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1 Extraction of mechanical work from stimuli-responsive 2 molecular systems and materials

3
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10 **Keywords**

11 Molecular switches, Molecular motors, Stimuli-responsive materials, Soft actuators
12
13

14 **Abstract**

15 Molecular switches and advanced molecular motors, which are the elementary building blocks
16 for the construction of molecular machines, have been recently integrated into soft materials
17 in order to generate macroscopic actuation under various types of external stimulations.
18 However, to produce a continuous work from these materials, and therefore to potentially
19 achieve more advanced tasks, important structural and dynamic aspects should be considered
20 at all length scales. Here we discuss the implementation of thermodynamic, photodynamic,
21 and dissipative molecular switches and motors in such stimuli-responsive materials. We also
22 highlight the different ratcheting strategies that can be implemented in these actuators to
23 confer them with the capacity of achieving unidirectional cyclic motion, and in order to
24 continuously and autonomously increase their work output.

25 **Towards a new generation of molecular systems and materials that can perform mechanical** 26 **tasks**

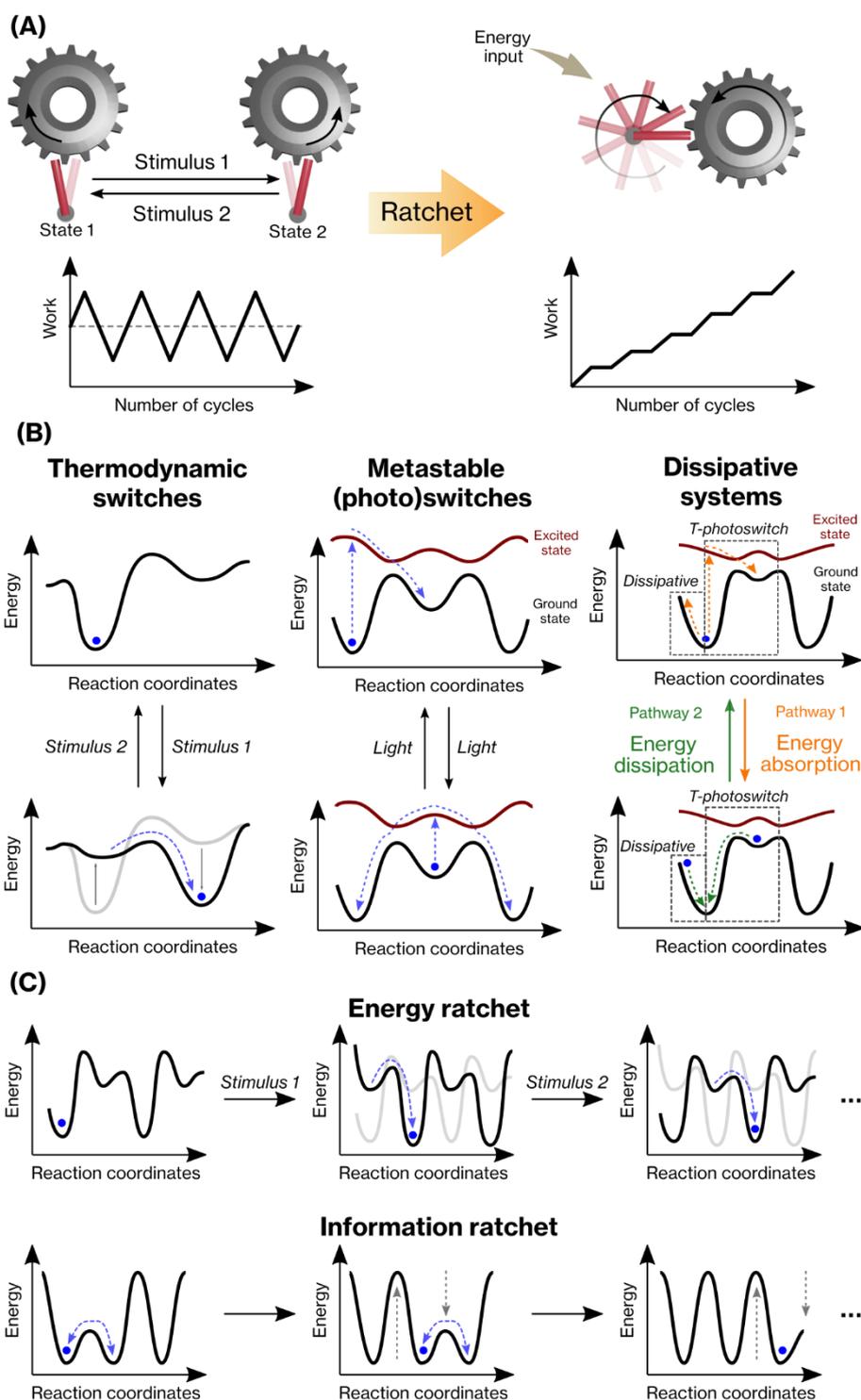
27 Machines convert an input of energy in mechanical forces and movement in order to
28 perform a task. In our everyday life at macroscopic scale, we are acquainted with machines
29 consuming electric or thermal energy for transport or automation. At nanoscale, living
30 organisms also make use of biomolecular machines to function :[1] for instance, kinesin
31 walkers or salmonella H⁺-driven motor use a chemical fuel (i.e. ATP) for the transportation of
32 cargos across the cells or for bacterial locomotion.[2,3] In both macro- and nanoscale
33 machines, the production of a unidirectional and repetitive mechanical actuation (such as a
34 continuous rotation) is mandatory to constantly increase the work they can produce on their
35 environment and to achieve complex tasks autonomously. However, if ratcheting devices are
36 common at macroscale, reaching unidirectional motion in a Brownian environment is a real
37 challenge which requires a deep thermodynamic control of the molecular actuation.

38 From a chemist point of view, the blossoming development of stimuli-responsive molecules
39 and materials therefrom is of particular interest to think about the design of new kinds of
40 mechanically active synthetic systems, capable of controlled actuation at different length
41 scales by consuming various sources of energy.[4] Nevertheless, the amplification of
42 nanoactuators up to the macroscopic scale is a difficult objective to reach because it requires
43 to finely engineer the coupling of dynamic molecular elements in space and time. In addition,
44 upon energy absorption, the mechanical work done by purely switching molecular actuators
45 in devices and materials is usually undone when resetting them to their original state due to
46 **microscopic reversibility** (see Glossary). Therefore, breaking spatial and time-reversal
47 symmetries in such systems constitute an important challenge for the design of truly **active**
48 **materials**. [5] In this direction, dissipative out-of-equilibrium “ratcheting” mechanisms must
49 be implemented during the system’s operation, in order to make use of the mechanical work
50 generated before the material returns to its starting state.

51 The present Review aims at providing physical and chemical strategies to incorporate
52 ratcheting mechanisms in the emerging domain of mechanically active molecular materials
53 (Box 1, Figure I, Key Figure). In a first section, we will survey the diversity of stimuli-responsive
54 materials that have been designed to generate mechanical motion, since all of them could be
55 potentially ratcheted. In a second part, we will highlight recent advances in the design of
56 ratcheting strategies at both the macroscopic and molecular scales in order to extract and

57 exploit mechanical work from actuation cycles. Even though we approach here this topic from
 58 a synthetic chemist point of view, we also wish to highlight the potential benefit of
 59 interdisciplinary research to develop the next generation of such active materials.

Box 1. Thermodynamics of molecular switches and motors



61

62 Upon appropriate stimuli, molecular switches can reversibly evolve between different
63 states which correspond to local minima of their energy profiles. In general, the switching
64 process takes place according to two different mechanisms. Either modification of the ground
65 state energy of the molecule leads to a different stable state, or the switch reaches a
66 metastable state of higher energy when supplied with energy.

67 In the first case, application of a stimulus changes the energetic profile of the molecule.
68 Consequently, the initial state is not the most stable one anymore and the system thermally
69 relaxes to its new thermodynamic equilibrium, whence the term 'thermodynamic switch'
70 (Figure IB, left). The relative populations of all states are governed by Boltzmann distributions.
71 Another stimulus can either revert the molecule back to its initial state or lead to another new
72 thermodynamic equilibrium.

73 The second scenario involves the absorption of energy to reach a metastable state.
74 Photoswitches follow this mechanism; those molecules absorb photons to reach an excited
75 state and relax to a metastable state of their ground energy, whence the term 'metastable
76 switch'. Since this conversion is not governed by thermal processes, the relative populations
77 of the different states do not follow Boltzmann distributions. From its metastable state, the
78 switch can reabsorb a photon to go back to its stable ground state through the excited state.
79 Therefore, by tuning the energetic barrier between the states and working with appropriate
80 wavelengths, one can reach long half-lives of the metastable configuration and actuate the
81 molecule between these two states (Figure IB, middle).

82 A third scenario involves so-called dissipative systems which are constantly being driven
83 out-of-equilibrium by absorbing energy and which are continuously dissipating this energy to
84 their surrounding when relaxing to their thermodynamically stable state (Figure IB, right). The
85 out-of-equilibrium state cannot be maintained without energy supply. Photoswitches with
86 short-lived metastable states are dissipative since the absorption of light energy breaks
87 microscopic reversibility when the switch concomitantly relaxes back to its global equilibrium
88 through a low activation barrier of the ground state. Molecular motors are also dissipative
89 systems, but where the energy dissipation preferentially occurs in one direction by
90 implementing ratcheting strategies. For instance, dissipative photoswitches change their
91 geometry during their operation but the molecular motion averages to zero over time; photo-
92 driven molecular motors, on the other hand, continuously move in one direction and their
93 motion can therefore be exploited at the nanoscopic scale to produce an increasing work on

94 their environment. Ratcheting strategies can be of different types and involve either *i)* “energy
95 ratchets” that have no reference to the position of the particle and in which biased potential–
96 energy minima and maxima are repeatedly modified (Figure 1C, top), or *ii)* “information
97 ratchets” which rely on modifying the height of an energy barrier depending on the position
98 of the particle on the potential-energy surface (Figure 1C, bottom).

99 **Macroscopic actuation from stimuli-responsive molecular materials**

100 Molecular switches may trigger various changes in chemical and physical properties at the
101 nanoscale upon appropriate stimulation, and these changes may be in turn amplified – by
102 diverse processes – up to the generation of macroscopic actuators.[6] As discussed hereafter,
103 such materials can be synthesized from switches involving thermodynamic, metastable, or
104 dissipative states (Box 1), and therefore they can differ by the way they use (i.e. absorb and
105 release) an external source of energy to convert it in molecular motion.

106 *Materials based on thermodynamic switches*

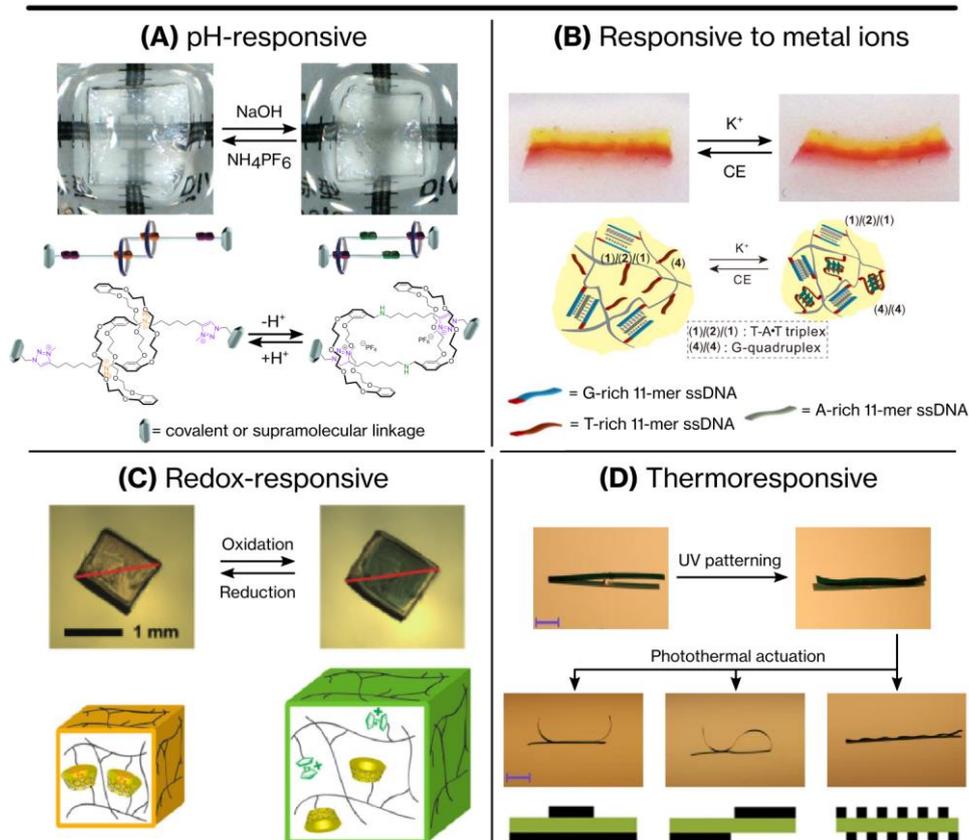
107 The functioning principle of a thermodynamic switch relies on the application of an external
108 stimulus to alter its ground state energy profile and to shift its thermodynamic equilibrium
109 (Box 1 and Figure 1B, left). The mechanical motion generated by such switches arises from
110 their reversible thermal relaxation between an initial state (becoming thermodynamically
111 unstable) and a final state (becoming thermodynamically stable). While chemoresponsive
112 switches reach a new stable state upon changes in their chemical environment (such as pH or
113 metal ions concentration), thermoresponsive switches are based on phase transitions leading
114 to different temperature-dependent equilibria.

115 Several strategies have been used to design *chemoresponsive (macro)molecular actuators*.
116 For instance, hydrogels based on pH-responsive polymers have different swelling equilibria
117 depending on protonation (or deprotonation) of basic (or acidic) side groups. P(HEMA-*co*-AA)
118 (poly[(2-hydroxyethyl methacrylate)-*co*-(acrylic acid)]) and P(HEMA-*co*-DMAEMA) (poly[(2-
119 hydroxyethyl methacrylate)-*co*-(2-(dimethylamino)ethyl methacrylate)]) were used to create a
120 microfluidic valve that could sort aqueous solutions depending on their pH, exploiting the
121 opposite swelling behavior of these two polymers under basic and acidic conditions [7].
122 Another strategy consists in using responsive supramolecular units in the system; for instance
123 by involving DNA sequences which are known to be sensitive to various stimuli [8,9]. In
124 particular, i-motifs [10,11], which are formed under slightly acidic pH, have been used to

125 design DNA-based bilayered actuators [12]. Upon acidification of the medium, cytosine-rich
126 DNA sequences form these i-motifs, which act as new physical crosslinks in the hydrogel,
127 therefore inducing a stress in one layer which bends the entire material. Using more complex
128 actuating units based on **molecular machines** using **mechanical bonds**, [13,14] our group
129 developed polymerizable **[c2]daisy chains** to form a contractile gel sensitive to pH changes
130 (Figure 1A) [15,16]. In basic conditions, the macrocycles preferentially bind the triazolium
131 stations and the molecule stands in a contracted state; in acidic conditions, however, the
132 secondary amines are protonated and the macrocycles preferentially bind the
133 dialkylammonium stations, resulting in an extended conformation. At the molecular scale, this
134 sliding motion occurs over approximately 1 nm but, when the [c2]daisy chains are polymerized
135 into a covalent network by copper-catalysed Huisgen[3+2] cycloaddition, the nanometric
136 displacements are correlated through space and are amplified up to the macroscopic scale.
137 The [c2]daisy-chain-based gels contract to approximately 60 % of their initial volume in basic
138 conditions and recover their initial shape in acidic conditions. Metal ions can also trigger
139 actuation in responsive materials. For instance, guanine-rich DNA sequences are sensitive to
140 monocationic ions, such as potassium or sodium, leading to the formation of G-quadruplexes.
141 Following a mechanism similar to the one described for materials based on i-motifs (*vide*
142 *supra*), bilayered actuators bending upon addition of potassium ions were designed (Figure
143 1B) [12]. Alternatively, DNA-DNA duplexes with cytosine-cytosine mismatches, which are
144 sensitive to silver ions, were used to fabricate metal-sensitive hydrogel actuators [17].
145 Supramolecular redox processes have also been considered as stimuli for actuators. In an early
146 example, Harada *et al.* developed a hydrogel actuator based on the redox sensitive ferrocene-
147 cyclodextrin interaction. In reductive conditions, these two molecules form an inclusion
148 complex in water because of the hydrophobicity of ferrocene. Under oxidative conditions,
149 however, the ferrocene switches to its cationic ferrocenium ion and electrostatic repulsion
150 breaks the complex with cyclodextrin. In the hydrogel, oxidation induces a reduction of the
151 crosslinking density due to the dissociation of inclusion complexes, which results in an
152 expansion of the material (Figure 1C) [18]. Recently, a similar material based on viologen-
153 cyclodextrin interactions was reported as redox responsive actuator. In that case, inclusion
154 complexes consisting of cyclodextrin and dimers made of reduced radical-monocationic
155 viologen act as additional reticulating units which break upon oxidation, leading to an
156 expansion of the material [19]. Alternatively, oligoviologen units inserted into a polymeric

157 hydrogel can act by themselves as redox-responsive units. Reduction of the viologens leads to
 158 the formation of complexes between the reduced radical-cationic species inducing the folding
 159 of the polymer chains and the subsequent material's contraction [20].

Thermodynamic switches



160
 161 **Figure 1. Representative examples of actuators based on thermodynamic switches. (A)** pH-
 162 responsive chemical gel based on [c2]daisy chains. Under basic conditions, the macrocycles
 163 preferentially bind the triazolium stations (purple) and the switch is in a contracted conformation. In
 164 acidic conditions, the secondary amines (green) are protonated and the macrocycles preferentially
 165 bind the dialkylammonium stations (orange), resulting in an extended state of the [c2]daisy chains.
 166 The molecular motion is amplified up to the macroscopic scale in the chemical gel. Black ticks in the
 167 snapshots are separated by 1 mm. **(B)** DNA-based actuator responsive to metal ions and schematic
 168 representation of the yellow layer. The red layer is mainly composed of PNIPAM, while the yellow layer
 169 is made of polyacrylamide. Upon addition of potassium ions, the yellow layer can form G-quadruplexes
 170 which act as new crosslinks, thus leading to a contraction of this layer and, hence, a bending of the
 171 material. CE stands for crown ether. The length of the gels is ~ 2 cm. **(C)** Redox-responsive actuator
 172 based on ferrocene-cyclodextrin complexes. In reductive conditions, ferrocene forms inclusion
 173 complexes with cyclodextrin because of its hydrophobicity; in oxidative conditions, the formation of
 174 the ferrocenium cation leads to dissociation. As the crosslinking density decreases, expansion of the
 175 gel occurs. **(D)** Reprogrammable thermoresponsive LCN actuator. An initial reversible photopatterning
 176 step, leading to a minimal deformation of the material, creates stress distributions in the network.
 177 Heating the material with light *via* photothermal agents actuates the material following these patterns
 178 (representation below). Scale bars: 5 mm. *Figure 1A: from 10.1021/jacs.7b06710, Figures 1 and 3.*

179 *Figure 1B: from 10.1021/jacs.6b10458, Figure 3. Figure 1C: from 10.1002/anie.201300862, Figure 3.*
180 *Figure 1D: from 10.1038/s41467-018-06647-7, Figure 4. The four of them have been adapted.*

181

182 Different strategies have also been proposed in order to reach *thermoreponsive actuating*
183 *devices*. One of them relies on the use of common thermoresponsive polymers such as
184 PNIPAM (poly(N-isopropylacrylamide)) which displays a **LCST** around 32°C in water, meaning
185 that its solubility substantially decreases above this temperature. As a result, PNIPAM-based
186 hydrogels shrink when heated. Recent reports involving PNIPAM include the design of bilayer
187 composites exhibiting bending motion [12,21,22], and of robotic devices such as grippers that
188 could reversibly grab and release an object [23]. **Liquid crystalline networks (LCNs)** are also
189 common thermoresponsive materials where the phase transition between the ordered,
190 liquid-crystalline phase and the disordered isotropic phase leads to volume changes. Since
191 light can be precisely addressed spatially and temporally, LCNs are commonly doped with
192 photothermal agents [24] such as carbon nanotubes [25], gold nanoparticles [26,27] or
193 organic dyes [28]. While most designs result in bistable actuators, recent reports have shown
194 reprogrammable systems where different final states can be reached. For instance, Lahikainen
195 and colleagues reported an azobenzene-based LCN that could be reversibly patterned with UV
196 light through photomasks. As a consequence, different stress distributions were achieved
197 inside the material, leading to different deformation modes once the material was heated *via*
198 **photothermal effect** (Figure 1D) [29]. Recently, incorporation of diarylethene units inside
199 these LCNs allowed actuation only when both UV and visible light were applied, thereby acting
200 as an AND logic gate [30]. Finally, Zeng and coworkers reported so-called ‘Pavlovian’ materials
201 based on LCNs [31] where the material, initially inert to light, could be ‘trained’ to become
202 light-sensitive by allowing the diffusion of photothermal agents inside the material during
203 simultaneous heat/light stimulation [32]. Interestingly, DNA-based materials have also been
204 reported as thermoresponsive actuators. The dissociation of DNA duplexes could be
205 controlled by heating the material with light using gold nanoparticles or nanorods as
206 photothermal agents, leading to a change in crosslinking density which triggered actuation
207 [33]. The reversibility of the DNA complexes formation in the absence of light allowed the
208 recovery of the initial shape.

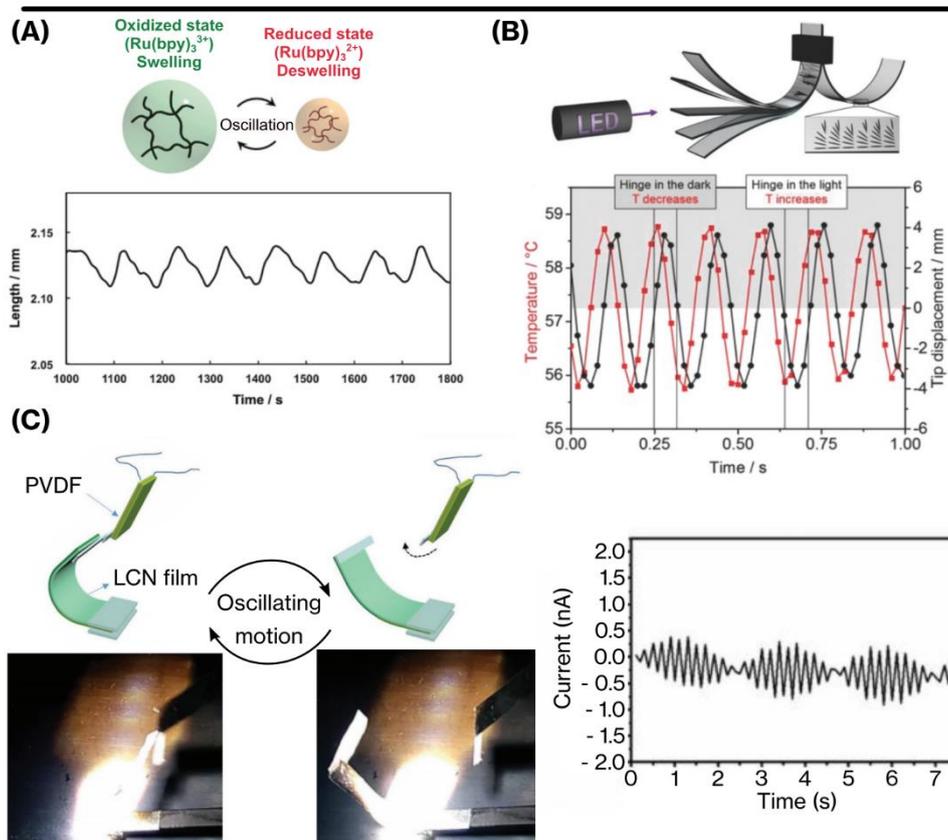
209 *Oscillating phenomena* have also been exploited to trigger back and forth actuation using
210 either chemoresponsive or thermoresponsive systems. This approach has the advantage of

211 cyclically modulate the global energy profile of a molecular material over time without the
212 need of sequential inputs. Most oscillating chemoresponsive materials are based on the
213 **Belousov-Zhabotinsky (BZ) reaction**. For instance, the redox-responsive catalyst of the BZ
214 reaction can be covalently incorporated inside PNIPAM-based hydrogels. The oscillating
215 change in hydrophilicity of the catalyst result in an oscillating modulation of the hydration
216 equilibrium of the polymer, thereby leading to an oscillating volume change of the material
217 (Figure 2A) [34,35]. An oil pump was recently reported with this type of material [36]. Other
218 oscillating reactions have also been used to design time-dependent actuating materials [37],
219 such as an enzymatic oscillating reaction powered by ATP that led to an oscillating
220 concentration in calcium ions. These ions could reversibly bind to phosphate groups along the
221 polymer chains of an hydrogel, thereby modulating the crosslinking density and thus inducing
222 periodic volume changes [38]. Oscillating materials can also be designed from
223 thermoresponsive materials. The groups of Broer and Meijer thoroughly investigated this
224 phenomenon with thermotropic LCNs doped with photothermal agents. In this case,
225 irradiation of the material induces its bending; the bent part, however, blocks the light source
226 from irradiating the material. It therefore relaxes back thermally to its initial position, allowing
227 the light source to irradiate again the LCN, which bends again. This self-shadowing effect leads
228 to a sustained oscillations of the polymer films (Figure 2B) [39–41]. Finally, such a kind of
229 device can be coupled to another material collecting and transducing the generated
230 mechanical motion. This was reported, for instance, with oscillating materials driven by
231 photothermal effect (*vide supra*) and coupled to piezoelectric PVDF (poly(vinylidene fluoride))
232 films [42]. The observed piezoelectric effect arises from the oscillation of the PVDF film, which
233 comes from the light-induced oscillatory motion of an LCN material. Consequently, the
234 oscillating motion of the LCN is transduced, *via* the PVDF, as an oscillating potential difference
235 between two electrodes. It is worth noting that this potential difference averages to zero over
236 time, highlighting that, overall, no continuous work is extracted (Figure 2C).

237 Although thermodynamic switches allow the design of a wide variety of materials, they are
238 often associated with several drawbacks. Chemoresponsive systems usually suffer from
239 substantial fatigue after a few operating cycles because of the accumulation of chemical waste
240 over time. Thermoresponsive materials, on the other hand, cannot be directly addressed very
241 precisely with temperature, thus requiring very often the use of photothermal agents, since

242 light can be more easily focused on precise spots at precise times. In the following section, we
 243 will see how light can be used to actuate materials following totally different energy profiles.

Oscillating materials



244
 245 **Figure 2. Representative examples of oscillating materials.** (A) Microgels based on PNIPAM were
 246 functionalized with tris(bipyridine)ruthenium ($\text{Ru}(\text{bpy})_3$). Since it is swollen in a BZ reaction medium,
 247 the oxidation state of $\text{Ru}(\text{bpy})_3$ cyclically changes over time and, hence, modifies the hydration
 248 equilibrium of the polymer gel (top). Consequently, the microgels cyclically swell and shrink over time
 249 (bottom). (B) LCNs with a splay alignment were doped with photothermal agents (top). Upon local
 250 irradiation, the photothermal effect from the dopants induces local heating of the material and,
 251 therefore, its bending. Consequently, the tip of the LCN films blocks the light beam from reaching its
 252 irradiation point; rapid heat dissipation triggers the unbending of the material to its initial state and
 253 the cycle is repeated (bottom). (C) Oscillating LCN films were used to modulate the potential difference
 254 between two electrodes. The oscillating motion of the light-sensitive was used to hit a PVDF film and
 255 induce its own mechanical oscillation (left). The oscillating deformation of the PVDF creates an
 256 oscillating potential difference between two electrodes (right). The ‘beating’ aspect is caused by a
 257 mismatch between the oscillation frequency of the LCN and the oscillation frequency of the PVDF (due
 258 to its intrinsic elasticity). Importantly, the potential difference averages to zero over time. *Figure 2A;*
 259 *from 10.1002/anie.201809413 Figures 1 & 5. 2B: from 10.1002/adma.201606712, Figure 2. 2C: from*
 260 *10.1002/adom.201800131, Figure 6.*

261

262 *Materials based on metastable switches*

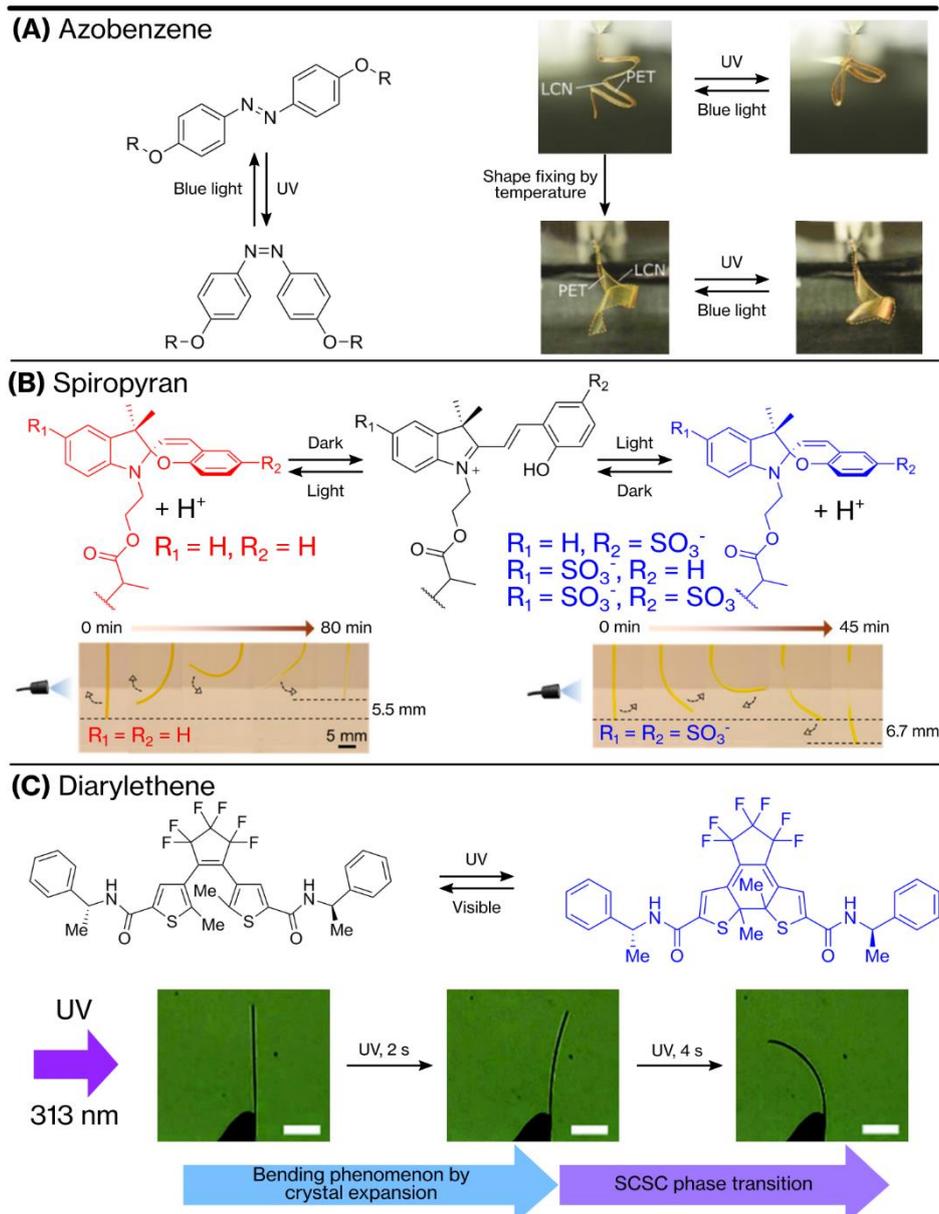
263 Under light irradiation, photoswitches can reach a metastable state of higher energy (Box
264 1 and Figure IB middle), thus leading to a state probability inaccessible for thermodynamic
265 switches following Boltzmann distribution. This excitation process is photodynamic as it is
266 reversible through the excited state between the metastable and stable ground states. In
267 addition, this reversibility can be complemented by a thermal process going from the
268 metastable state to the stable one when the energy barrier of the ground state is low enough
269 to be crossed, thus leading to dissipative systems which can be maintained out-of-equilibrium
270 under light irradiation (Box 1 and Figure IB, right). Note that such photoswitching systems do
271 not follow the principle of microscopic reversibility, and as it is the case for switches purely
272 actuating back and forth along their ground states such as chemical systems displaying
273 **detailed balance**. Consequently, an actuating material based on photoswitches can reach,
274 depending of the height of the ground state energy barrier, either a metastable shape that
275 can be reset by photoexcitation, or an out-of-equilibrium shape that eventually relaxes back
276 thermally.[43] Several molecular photoswitches have been recently implemented to access
277 actuating macroscopic materials [44,45].

278 *Azobenzene derivatives* are probably the most used ones. Upon light irradiation, the stable
279 *trans*-isomer is isomerized to its metastable *cis*-form. This process is reversible either by
280 thermal relaxation or by light irradiation [46]. *Trans*-azobenzene, with an elongated shape,
281 has been widely used as dopant in LCNs which can then actuate according to either a
282 photothermal or a photomechanical mechanism. On one hand, since azobenzene absorbs
283 light, it can be used as a photothermal agent to trigger the actuation of thermoresponsive
284 LCNs by the photothermal effect. On the other hand, the photomechanical effect, which arises
285 from the bent structure of the *cis*- isomer, can induce destabilization of the liquid crystalline
286 phase leading to disorder which results in a volume change of the material. However, the
287 relative contribution of each mechanism is still a subject of investigations [47]. LCNs have great
288 potential to be used in soft robotics because of their mechanical properties and their efficient
289 stimuli-responsiveness; therefore, doping them with light-sensitive molecules paves the way
290 towards remotely controlled soft robotics systems.[48,49] While most azobenzene-based
291 LCNs lead to materials which can actuate between two states [50], recent reports presented
292 reprogrammable materials including for instance liquid crystalline elastomers [51] or
293 LCN/thermoplastic composite materials [52]. In this last example, the presence of a

294 thermoplastic polymer allows for shape molding and reprogramming at a temperature close
295 to the glass transition temperature while light is used for actuating the LCN (Figure 3A) [52].
296 Recent developments also include the design of more complex materials that are multi-stimuli
297 responsive [53,54] or that can get crossed-information from the environment to trigger their
298 actuation [55]. Azobenzenes in their *trans*- form are also known to form inclusion complexes
299 with cyclodextrins [56]. Upon UV light irradiation, the formation of the *cis*- isomer leads to the
300 dissociation of the complex. This unthreading process that has been exploited in chemical gels
301 based on [c2]daisy chains [57] and **[2]rotaxanes** [58] leads to a volume change of the material
302 upon light irradiation.

303 *Spiropyran* has also been widely used for the design of photoactuated materials [6,59].
304 Under light irradiation, it can reversibly isomerize between its closed spiropyran form and its
305 open merocyanine form. The stimuli-responsiveness of spiropyran-based materials originates
306 from the difference in polarity between these two isomers. In water, in the absence of any
307 charged substituents, the zwitterionic merocyanine is the most stable isomer and its ring
308 closure under light irradiation leads to the neutral spiropyran, which is less solvated by water.
309 When incorporated in a hydrogel, this change in solubility induces a shrinkage of the material
310 upon light irradiation, subsequently leading to a bending towards the light source [60]. This
311 tendency can be reversed if the spiropyran is functionalized with negatively charged sulfonate
312 groups which increase the net charge of the molecule in its closed form (Figure 3B) [61]. As
313 for azobenzene, new materials with improved performance are still regularly reported. For
314 instance, the group of Stupp designed a hybrid hydrogel made of supramolecular nanofibers
315 that are chemically cross-linked to a photo-responsive chemical network containing
316 spiropyran side chains [62]. As a gradient of hydrophobicity occurs upon light irradiation, a six-
317 arm flower-shaped hydrogel was bent in different configurations by precisely addressing the
318 light on each petal.

Metastable switches



319

320 **Figure 3. Representative examples of actuators based on metastable switches. (A)** Reprogrammable
 321 azobenzene-based LCN. The LCN is prepared on a thermoplastic substrate (PET, poly(ethylene
 322 terephthalate)) that can be deformed when heated above its glass transition temperature. Different
 323 modes of actuation under UV light can therefore be achieved with a single material. The length of the
 324 material is 2 cm. **(B)** Spiropyran-based gels. When merocyanine has no sulfonate group, ring closure
 325 under UV decreases the net charge of the molecule, leading to a contraction towards the light source.
 326 Yet, when merocyanine has sulfonate groups, ring closure under UV increases the net charge of the
 327 molecule, leading to an expansion of the gel and, therefore, a bending motion away from the light
 328 source. In both cases, for prolonged irradiation times, unbending occur as the deformational gradient
 329 disappears. **(C)** Diarylethene-based crystal. The crystal is irradiated from the left side. Under UV, the
 330 crystal first bends away from the light source because of the change in geometry of the photoswitch
 331 which leads to an expansion of the crystal. For longer irradiation times, however, the higher population
 332 of photocyclized molecules triggers a single-crystal-to-single-crystal transition with smaller final lattice

333 parameters, leading to a bending motion towards the light source. Scale bars: 250 μm . Figure 3A: from
334 10.1002/anie.201915147, Figure 4. Figure 3B: from 10.1021/jacs.0c02201, Figure 4. Figure 3C: from
335 10.1039/D0SC05388K, Figure 1.

336

337 *Diarylethenes* can also be used to generate mechanical work because light irradiation
338 triggers the electrocyclization of the molecule. When organized in crystalline lattices, this
339 change in geometry can be translated up to the macroscopic scale by reorganization of the
340 irradiated crystalline phase. Since the first report in 2007 [63], many more systems have been
341 described (Figure 3C) [64–66].

342 In the first part of this Review, we have discussed different mechanisms that can be used
343 to generate mechanical actuation from molecular materials. However, in most cases, the work
344 performed during the actuation comes undone when the material returns to its initial state.
345 In order to extract increasing amount of work from such materials and to use repeatedly the
346 mechanical work produced to perform a task, one should enforce them to undergo
347 unidirectional motions by “ratcheting” their actuations.

348 **Extracting continuous mechanical work from molecular systems and materials by** 349 **implementing ratchet mechanisms**

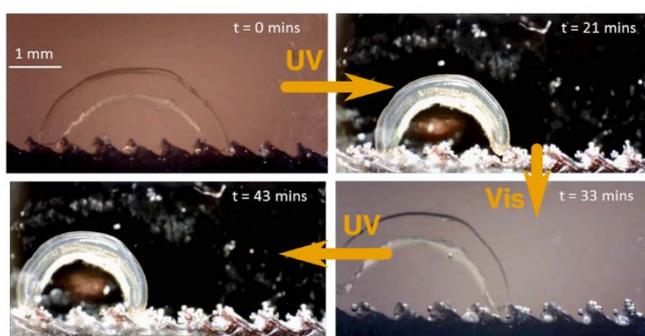
350 To produce a continuously increasing mechanical work on its environment, an actuator must
351 involve a symmetry-breaking process, as the system must follow a distinct trajectory when
352 returning back to its initial stable state (Box 1 and Figure 1A, right). Symmetry breaking of
353 actuating molecular materials can take place by implementing different types of **ratchets**
354 acting at different length scales. They can for instance (i) take advantage of an asymmetric
355 external stimulation; (ii) involve a built-in asymmetric response of the material, or (iii) rest on
356 the design of a ratchet mechanism at the nanoscale in order to upgrade molecular switches in
357 **molecular motors** (Box 1 and Figure 1C).[67,68]

358 *Asymmetric interaction with the environment.* One possibility to achieve unidirectional motion
359 of an actuating material is to make it interacting with a ratcheted surface, as already
360 demonstrated with spiropyran-based gels [69,70]. Oriented translational motion as well as
361 rotation over several cycles was reported for such materials [62]. A bent gel was also cyclically
362 swollen and shrunk with light on an asymmetric ratcheted surface (Figure 4A). The
363 dissymmetric geometry of this serrated surface precluded motion to the right, thus forcing
364 the material to repeatedly move in the same left direction under sequential light irradiation

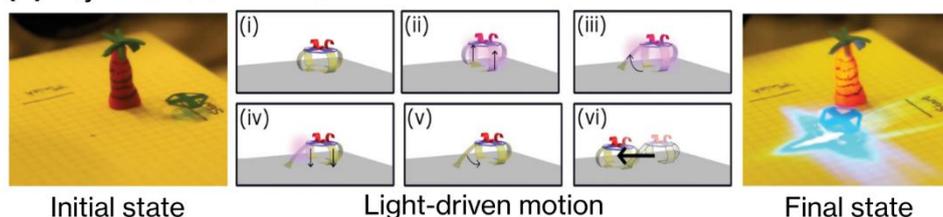
365 [69]. An alternative strategy consists in an asymmetric stimulation of the actuating system.
 366 Early reports show that either simultaneous or alternate UV and visible light irradiation could
 367 induce the rolling motion of a belt made of azobenzene-based LCNs [71] or of a gear using
 368 diarylethene-based crystals, respectively [72]. Recently, Pilz da Cunha *et al.* reported a soft
 369 robotic tetrapod with four LCN legs that could move and transport objects by selective and
 370 sequential irradiation of the legs (Figure 4B) [73]. Fischer and coworkers reported the
 371 translational motion of a tubular LCN caused by a wave-like propagation of a local expansion
 372 of the material. Light irradiation was locally applied progressively along the length of the
 373 network, biomimicking the motion of earthworms (Figure 4C).[74]

Macroscopic ratchets

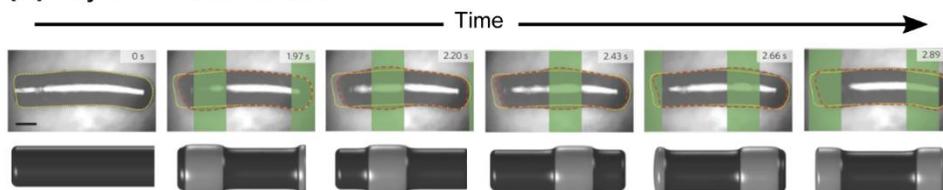
(A) Ratcheted surfaces



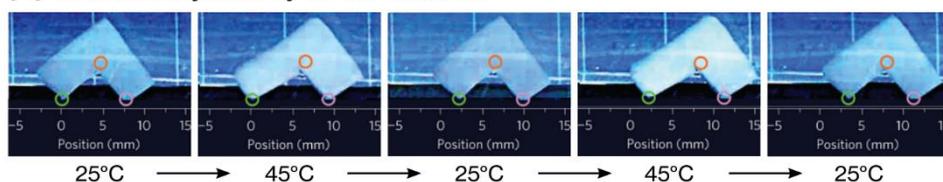
(B) Asymmetric stimulation



(C) Asymmetric stimulation



(D) Inherent asymmetry of the material



374

375 **Figure 4. Design of macroscopic ratchets. (A)** Spiropyran-based gel ‘walking’ on a ratcheted surface.
 376 The material itself is cycling between two shapes, while the asymmetry of the surface makes it move

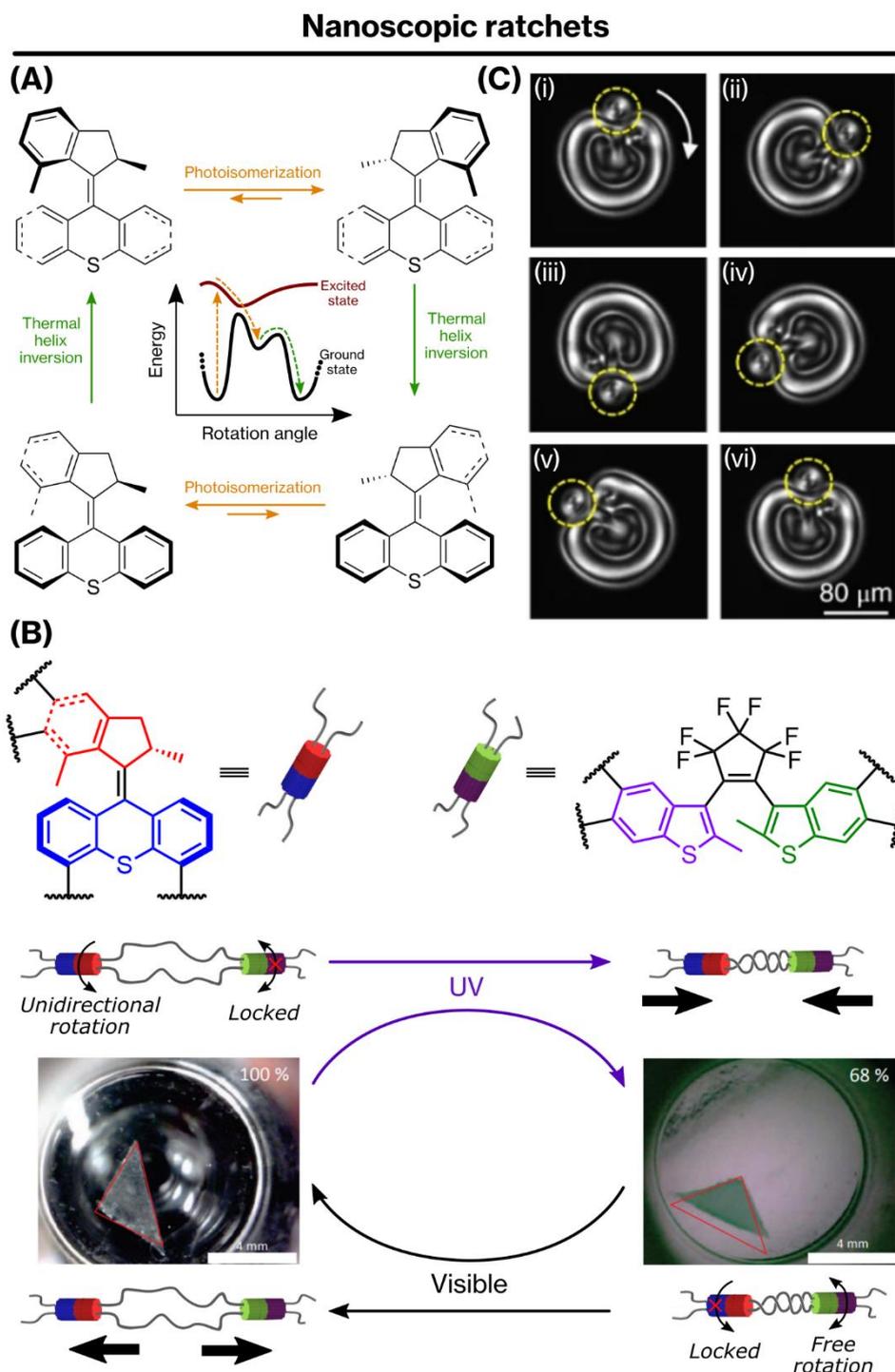
377 preferentially to the left. **(B)** Locomotion of a soft robotic device over more than 4 mm by asymmetric
378 light stimulation according to the following mechanism: (i) a platform is mounted on four azobenzene-
379 based LCN 'legs', (ii) irradiation of two opposite legs lifts the device while (iii) irradiation of a third leg
380 with a tilted angle induces unfolding, (iv) stopping irradiation on the two opposite legs lowers the
381 platform, (v) light removal from the third leg induces bending back to its initial shape, and (vi) a
382 translating motion occurs as this bending motion drag the whole system. Snapshots on the left and
383 right sides show the position of the platform before and after this sequence, respectively. **(C)**
384 Snapshots of an LCN-based tubular material (top) with the corresponding schematic representation of
385 the volume changes (bottom). Asymmetric light irradiation leads to the directional motion of the
386 material. Local light irradiation (green areas) trigger volume expansion. The light beam travels along
387 the length of the material, causing a wave-like propagation of the deformation, which in turn induces
388 the translational motion of the tube, similar to the one of an earthworm. Scale bar: 200 μm . **(D)**
389 Anisotropic PNIPAM-based gel containing precisely-oriented titanate nanosheets. The anisotropic
390 swelling behavior drives the motion of the gel preferentially to the right side when the temperature is
391 cycled above and below the LCST. Figure 4A: from 10.1016/j.snb.2017.05.005, Figure 5. Figure 4B: from
392 10.1002/adv.201902842, Figure 3. Figure 4C: 10.1038/nmat4569, Figure 2 Figure 4D: from
393 10.1038/nmat4363, Figure 5.

394
395 *Inherent asymmetry of the macroscopic material.* An alternative approach to extract
396 mechanical work consists in using materials that are inherently asymmetric at macroscopic
397 level. For instance, Kim and coworkers developed a PNIPAM-based gel containing
398 macroscopically aligned titanate(IV) nanosheets, and which displays an anisotropic
399 thermoresponsive swelling behavior. Interestingly, directional motion of a L-shape cut
400 material occurred upon heating/cooling cycles, resulting from the anisotropic shape change
401 which leads to an unidirectional translation of the centroid of the gel (Figure 4D) [75].
402 Microplatelets coated with azobenzene have been reported to perform continuous rotation
403 under light irradiation when immersed in a liquid crystal. A feedback mechanism takes place
404 between azobenzenes and mesogens at the interface of the object, modulating the effective
405 light beam irradiating the material and, therefore, leading to an unidirectional rotation of the
406 platelets [76]. Recently, photoresponsive micrometer-sized crystals capable of continuous,
407 unidirectional twisting motion were reported. Light-induced $E \rightarrow Z$ isomerization of the
408 allylidene malonitrile induced disruption of the crystalline phase of the material which
409 resulted in anisotropic stresses leading to motion [77].

410 *Ratcheting at the nanoscale: molecular motors.* As already discussed, switches can reach
411 several global or local minima of their energy profile depending on the stimulus applied (Box
412 1). A peculiar situation arises when the high energy state of a switch (pathway I) is
413 continuously populated by energy absorption, and continuously depopulated by thermal

414 energy transfer to its surrounding (pathway II) (Box 1 and Figure IB, right). Here, the resulting
415 out-of-equilibrium situation can be ratcheted if the energy dissipation is enforced to occur in
416 one preferential direction by molecular symmetry breaking, leading to a so-called molecular
417 motor capable of unidirectional nanoactuation (Box 1, Figure 1C). Therefore, in contrast to
418 mechanical switches which influence their surrounding environment as a function of their
419 states, molecular motors move their subcomponents along a nonreversible energy profile,
420 and influence their surrounding environment as a function of their trajectory. This confers
421 them with the unique property to progressively and repeatedly increase the work they can
422 perform on their environment. For instance, the group of Leigh reported the first chemically
423 fueled molecular motor prepared from a **[2]catenane** [78]. Proper design of this interlocked
424 structure allowed the unidirectional chemically powered rotation of one macrocycle with
425 respect to the other by involving an information ratchet mechanism.[79] Nevertheless, most
426 synthetic molecular motors are concomitantly photo- and thermally actuated with a
427 ratcheting mechanism involving the presence of stereogenic centers.[80] The most common
428 molecules of this type are overcrowded alkenes initially developed by the group of Feringa
429 (Figure 5A) [81]. In such molecular motors, a first photochemical *trans*→*cis* isomerization
430 takes place, leading to an unstable helical conformation which can relax to a stable one by
431 thermal atropisomerization, thus leading to a net 180° rotation. This thermal helix inversion
432 step is biased towards one particular direction due to the presence of an asymmetric carbon
433 recovering its favored pseudo-axial conformation from an unfavored pseudo-axial one as
434 obtained after light-irradiation. The repetition of these two steps completes a net
435 unidirectional 360° rotation. More recently, hemithioindigo motors have been developed,
436 following the same mechanistic principles but rather being driven by visible light [81]. In these
437 motors, the ratchet mechanism is encoded in the molecule itself. If such molecular motors are
438 still not often exploited to extract mechanical work at higher length scales in materials, a
439 number of innovative examples exploit the change in geometry at the photostationary state
440 reached after irradiation. For instance, when overcrowded alkenes are used as chiral dopant
441 in a liquid crystal, irradiation produces a change in the helicity of the motors, leading to the
442 deformation of the cholesteric LC phase and subsequently inducing the rotation of a nanorod
443 on the surface. Then, stopping the irradiation reverts the motion, cancelling the initial work
444 produced through a reverse rotation of the nanorod [82]. The group of Feringa also reported
445 supramolecular fibers containing amphiphilic overcrowded alkenes, where irradiation led to

446 bending towards the light source due to a structural disordering of the supramolecular packing
 447 [83–85].



448
 449 **Figure 5. Design and application of molecular motors.** (A) Mechanism for the unidirectional rotation
 450 of second-generation light-driven rotary motors based on overcrowded alkenes. It consists of two
 451 photochemical steps and two thermal isomerization steps. In the most stable configuration, the methyl
 452 group of the asymmetric carbon of the upper part has a pseudoaxial conformation. After the
 453 photoisomerization steps, the motor has an opposite helicity and, in this configuration, this methyl
 454 group has a less stable pseudoequatorial position. The most stable conformation is restored after

455 thermal helix inversion. This ratcheted design of the molecule leads to unidirectional rotary motion.
456 **(B)** Snapshots and schematic representation of chemical gels formed by rotary molecular motor
457 crosslinks (red and blue cylinders) and diarylethene-based elastic releasers (purple and green
458 cylinders). Upon UV irradiation, motors twist pairs polymer chains together, increasing the number of
459 physical crosslinks and, hence, reducing the volume of the gel. The elastic energy stored in the material
460 from the torque produced by the molecular motors can be restored upon visible light irradiation over
461 48 hours, as diarylethene units switch to their open form that can freely rotate and untwist the chains,
462 recovering the initial volume of the gel. In other words, under UV, the work performed by the
463 unidirectional motion of motors can be stored in the material because the diarylethenes are in their
464 closed, 'locked' conformation. However, under visible light, the diarylethene modulators isomerize to
465 their open form with free rotation around single bonds. Consequently, they will tend to rotate in the
466 opposite direction to that of the motors to untwist the polymer chains. Overall, the process describes
467 a continuous and unidirectional trajectory to be activated and reset. **(C)** Liquid-crystalline pattern
468 continuously rotating under irradiation inside a molecular-motor-doped liquid crystal. The pattern is
469 observed by polarized optical microscopy between crossed polarizers. The rotation of the pattern rises
470 from a diffusion-driven feedback process occurring when the motor is isomerized. The torque
471 produced can be used to transport a microscopic object (circled by yellow dotted line). Full rotation
472 takes place in ~23 minutes (from (i) to (vi)). *Figure 5B: from 10.1038/nnano.2017.28, Figure 1 and*
473 *Supplementary Figure 4. Figure 5C: from 10.1038/s41565-017-0059-x, Figure 5.*

474
475 Our group reported on the formation of chemical gels incorporating such molecular motors
476 as active crosslinks, and in which the work produced by each motor is directly stored as elastic
477 energy in the network [86]. Indeed, because the rotation of the motors under UV irradiation
478 induces a twisting of pairs of polymer chains, the increasing number of crosslinks from
479 entanglements triggers a contraction of the material (through syneresis), together with an
480 increase of its elastic modulus [87]. Interestingly, this elastic energy can be released by
481 integrating light-triggered diarylethene moieties as additional crosslinking units, and through
482 unwinding of the polymers chains. Because this unwinding take place at a different
483 wavelength and in different locations of the materials, the entire system can be maintained
484 out of thermodynamic equilibrium and ratcheted by the opposite directional rotation of the
485 molecular motors (for instance turning clockwise) and molecular releasers (enforced to
486 conversely turn anticlockwise) (Figure 5B) [88]. Therefore, the materials as a whole can
487 contract and expand as a function of the trajectories and the frequencies of its molecular
488 components and can be considered as intrinsically motorized. Using a different approach,
489 Katsonis and Brasselet exploited the change in helicity of the molecule during the rotation of
490 the motor, coupled to a diffusion-driven feedback mechanism, to create a continuously
491 rotating pattern inside a liquid crystal under light irradiation. The torque produced was used

492 to transport a cargo at microscale (Figure 5C) [89]. Irradiation of the motor leads to
493 concentration gradients of its different states inside the liquid crystalline medium. In return,
494 these concentrations gradients form different supramolecular structures between the motors
495 and the liquid crystal that create a diffusion gradient inside the material. The interplay
496 between concentration gradients and diffusion gradients leads to the formation of patterns
497 that break their axial symmetry above a critical power, which then lead to the rotation of the
498 pattern over time. While the unidirectional rotation of the motor is not directly responsible
499 for the rotation of the liquid crystalline medium, it still highlights the potential application of
500 the changes in helicity of the motor during its rotation cycle to design complex stimuli-
501 sensitive supramolecular systems. These two last examples pave the way to the integration of
502 molecular motors in globally dissipative systems in order to ratchet molecular materials at all
503 scale.

504 **Concluding remarks and future perspectives**

505 The recent advances in the design and synthesis of mechanically active molecular materials
506 are of both fundamental and practical interests. In particular, numerous progresses have been
507 made by incorporating stimuli-responsive molecular units into polymer matrices. The various
508 natures of these molecules permit to actuate materials using different sources of chemical or
509 physical energy. As detailed above, the generated actuation can take place by several
510 fundamentally distinct mechanisms leading to important thermodynamic consequences at all
511 scales. One of the challenges in this approach is now to generate materials that can produce
512 a continuous work on their environment, which requires the implementation of ratcheting
513 strategies. With the recent development of ratcheting mechanisms at the nanoscale and the
514 rise of molecular motors, new opportunities appear to exploit the work they can continuously
515 produce at nanoscale by its amplification in macroscopic materials. A few examples have
516 already shown that the ratcheted actuation of molecular motors can be preserved in properly
517 designed artificial materials, but basically everything remains to be explored in this new kind
518 of integrated motorized molecular systems. In particular, the rationalization of the ratcheting
519 amplification from nano- to macroscale should be understood and generalized. Their full
520 potential in terms of non-classical actuation and efficiency should also be clarified in
521 comparison with simpler switching systems. In this direction, a number of stimulating

522 challenges are certainly facing synthetic chemists and their colleagues at the interfaces with
523 physics and engineering for the years to come (see Outstanding Questions).

524

525 Glossary

526 **[2]catenane:** mechanically interlocked structure composed of two intertwined
527 macrocycles. The term is derived from the Latin for “chain” (catena).

528 **[2]rotaxane:** mechanically interlocked structure composed of dumbbell shaped molecule
529 threaded through a macrocycle. The term is derived from the Latin for “wheel” (rota) and
530 “axle” (axis).

531 **Active material:** material that can perform a task by energy dissipation from its
532 environment. In particular, when such materials can sense and adapt to what happens in their
533 environment, when they display motility, or if they reorganize themselves to perform multiple
534 tasks, they are sometimes named as “life-like” materials.

535 **BZ reaction:** Belousov-Zhabotinsky reaction; an oscillating redox reaction taking place in
536 acidic aqueous solution in the presence of bromine derivatives, transition metal catalysts and
537 reducing agents, and driven by non-linear thermodynamics.

538 **[c2]daisy chain:** mechanically interlocked rotaxane composed of two identical molecules
539 consisting of a ring (macrocycle) covalently linked to an axle. The axle of one molecule is
540 threaded through the macrocycle of the other one, thereby leading to a cyclic topology [c2].

541 **Detailed balance:** principle stating that, at equilibrium, every process occurs at the same
542 rate than its reverse process. This principle is therefore tightly related to microscopic
543 reversibility.

544 **LCN:** Liquid Crystalline Network; a polymer network composed of mesogenic units. The
545 phase transition from the ordered mesophase to the disordered isotropic phase leads to
546 volume expansion when the material is heated. Cooling the material back to its liquid
547 crystalline phase allows the recovery of its initial shape.

548 **LCST:** Lower Critical Solution Temperature; critical temperature under which a polymer is
549 fully miscible in a solvent, for any composition. Conversely, the UCST (Upper Critical Solution
550 Temperature) is the critical temperature above which a polymer is fully miscible in a solvent,
551 for any composition. Crossing these critical temperatures can lead to macroscopic
552 shrinkage/expansion of the polymer materials.

553 **Mechanical bond:** entanglement in space between two or several molecular components
554 and that cannot be undone without breaking a covalent bond. Among the possible
555 mechanically interlocked structures, there are catenanes and rotaxanes, for instance.

556 **Microscopic reversibility:** principle stating that, the probability of any trajectory of a
557 microscopic process through phase space equals that of the time reversed trajectory. It is
558 tightly related to detailed balance for chemical reactions at equilibrium.

559 **Molecular machine:** molecular assembly that can perform a task through the controlled
560 mechanical actuation of its elementary parts under an appropriate stimulus.

561 **Molecular motor:** molecule capable of repetitive directional motion when fueled with a
562 source of energy. There can be linear molecular motors, like molecular walkers, or rotary
563 molecular motors, like motors based on overcrowded alkenes. The unidirectionality is
564 provided by a 'ratcheting' mechanism contained within the molecular motor.

565 **Photothermal effect:** phenomenon where a material emits heat after being excited by light
566 irradiation.

567 **Ratchet:** macroscopically, a ratchet is a device with asymmetric teeth that bias its continuous
568 motion in one preferential direction (because preventing motion in the opposite direction).
569 By analogy, at the nanoscopic scale in Brownian environment, ratcheted energy profiles are
570 asymmetric and can therefore drive the net unidirectional motion of a system when pumping
571 energy from their environment. In particular, mechanically active molecular systems can make
572 use of such ratcheting strategies to continuously move a particle up to an energy gradient.

573

574 Highlights

575 A wide variety of stimuli-responsive materials has been recently developed. In particular,
576 the integration of thermodynamic or photodynamic molecular switches in appropriate
577 materials can trigger their macroscopic actuation, possibly in combination with oscillating
578 phenomena.

579

580 Most of these systems, however, cannot progressively perform work on their environment
581 because they lack spatial asymmetry in their actuation trajectory. Consequently, any work
582 done in one direction is cancelled once the systems return to their initial state. To create

583 actuators that can produce continuous work, ratcheting strategies must be implemented to
584 break the spatial symmetry during their operation.

585

586 Macroscopic ratchets can be designed by coupling the whole material with an engineered
587 asymmetric environment during its actuation. Moreover, ratcheting mechanisms can also be
588 implemented in dissipative systems at nanoscale by breaking the spatial symmetry of
589 molecular switches' energy profile, thereby accessing molecular motors.

590

591 Outstanding Questions

592 Will the integration of molecular motors in macroscopic materials be limited to a few and
593 very specific examples, or can it be implemented by the design of more general and
594 rationalized approaches? In particular, how to preserve – or even amplify –, up to the
595 macroscopic scale, the dissipative out-of-equilibrium ratcheting actuation of a molecular
596 motor when integrated in a material?

597 Which efficiency can be reached by these systems, in terms of energy conversion, motion's
598 trajectory, workload, speed of actuation, and power? Would these materials present clear
599 advantages compared to simpler switching materials in terms of functioning autonomy and
600 work production?

601 Are chemically fueled molecular motors capable of integration in actuators? Although
602 famous examples in biology teach us that this is physically possible, how can we simplify
603 enough artificial systems to make them accessible to synthetic chemists while keeping enough
604 functional efficiency?

605 How to couple such molecularly motorized materials with appropriate devices in order to
606 transduce their mechanical actuation in other types of energy? How to integrate them with
607 other molecular elements (or macroscopic segments) to access multitasking materials? How
608 to engineer them and to interface them with their environment in order to control them
609 and/or to generate autonomous feedback loops leading to adaptation? Can we push such
610 systems sufficiently far away from equilibrium to generate self-organizing emergent behaviors
611 (reaching for instance bifurcation points in their trajectories)?

612 Can we make such materials cheap and sustainable enough for useful applications, in
613 particular by simplifying their chemical structures and by improving their resistance to
614 fatigue?

615 What could be the potential applications of such materials going from energy storage and
616 catalysis, to soft robotics and medicine? Can they become essential part of more complex
617 intelligent materials?

618

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624

625 **Conflict of interests**

626 The authors declare no conflict of interests.

627

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