bound [3]rotaxanes (Figure 3). The rotaxane direction seems to have stalled. And so, we have yet to see how the cantilevers can be applied in producing useful work. One direction might be “simple” ratcheting similar to the example described in Figure 2. Nonetheless, this study beautifully demonstrates how the harnessing of the collective motion of a myriad of molecules can be used in converting molecular level motion into a macroscopic event.

The next example is about the use of azobenzene as part of a machinery that controls the motility of microtubules with high spatiotemporal fidelity (Figure 4). The system was developed by Tamaoki and co-workers\(^ {52}\) who attached azobenzene to small peptides that inhibit the activity of kinesin (an ATPase protein motor). The idea behind this approach is straightforward; the azobenzene in the trans form inhibits the kinesin-driven gliding motion of microtubules, while the cis form does not. A gliding motility assay was used to show how the switching of the azobenzene antagonist controls the function of glass-surface bound kinesin motors, thus affecting when the fluorophore-labeled microtubule can move and stop. By using a push—pull azobenzene system that has a fast cis \(\rightarrow\) trans thermal relaxation half-life, it was shown how a single activation wavelength could be used to start and quickly stop the motility of a single microtubule without affecting the movement of others around it. This study is a very promising example of the successful integration of artificial switches with biological machines and how the synergy between these two can push the function of the latter, i.e., controlled cargo movement, beyond biological environments.\(^ {53}\) The issue is that this approach also imposes restrictions on the use of the biological system as it cannot be regenerated in the usual manner it does in nature, thus limiting the cycles that can be used. It is worthwhile to note here that this effort is reminiscent of the use of molecular switches and motors in altering the wettability of surfaces, which has been used in controlling the movement of droplets even against a gradient.\(^ {54-57}\)

The above examples constitute two different approaches for the use of surface bound switches and machines in the production of work. The fact that they are all at the solid/solution interface does not mean that this option is the only possible one moving forward, as other options do exist.\(^ {20,21}\) I just want to show the interest of the community in the directional control of cargo movement on surfaces as a means of fabricating, for example, nanoelectromechanical, lab-on-a-chip, or micro-

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**Figure 3.** Deflection of Au microcantilevers covered with [3]rotaxanes as a function of chemical reduction and oxidation is monitored using a laser beam. Reprinted with permission from ref 50. Copyright 2005 American Chemical Society.

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**Figure 4.** (a) The azobenzene linked peptide deactivates the function of kinesin when in the trans form, and motility is turned ON in the cis form. (b) This process was used in selectively moving a microtubule while leaving others at rest. Reprinted with permission from ref 52. Copyright 2017 American Chemical Society.
fluidic devices, and alternatively, the conversion of external input energy into mechanical force. Either way, there are many challenges that need to be addressed to get these systems to work in real-life scenarios, and these are not necessarily confined to the field but need to be addressed in general in surface science. For example, having better control over the assembly of switchable systems on surfaces is imperative as this can help in engineering coupled hierarchical, and cooperative motion, which will enhance the production of work. Such control can also enable the assembly of different types of switchable systems on the same surface so that they can operate in tandem and even control or feed into each other’s function. Advancement in this arena will help in designing wave fronts on the surfaces that can be used in nanoscale cargo movement, something that has yet to be demonstrated in purely artificial systems. Better control over patterning of surfaces will enable the movement of cargo on different “tracks” or obtaining anisotropic movement of surfaces as a result of the different coverage density of molecules. Progress in these directions will also enable the design of systems that can control interfacial properties, surface conductivity, polarity, zeta-potential, and tension. Finally, the script can be turned around by using molecular machines to control the self-assembly on surfaces, but accomplishing this goal will require solutions to many of the issues mentioned throughout the Outlook.

LIQUID-CRYSTAL POLYMER MACHINES

The use of liquid crystal (LC) polymers/elastomers in the amplification of molecular motion into large amplitude (microscopic) structural changes is a relatively mature sub-field. This approach works because the LC order is retained in the polymer, allowing for the ordering/alignment of the molecular triggers in the soft material. In general, azobenzenes have been used in these applications, and so we will focus on these photoswitches here, though hydrazones and overcrowded alkenes motor containing systems are now making an appearance as well. The basic working principle is very straightforward; the trans to cis isomerization of azobenzene causes an order-to-disorder transition that builds stress through the cross-linked polymer resulting in its deformation. In general, this process is used in designing various actuators that can be used in lifting weights, thus working as molecular muscles. Of interest here is the use by Ikeda and co-workers of such LC elastomers in designing a light-driven macroscopic motor that can continuously rotate clockwise by virtue of the contraction and expansion of a LC film connecting a homemade bi-pulley (Figure 5). The way this machine works is by the judicious use of UV and visible light sources at different positions on the pulley. The former contracts one side of the “belt”, while the latter expands it resulting in the observed movement. What is interesting here is that exposing different areas of the “belt” to different light sources circumvents reaching the photostationary state (PSS), thus allowing for the continuous movement of the pulley. This criterion is a prerequisite for the real-life application of light activated molecular machines, but this methodology seems to be underutilized.

This concept of using the deformation caused by the trans → cis isomerization of azobenzene was used by Yu and co-workers in the fabricating of capillary tubes that can be used in controlling the motion of fluid slugs, i.e., a light-controlled microfluidic device (Figure 6). The tubular microactuators were made from linear LC polymers assembled into a lamellar structure, and attenuated visible light was applied to induce an asymmetric deformation that propelled the liquid through capillary force. Not only does this system move different solvents, but it can also mix them, make them go around curves, up a slope, and even use the fluid to carry cargo around. What is interesting here is that the deformation of the polymer is not stemming from the typical order-to-disorder transition observed in azobenzene but rather from its realignment along the propagation direction of the actinic light source through trans → cis → trans isomerization, i.e., Weigert effect. This process in turn causes elongation along the y-axis of the tube, while decreasing its thickness along the x-axis, forming an asymmetric cone, which generates the capillary force needed to move the solvent slugs.
And what is next for photoactive LC polymers? Patterning different LC alignments in the same polymers to obtain different responses will increase the persuasiveness of such systems. When this approach is coupled with light-dose dependent deformations, then materials can be developed that can “decide” based on an external stimulus when and how to actuate.68 The development of new strategies, such as self-shadowing,69 that enable such films to oscillate, work continuously, and even move while carrying cargo will also contribute to their integration into real-life applications. Finding new actuation mechanisms and developing new systems that can show multistate switching will also be important down the road.61 Much progress has been made in the past few years in some of these areas with very promising results. Still more needs to be done as there are a few issues to be tackled. For example, there is no general methodology that can be used to insert a new photoswitch, for example, into a LC polymer, and so mixture optimization is a prerequisite every time a new component is introduced. Having a better understanding of how all components of an LC elastomer work together to get ideal actuation will help on this front, as it can lead in the future to formulations whose properties can be predicted a priori. Simulations will be an important aspect of such an endeavor. Engineering polymers that are not limited to one-dimensional motion, i.e., translation or bending, will be imperative, in robotic applications, for example.70 The coupling of such LC polymers with 3D printing technologies71 might be one way toward this goal. Finally (for this list) the light-penetration depth issue mentioned earlier needs to be addressed as well, which might be easier to tackle in polymers. One approach might be the use of negative photochromic compounds to minimize filter effects, thus allowing for the use of thicker polymers.

**LIQUID CRYSTAL MACHINES**

Liquid crystals are ordered soft materials that can amplify, through their long-range self-assembly the tiniest of molecular motion; i.e., they can be considered as molecular amplifiers.72 LCs can also be encoded with chiral information,73 which can be manipulated reversibly to control, for example, the photo-physical properties of the system (usually a surface).74 In general, photoswitches are used in such applications, though some examples of chemically and electrochemically activated LCs have been reported.75–77 The limitation of LCs is that they are, as the name implies, liquids, and so tapping into them in the production of work becomes more challenging. An exemplary work in this direction was reported by Feringa and co-workers78,79 who showed how the light-induced flipping of the helicity of overcrowded alkene motors can be used in rotating a macroscopic object set on top of a LC surface (Figure 7). This approach works because the change in motor chiral information is transmitted to the LC, inducing it to invert its helical screw sense, which in turn results in the rotation of the film’s fingerprint pattern. Continuous irradiation results in the unwinding of the helical LC structure, thus losing its fingerprint pattern, and then rewinding of the helical structure with the opposite handedness. The unidirectional rotation of the macroscopic object persists throughout the process until the system reaches the PSS, and then it stops. Recently Katsonis and co-workers80 showed, through a judiciously modified design, how the asymmetric diffusion of the two motor stereoisomers, which is brought about by light-induced revolution of chiral LC structures, helps in circumventing the PSS obstacle. This strategy is an important step toward designing machines that can operate continuously in the presence of an external input.

Going forward in this direction will require some careful thinking of how to change the motion transduced from the LC surface to rotation, as this motion will open the way for the moving cargo, i.e., mass transport. The fact that the above-mentioned actuation mechanism relies on a change in the helical sense of the photoactive unit means that a motor is not necessary for obtaining the desired function, allowing for the diversification of the photochromic units that can be used.81 When combined with carefully designed films, boundary conditions, and patterned tracks, one can imagine using the change in the helical structure of LCs in the controlled linear propagation of objects. The PSS limitation will still curb the extent of propagation, and hence, judicious solutions to this issue will be needed. What is sure is that this area is less developed than others, and more effort is needed for it to mature into a useful avenue for the design of molecular machines.

**MACHINES IN POLYMERS**

Amorphous polymers have been less used and studied in the context of molecular machines compared to the more organized LC polymers, mainly because of the difficulty in imparting synchronized and ordered motion in such irregular materials. Nonetheless, the photoactuation of azobenzene-based polymers has been successfully demonstrated.11 For the sake of diversity, I want to focus here though on other promising strategies. The first one entails the use of [c2]daisy chains,82 which are mechanically interlocked12 cyclic dimers in which the monomeric units can be made to slide past each other, resulting in the contraction/expansion of the molecule (Figure 8a). When [c2]daisy chains are incorporated into polymers, their synchronous and collective molecular level motion can be amplified into macroscopic level actuation. Harada and co-workers83 recently showed how this strategy can be used in designing molecular muscles.84 Their system relies on the fact that α-cyclodextrin (α-CD) binds stronger with trans-stilbene than with cis-stilbene, allowing for the light-induced sliding of the α-CD ring from the stilbene station to a poly(ethylene glycol) collection area upon trans → cis isomerization. This motion in the [c2]daisy chain monomer is propagated throughout the polymer, resulting in the contraction/expansion of the cross-linked hydrogel. This phenomenon was sub-
sequently used in actuating a polymer film, and even performing mechanical work by pulling a weight against gravity. What is interesting here is that the actuation occurs reversibly even in the dry gel, which is a departure from most other reports on [c2] daisy chain polymers, which work only in solution, thus limiting their practical use. Moreover, the contraction/expansion in this hydrogel is faster and more efficient than in an earlier example that relied on azobenzene as the photo-trigger,85 showcasing the benefits of having a diverse array of switchable units for practitioners to work with.86

The next example is by Giuseppone and co-workers87 who used the unidirectional rotation of overcrowded alkene motors to braid polymer chains together, resulting in the contraction of a toluene submerged polymer gel (Figure 9). This process was shown to be irreversible, as the polymer entanglement could not be undone; thus, the free energy stored in the tense gel could not be released on command. To tackle this limitation, a “modulator” made of diarylethene was introduced in the second generation material,88 with the aim of taking advantage of the free rotation around the C–C single bond of the open form of DA to release the elastic energy stored in the gel. This strategy worked as the motor and DA require two different wavelengths of light to be activated. Consequently, when the gel was irradiated with UV light, it contracted as a result of motor rotation, while the DA remained inactive. Subsequent irradiation with visible light switched the DA to its open form while the motor stopped spinning, thus allowing the gel to return, to a certain extent, to its original shape. Unfortunately, this material was not coupled with a load, and so the free energy trapped in the gel dissipated to the environment; i.e., no useful work was performed. Nonetheless, this example is a beautiful proof of concept showing how molecular level directional rotation can be tapped into influencing the physical properties of an amorphous polymer, resulting in its reversible actuation when coupled with a tension release mechanism.

These two studies show how the harnessing of collective molecular motion can be used in overcoming the difficulty of amplifying molecular motion through different length scales in amorphous polymers. To push things further, and enhance the capabilities of such systems, several challenges (including ones

Figure 8. (a) The photoinduced sliding of α-CD from the stilbene station toward the poly(ethylene glycol) collecting area in a [c2] daisy chain can be used (b) in forming dry gel photoactuators. Adapted with permission from ref 83. Copyright 2018 American Chemical Society.

Figure 9. (a) The photoinduced contraction of the polymer fibers upon motor rotation (b) results in the contraction of a toluene submerged gel. (c) The inclusion of a diarylethene modulator in the polymer allows for the untangling of the polymer chains, thus making the actuation process reversible. (d) The structures of the overcrowded alkene motor and diarylethene used in the studies. Adapted with permission from refs 87 and 88. Copyright 2015 and 2017 Springer Nature.
mentioned earlier in the LC polymer section) need to be tackled. In general, the switching process in such materials is slow, resulting in long irradiation times that lead to photodegradation, which restricts the number of switching cycles that can be obtained. Moreover, in most cases such polymers only work in solution, i.e., not as free-standing dry polymers, which further encumbers their practical use. Having better control over the hierarchical assembly of the polymers, using self-assembly techniques for example, will address some of these setbacks. The end goal with this strategy will be to bundle the polymer fibers together and align them along the direction of actuation, like in muscle fibers, to enhance the polymer’s mechanical robustness, and hence, performance. Using visible light-activated switches or motors whose motion can be synchronized and made cooperative will improve the switching efficiency, reduce (photo)damage, and increase number of cycles. And finally, coupling such polymeric gels with 3D printing techniques will further contribute to their structural organization and enable their integration with other systems, thus facilitating the transduction of their mechanical motion/built-in tension into useful work.

■ MACHINES IN SOLUTION

The disorder in solution makes it very challenging to extract useful work from artificial molecular machines. In the context of the bicycle analogy, the disorder will result in a chaotic back-and-forth peddling (i.e., Brownian motion), instead of a well-defined directional movement. To impart “directionality” in solution, a systems chemistry approach is required, enabling different components in the solution to communicate with each other so as to control reaction rates, catalysis, feedback loops, and assemblies in a manner that is seamless and in certain cases even orthogonal, which will necessitate compartmentalization. That is, a rudimentary artificial cell needs to be designed for artificial molecular machines to function in solution, and this explains the rarity of such systems. Nonetheless, most reports on molecular switches and motors are about their solution phase function as this is where the basic proof of principle is tested and demonstrated, and fundamentals of molecular motion are studied. So far, we have focused on photoactivated systems, and now I will switch gears a bit and go over some chemically activated ones. First though, I need to comment briefly on chemical versus light stimulus in activating molecular systems. One of the biggest practical challenges in using chemicals as the input is the production of waste, which will accumulate in a closed system such as a flask. To address this issue, we need to get out of the flask and move into flow systems. How cool will it be if a light-controlled capillary system like the one mentioned above (Figure 6) is used in the control of the flow of chemically activated systems, a light-based machine controlling and directing a chemically activated one! But I digress. As mentioned earlier, a fundamental issue in using chemical input is microscopic reversibility, which makes their use in producing useful work challenging. This issue can be circumvented by external pumping, i.e., externally modulating the chemical environment, and hence reaction coordinate, leading to an energy ratchet mechanism, which is the default pathway when light is used as the input. Using chemical catalysis on the other hand will not solve the issue because it requires an information ratchet mechanism; i.e., the kinetic barriers are controlled by the reactants/species in the solution. This disparity explains why light is more prevalent in producing molecular-based work. On the other hand, a benefit of using chemical input is that there is no “photostationary state”, and so the switching can be complete in both directions. One can also make the argument that there must be a value for using chemical input as nature settled on chemical activation for most biological machines. But unlike biology, we are not constrained by the necessity of a thick barrier layer, i.e., skin that blocks light penetration. So, this argument might be conditional. What stands is that chemically activated machines are functionally more biocompatible, and so it will/might be easier to integrate them into and with biological systems.

The first example I want to elaborate on in this section is from Stoddart and co-workers, who recently showed how an artificial molecular pump can be made using rotaxanes by taking advantage of an energy ratchet mechanism. The concept (Figure 10) relies on the kinetic trapping of CBPQT4+ (dark blue) on a collecting axle comprised of an oligomethylene chain using a “steric speed bump” in the form of an isopropylphenylphenylene group (IPP; green). In the first step of the operation, the CBPQT4+ and the bipyridine (BPY2+; light blue) station are reduced with the help of Zn dust. This process results in the...

![Figure 10. A schematic representation of the function of a rotaxane-based molecular pump. A reduction/oxidation cycle forces a CBPQT4+ ring to a collection area where it gets kinetically trapped because of the IPP stopper, allowing for the pumping of more rings on the axle. Reprinted with permission from ref 97. Copyright 2015 Springer Nature.](https://dx.doi.org/10.1021/acscentsci.0c00064)
threading of the ring over the 3,5-dimethylpyridinium (PY; light blue) stopper and its subsequent complexation with the reduced BPY$^{2+}$ through favorable radical–radical interactions, which is the driving force for threading. Next, the station and ring are oxidized using nitrosonium hexafluorophosphate, thus nulling the stabilizing interaction between ring and station and replacing it with a repulsive one. At this stage, the ring has either of two options—dethread by passing over the charged PY$^+$ stopper or go over IPP toward the collecting axle on the other side of the molecule. The energy barrier for the latter process is lower because there is no electrostatic repulsion, thus pushing the ring toward the collection area. This cycle can be repeated numerous times, thus collecting multiple CBPQT$^{4+}$ rings on the axle as the IPP ensures that the complexed ring is stuck in the collection area throughout the redox cycles. What this pump is doing is driving the system out-of-equilibrium by virtue of kinetically trapping the rings on the collection area, but still there is no work being produced as there is no way yet to take advantage of the stored energy. This example of a molecular pump is not the only one in the literature, as Credi and co-workers$^{98}$ have demonstrated a similar concept using a structurally simple rotaxane, where a light-activated azobenzene acts as the “speed bump”. In both cases there is a need to couple the pumps with another system, i.e., use it as machinery, for it to produce work. One option is to incorporate them into membranes$^{99}$ so that the pump will move the macrocycles from one side of the membrane to another, thus creating a chemical gradient. Efforts in this direction are underway in both laboratories, and so this might be just a matter of time.

The next example also relies on steric barriers and differences in kinetics, but this time the directional motion of a macrocycle relative to another is decided by the speed at which a reaction takes place (Figure 11). Leigh and co-workers$^{100}$ showed that the position of the small benzylic amide macrocycle (blue) in a [2]catenane affects the rate of the acylation reaction that installs the bulky 9-fluorenylmethoxycarbonyl groups (red) on the ring. The rate is faster at the site farther away from the small macrocycle, while the rate of bulky group cleavage is unaffected by the ring’s position, i.e., information ratcheting$^{7}$ can be used to make the small ring rotate directionally on the “track” made from the larger one. By judicious use of conditions, it was shown that indeed the small ring moves from one fumaramide station (green) to another in a directional manner, and that this motion can be continuously sustained. This beautiful example demonstrates how careful control over reaction kinetics can be used in devising molecular motors. Again, as before this system needs to be coupled with a load or used as a machinery to take advantage of the directional motion in producing useful work. One possible option is to assemble such motors anisotropically on nanoparticles and use the collective directional motion of the motion and the flux from the catalytic reaction to move objects in solution.$^{101}$

As one can appreciate from these examples, we are seemingly at the cusp of breaking the barrier of using molecular machines in solution, which should allow for the design of chemical gradients that can be used in mass transport, for example. Much more needs to be done before we can achieve this goal. We need to be able to devise new ways to control catalysis and catalytic rates,$^{102}$ be able to engineer synchronized motion through intermolecular communication,$^{103}$ control the timing of events through molecular clocks,$^{104}$ design switches and motors that can change components (using dynamic covalent chemistry, for example)$^{105}$ and hence properties depending on environmental input, use flow systems as a mechanism for waste management,$^{106}$ get better at designing useful out-of-equilibrium systems and assemblies$^{29}$ that are properly fueled by chemicals and controlled via feedback loops,$^{97}$ learn how to compartmentalize reactions and reactants so as they can be used orthogonally at will,$^{107}$ and be able to use self-replication$^{108}$ to replace fatigued components. It seems that we need to learn how to organize solutions, as it is only then that we will be able to translate the collective motion of switches and motors into what machines do—produce work.

**CONCLUSIONS**

When one is asked what is the future of the field of artificial molecular machines, the looming question seems to be—when will there be real-life applications? At this stage, I do not think this should be a raison d’être for the field. Practitioners should focus on the fundamental science and answer basic scientific questions that need to be first addressed to be able to lay the groundwork for such a goal. Considering the frenzy activity in the field, I am optimistic that with time, there will be such applications, but for these to come to fruition, more cooperation...
with industry is needed. If my arm was twisted and I had to bet a dollar on which direction the first one will come from, I would put in on photoswitchable LC polymers, especially if they are coupled with 3D printing. This area is the most highly developed, as far as interfacing different scales are concerned, and so the "lowest" lying fruit(s) seems to be in this direction. Of course, a game-changing idea might come from a different and unexpected venue as well, and so this is only conjecture at this stage.

Finally, it seems that the field is at a crossroads. In certain aspects, it has reached maturity as we have a much better understanding of how to design and control molecular motion, and in general we know, at least theoretically, what needs to be done to translate this motion into useful work. On the other hand, the field is in its infancy as we still do not know the nitty-gritty details of how to integrate molecular systems together nor to the outside world to achieve the complexity found in nature. Considering the influx of new ideas, development of new switchable systems and motors and the growing interest in the field from different disciplines, one thing is for sure, exciting times lie ahead of us.

AUTHOR INFORMATION

Corresponding Author
Ivan Aprahamian – 6128 Burke Laboratory, Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755, United States; orcid.org/0000-0003-2399-8208; Email: ivan.apraphamian@dartmouth.edu

Complete contact information is available at: https://pubs.acs.org/10.1021/acscentsci.0c00064

Notes
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DEDICATION
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