

DRIVING SUPRAMOLECULAR SYSTEMS UPHILL WITH ARTIFICIAL MOLECULAR MOTORS

NICOLAS GIUSEPPONE*

*University of Strasbourg, Department of Chemistry, and Institut Charles Sadron - CNRS
23 rue du Loess, 67000 Strasbourg, France

Molecular motors as components of active chemical systems

Although the nature of life and its origin are still a matter of debate, there is a scientific consensus on the peculiar capacity of living systems to self-organize from simple molecules to more complex (supra)molecular systems that support the emergence of key dynamic functions (*e.g.* self-regulation, adaptation, and self-replication)[1]. In particular, one can mention an important common principle through the words of physicist and Nobel Laureate Erwin Schrödinger in his famous 1944 paper *What is life? The physical aspect of the living cell*, in which he states that “Living matter avoids to decay to equilibrium”[2]. Indeed, it is now well understood that life self-organizes matter out of thermodynamic equilibrium through a number of molecular processes and machineries. In this thermodynamic context, living systems can be qualified as “active” because they produce a physical work on their environment. For instance they can create concentration gradients by powering ion pumps, drive complex endergonic chemical transformations and reaction networks, transport cargo between well-defined locations, contract muscles, provide flagellar motion for propelling cells, and ensure the dynamics of the microtubules during the cell division. In all these processes, the active systems are thermodynamically driven uphill through energy consumption and (transient) energy storage, and they subsequently generate the necessary functions when needed. Interestingly, this escapement of thermodynamic equilibrium is often mediated by biomolecular motors which can perform tasks from nano- to macroscale through the controlled mechanical actuation of their elementary parts when fueled by an appropriate source of energy[3]. In the past 40 years, often inspired by living systems, synthetic and supramolecular chemists have achieved a series of breakthroughs leading to the design and first syntheses of fully artificial molecular machines and motors[4]. In particular, the Nobel Prize for chemistry 2016 was awarded to Profs. J.-P. Sauvage, F. Stoddart and B.L. Feringa for their seminal works on this topic. For instance, Sauvage and Stoddart managed to introduce a new kind of chemical bond, named today as “mechanical bond”,[5] which allows controlled movements of large amplitudes within molecular components such as catenanes and rotaxanes. Since then, a series of advanced works by the groups of

Stoddart, Leigh, Credi, and others have demonstrated the possible ratcheting of these mechanical bonds out of equilibrium upon various sources of energy (including light, redox, and chemical fuels). Following a different approach using photoswitches, the pioneering works of Feringa gave birth to the first example of an artificial molecular motor in the literature, capable of constant and unidirectional rotation under light irradiation with frequencies up to the MHz regime.[6]

By looking at the current state of the art in this field of research, one can expect that the next generation of artificial (supra)molecular systems and materials will advantageously implement such “active” molecular machines in order to escape “dead” thermodynamic equilibrium and to generate advanced functions that mimic living processes.

Our recent research contributions on artificial molecular machines that work on all scales

With my collaborators, we recently focused on a series of investigations to amplify the motion and the mechanical work produced by artificial molecular machines and motors up to the macroscopic scale.[7]

First, we developed covalent and supramolecular polymers made of bistable [c2]daisy chain rotaxanes to access contractile materials sensitive to pH variations (Figure 1) [8].

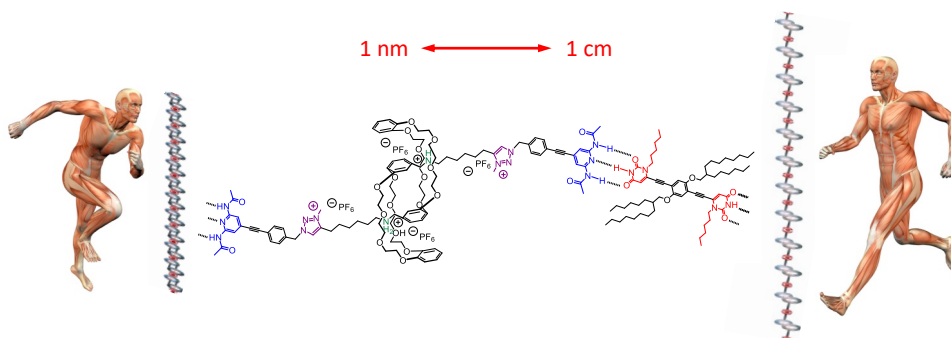


Fig. 1. A supramolecular polymer which integrates the collective actuation of multiple mechanical bonds. In this generic example, the supramolecular polymerization of bistable [c2]daisy chain rotaxane monomers leads to contractile polymer chains. The molecular structure is represented in its extend state with the macrocycles bound to the ammonium stations.

In acidic conditions, the macrocycles of the [c2]daisy chain preferentially bind the ammonium stations and the molecule stands in an extended state; however, under basic conditions, the secondary ammonium stations are deprotonated, and the macrocycles preferentially bind the triazolium stations, resulting in an contracted conformation. At the molecular scale, this sliding motion occurs over approximately 1 nm, but when the [c2]daisy chains are integrated into main chain polymers or into polymer bundles and networks, the collective nanometric displacements are correlated through space and can be amplified up to the macroscopic scale. For instance, we have shown that polymer gels

made of [c2]daisy chain rotaxanes can contract and expand by approximately 60% of their initial volume. It should be mentioned that in these particular systems the [c2]daisy chain acts back and forth reversibly, and that the work produced in one direction is undone during the reverse process. Hence, this switching situation where the machine influences its surrounding only as a function of its state is not sufficient to progressively increase the mechanical work performed on its environment, as opposed to what can be achieved in an out of equilibrium manner by living systems.

To go one step further in this direction, we have demonstrated that light-driven rotary motors can be introduced as active reticulating units in polymer networks, and that they can induce – upon autonomous cycling rotation – the twisting of the polymers chains up to the macroscopic contraction of the material (Figure 2A).[9]

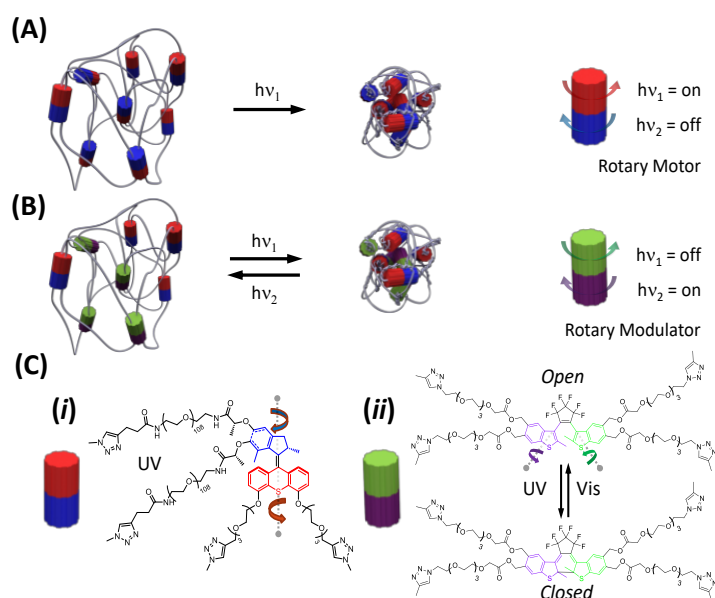


Fig. 2. **Mechanically active motor-polymer networks.** (A) Schematic representation of a polymer–motor network that, under UV ($h\nu_1$), produces a continuous, unidirectional rotation of the motor part (red and blue cylinders) with subsequent winding of the polymer chains leading to a macroscopic contraction of the entire network. (B) Schematic representation of a polymer–motor–modulator gel that proceeds as in (a) when exposed to UV light, but unwinds the polymer chains when exposed to visible light ($h\nu_2$) by activating the modulator part (green and purple cylinders). (C) Chemical structures that compose the polymer–motor–modulator involving (i) enantiopure crowded alkenes as motors and (ii) photoswitchable dithienylethenes as modulators.

Because the Feringa's motors we used rotate unidirectionally (Figure 2C(i)), the coiling of the polymer chains leads to the formation of a variable number of chiral twists which preserve the information on the motors' trajectories. A system of second generation was subsequently designed to make it fully reversible.[10] It uses elementary modules made of a combination of two different mechanically active molecular units: one rotary motor and one rotary modulator linked by polymer chains (Figure 2B). The rotary modulator is

based on a tetrasubstituted dithienylethene photoswitch (Figure 2C(ii)). Its role is to function as an on-demand elastic releaser that operates at a wavelength different from the wavelength that actuates the motor. As the individual cycling units of the module can be actuated out-of-equilibrium at two different wavelengths, the work output at a steady state can be finely tuned by modulation of frequencies with the motor turning clockwise and the modulator anticlockwise. The importance of these achievements compared to the state of the art was twofold: (i) the demonstration that these directional out-of-equilibrium cycling motions can be coupled to polymer chains and amplified up to the macroscale; and (ii) the proof that molecular motors can influence a whole system as a function of their trajectories, and not only as a function of their state as usually observed with switches. This unique out-of-equilibrium control of motor-polymer conjugates was also implemented in the mechanotransduction of living cells,[11] in the transport of metal ions through phospholipid bilayers,[12] and in the determination of the work, torque and force that can be generated by a light-driven rotary motor.[13]

These series of works illustrate the possibility to couple molecular machines, including switches and motors with their environment through (supramolecular) polymers chains, and to possibly push these systems progressively energetically uphill, far from thermodynamic equilibrium, in order to store and make use of their mechanical work therefrom.

Outlook to future developments of research on mechanically active supramolecular systems

In the past forty years, a series of fantastic scientific achievements by synthetic molecular chemists led to the first syntheses of molecular machines and motors. However, up to now, these fascinating objects have mainly been designed and synthesized as individual units, and essentially studied on their own. This was understandably requested by the imperative need to understand and control their mechanism of actuation, but a remaining question is still recurrent in the scientific community and beyond: “what could molecular machines be useful for?”. I believe that this question will be answered only if we understand how to interconnect these machines with their environment. By building further on our original works, we not only want to apply already existing knowledge on molecular motors, but we also want to answer remaining fundamental questions that have not yet been answered even theoretically: (i) Will the integration of molecular motors in (supra)molecular systems and materials be limited to a few and specific examples, or can it be implemented by the design of more general and rationalized approaches? In particular, how to preserve – or even amplify – the out-of-equilibrium ratcheting actuation of a molecular motor when integrated in a material, possibly up to the macroscopic scale? (ii) Which efficiency can be reached by these systems, in terms of energy conversion, motion’s trajectory, workload, speed of actuation, and power? Would these materials offer decisive advantages compared to simpler switching materials in terms of functioning autonomy and work production? (iii) How to couple such

molecularly motorized materials with appropriate devices in order to transduce their mechanical actuation in other types of energy? How to integrate them with other molecular elements (or macroscopic segments) to access multitasking materials? How to engineer them and to interface them with their environment in order to control them and/or to generate autonomous feedback loops leading to adaptation? Can we push such systems sufficiently far away from equilibrium to generate self-organizing emergent behaviors (reaching for instance bifurcation points in their trajectories)? These questions should support new endeavors in the course to reach advanced dynamic systems capable of mimicking complex functions such as those encountered in living systems.

Acknowledgments

I am deeply grateful to all my past and present collaborators, who have vastly contributed to build part of the knowledge presented in this proceeding. I also want to thank the various institutions and funding agencies which supported our research works, including the University of Strasbourg and the CNRS, the European Commission (in the framework of the ERC, ITN-MSCA, and FET-open programs), the ANR, the Institut Universitaire de France, the LabEx CSC of Strasbourg, and the icFRC (Jean-Marie Lehn Foundation).

References

1. P. L. Luisi, *The Emergence of Life*; Cambridge University Press: Cambridge (2006).
2. E. Schrödinger, *What is Life? The Physical Aspect of the Living Cell*; Cambridge University Press (1944).
3. M. Schliwa, G. Woehlke, *Nature* **422**, 759 (2003).
4. S. Erbas-Cakmak, D. A. Leigh, C. T. McTernan, A. L. Nussbaumer, *Chem. Rev.* **115**, 1081 (2015).
5. Bruns, C. J.; Stoddart, J. F. *The Nature of the Mechanical Bond*; John Wiley & Sons, Inc.: Hoboken, NJ, USA (2016).
6. N. Koumura, R. W. J. Zijlstra, R. A. van Delden, N. Harada, B. L. Feringa, *Nature* **401**, 152 (1999).
7. D. Dattler, G. Fuks, J. Heiser, E. Moulin, A. Perrot, X. Yao, N. Giuseppone, *Chem. Rev.* **120**, 310 (2020).
8. E. Moulin, L. Faour, C. C. Carmona-Vargas, N. Giuseppone, *Adv. Mater.* **32**, 1906036 (2020).
9. Q. Li, G. Fuks, E. Moulin, M. Maaloum, M. Rawiso, I. Kulic, J. T. Foy, N. Giuseppone, *Nat. Nanotechnol.* **10**, 161 (2015).
10. J. T. Foy, Q. Li, A. Goujon, J.-R. Colard-Itté, G. Fuks, E. Moulin, O. Schiffmann, D. Dattler, D. P. Funeriu, N. Giuseppone, *Nat. Nanotechnol.* **12**, 540 (2017).
11. Y. Zheng, M. K. L. Han, R. Zhao, J. Blass, J. Zhang, Zhou, *et al. Nat. Commun.* **12**, 3580 (2021).
12. W.-Z. Wang, L.-B. Huang, S.-P. Zheng, E. Moulin, O. Gavatt, M. Barboiu, N. Giuseppone, *J. Am. Chem. Soc.* **143**, 15653 (2021).
13. C. Gao, A. Vargas Jentzsch, E. Moulin, N. Giuseppone, *J. Am. Chem. Soc.* **144**, 9845 (2022).