Making molecular machines work

In this review we chart recent advances in what is at once an old and very new field of endeavour — the achievement of control of motion at the molecular level including solid-state and surface-mounted rotors, and its natural progression to the development of synthetic molecular machines. Besides a discussion of design principles used to control linear and rotary motion in such molecular machines, this review will address the advances towards the construction of synthetic machines that can perform useful functions. Approaches taken by several research groups to construct wholly synthetic molecular machines and devices are compared. This will be illustrated with molecular rotors, elevators, valves, transporters, muscles and other motor functions used to develop smart materials. The demonstration of molecular machinery is highlighted through recent examples of systems capable of effecting macroscopic movement through concerted molecular motion. Several approaches to illustrate how molecular motor systems have been used to accomplish work are discussed. We will conclude with prospects for future developments in this exciting field of nanotechnology.

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Consider a world composed of nanometre-sized factories and self-repairing molecular machines where complex and responsive processes operate under exquisite control; where translational and rotational movement is directed with precision; a nano-world fuelled by chemical and light energy. What images come to mind? The fantastical universes described in the science fiction of Asimov and his contemporaries? To a scientist, perhaps the ‘simple’ cell springs more easily to mind with its intricate arrangement of organelles and enzymatic systems fuelled by solar energy (as in photosynthetic systems) or by the chemical energy stored in the molecular bonds of nucleotide triphosphates (for example, ATP). Understanding and harnessing such phenomenal biological systems provides a strong incentive to design active nanostructures that can operate as molecular machines, and although our current efforts to control motion at the molecular level may appear awkward compared with these natural systems, it should not be forgotten that nature has had a 4.5 billion year head start.

Biological motors convert chemical energy to effect stepwise linear or rotary motion, and are essential in controlling and performing a wide variety of biological functions. Linear motor proteins are central to many biological processes including muscle contraction, intracellular transport and signal transduction, and ATP synthase, a genuine molecular rotary motor, is involved in the synthesis and hydrolysis of ATP. Other fascinating examples include membrane translocation proteins, the flagella motor that enables bacterial movement and proteins that can entrap and release guests through chemomechanical motion. In recent years the development of biomolecular motors (and natural–synthetic hybrid systems) towards the construction of sensors, actuators and transporters has seen tremendous progress. Biological motors are important components in the fabrication of dynamic smart materials, and semi-synthetic DNA-based structures have been explored in building a variety of mechanical motor-like functions.

Although biological motors are capable of complex and intricate functions, a key disadvantage of their application in vivo arises in their inherent instability and restrictions in the environmental conditions they operate in. Whereas nature is capable of maintaining and repairing damaged molecular systems, such complex repair mechanisms are beyond the capabilities of current nanotechnology. By contrast, wholly synthetic systems, which can tolerate a more diverse range of conditions than biological machines, offer considerable advantages in the development of complex nanomachinery.

Furthermore the sheer excitement of being able to build completely artificial motors and machines of nanodimensions, in the bottom-up approach promulgated by Feynman several decades ago, has provided the drive to attempt the synthetic challenges that such molecular machines present. A synthetic approach to the construction of molecular devices not only serves to mimic and build on the elegant systems nature has to offer but also can be used to develop systems that are not restricted to nature’s small, albeit versatile, synthetic toolbox.

Central to any molecular machine is the motor component and hence it is conceivable that molecular motors and machines (Fig. 1) will play as prominent a role in the nanotechnological revolution of the twenty-first century as their macroscopic counterparts — the steam and internal combustion engines — played in catalysing the industrial revolution of the nineteenth century.

MOLECULAR MOTION

Before surveying various approaches taken towards developing artificial molecular machines, it may be pertinent to first address a
Figure 1 What makes a molecule a machine? In this example of a molecular machine we are able to switch between two molecular states (shapes) in a controlled manner as part of a repetitious mechanical cycle. An azobenzene molecule can exist in two forms (left: trans with the bulky groups on opposite sides of the double bond, and right: cis with the bulky groups on the same side). The bulky groups can be moved closer together or further apart by switching between the cis and trans forms (see also, Fig. 8b). This switching can be performed by using light of two different colours, one to go from cis to trans, the other to reverse the process.

Figure 2 Examples of non-directionally controlled molecular rotors. a, A molecular rotor (left) where hindrance to rotation of the central phenyl ring (the rotor) is removed by the upper and lower bulky molecular end units (the stators). Sufficient spacing for the phenyl rings is generated to allow fast rotation in the solid state as illustrated for two rotor units (right). Reproduced with permission from ref. 32. Copyright (2005) National Academy of Sciences, USA. b, An electrochemically driven rotor where the upper and lower carborane (polyhedral clusters comprising boron and carbon atoms) moieties are bound as ligands to a nickel ion functioning as a ‘ball-bearing’. Oxidation and reduction of the nickel centre (the Ni²⁺ / Ni⁴⁺ redox cycle) leads to rotation of the upper ligand relative to the lower ligand, changing the relative position of the alkyl groups (R¹ – R⁴) attached to the carborane ligands. Reprinted with permission from ref. 36. Copyright (2004) American Association of the Advancement of Science.
reversed but progresses in a linear or rotary fashion. The problems associated with random thermal motion of molecules have been emphasized in discussions of ratchet-type motors ("if you can’t beat the chaos why not exploit it?"?) and nanomachines ("navigators on the nanoscale have to accommodate to the brownian storms?"). It is in this direction that several groups have approached the challenge of controlling motion in molecular ratchets based on rotaxanes and catenanes.

Molecular rotor systems that embrace thermal brownian motion are ubiquitous. Numerous groups have focused on designing systems to understand molecular motion at the molecular and submolecular level in so-called technomimetic rotors (Fig. 2)\(^1\)\(^\text{-}\)\(^3\)\(^7\). It is important to note, however, that these systems do not allow for directional control of movement. The dynamic processes observed for molecular rotor systems in solution, on surfaces and in the solid state are the subject of a recent comprehensive review and will not be discussed in depth here.\(^9\)\(^\text{-}\)\(^10\)

Although the majority of studies described have focused on molecular systems in solution, recent reports on crystalline molecular rotors\(^12\)\(^\text{-}\)\(^23\) (Fig. 2a) have addressed pertinent questions with regard to speed, friction and potential wear in a non-fluidic environment. Not only is fast free rotation in the solid state observed, but it was shown that, by careful consideration of the nature of the stator units and the molecular packing in the crystal lattice, the barrier to rotation can be reduced to near negligible levels. For instance, rotary motion around a carbon–carbon single bond can be extremely fast (up to 100 MHz), albeit with no control over the directionality of the rotation.\(^13\) It is worth remembering that molecular machines and molecules in general are not rigid, but undergo changes in their shape incessantly. From these studies it is clear that the dynamics within molecules and molecular flexibility are crucial factors to take into account in the design of artificial systems.\(^5\)\(^\text{-}\)\(^6\)

Although the direction of the motion in these systems is random, important design features demonstrate how control over rotary motion might be realized. For example, in the carbazole rotors\(^5\)\(^\text{-}\)\(^6\) shown in Fig. 2b, it has been suggested that unidirectionality of rotation might be achieved by the introduction of additional asymmetry using bulky groups. Despite these advances, brownian motion presents a tremendous challenge to the construction of molecular machines. Approaches can be taken to overcome the brownian turbulence, such as immobilization of molecular machines in membranes and on surfaces (see below) and construction of machines large enough to overcome brownian motion.

**BETWEEN BROWNIAN AND NEWTONIAN MOTION**

With the latter approach, to be able to build larger synthetic machines, the question arises as to how large the machines need to be. Where does the boundary between the domination of macroscopic ‘controllable’ newtonian motion and random brownian motion lie? The recent work of Whitesides\(^40\), Sen\(^1\)\(^\text{-}\)\(^4\), Ozin, Manners\(^4\), and co-workers, although based on non-molecular systems, provides some insight. In their multimetallic systems, a combination of a metal capable of catalysing the decomposition of hydrogen peroxide (the chemical fuel) and a relatively inert metal allow for the generation of a local oxygen gradient and/or (difference in) surface tension, which provides the stimulus to move the metallic object with limited directional control (Fig. 3).

It is clear that the size of the object is critical to both the mechanism by which movement is induced and the extent of non-brownian motion involved.\(^4\)\(^\text{-}\)\(^6\) For objects > 50 µm in size, the movement induced by oxygen evolution is related to the physical effect of bubble formation, whereas for particles < 1 µm in size, the motion of the particles is indistinguishable from the inherent brownian motion of the system. Between 1 and 20 µm, however, movement is driven neither by brownian motion nor bubble formation but rather by oxygen concentration gradients\(^4\)\(^\text{-}\)\(^5\) in a manner proposed to be similar to that used by some bacteria.\(^4\) Achieving directional control in these systems is difficult but not impossible. It was demonstrated that the directionality can be controlled magnetically by using platinum–nickel–gold rods, in which platinum acts to create the oxygen gradient (that is, uses the fuel to generate propulsion, Fig. 3a) whereas the anisotropy of a magnetic nickel layer allows for control of the direction of the movement.\(^4\)

Extension of this approach to molecular systems capable of chemically fuelled autonomous movement has been demonstrated recently, in our group, through the use of a synthetic catalyst that can effect efficient hydrogen peroxide decomposition (Fig. 3b).\(^4\)\(^5\) Despite the fact that control over directionality of the translational movement is limited thus far, this latter molecular system demonstrates that the conversion of chemical to kinetic energy, and thereby movement of a micro-object, with the concerted action of molecular-scale motors is feasible.

Although in the previous example hydrogen peroxide was used as the chemical fuel to effect motion, in molecular systems, powering motion can be achieved by other chemical fuels, pH and redox changes and of course by light.\(^4\) Ideally the fuel used should not involve the generation of waste products, damage to the molecular machine and should allow for reversible external control, hence although chemically fuelled systems have been
In the following sections we will describe several recent examples of molecular machines that can achieve controlled use of fuel to effect motion, and highlight key examples of how some of these systems demonstrate that molecular (nanoscopic) motion can realize effective macroscopic work.

**UNIDIRECTIONAL ROTARY MOLECULAR MOTORS**

Biosystems frequently rely on ATP as their energy source, however very few examples of artificial motors that use exothermic chemical reactions to power unidirectional rotary motion have been reported to date. To build synthetic molecular rotary motors, it is apparent that three criteria must be satisfied: (i) repetitive 360° rotation, (ii) consumption of energy and, of course, (iii) control over directionality.

Kelly and co-workers have achieved limited (120°) unidirectional rotation around a single carbon–carbon bond in a modified molecular ratchet using phosgene as the chemical fuel. Recently, our own group reported the unidirectional 360° rotation of a synthetic molecular motor fuelled entirely by a sequence of chemical conversions (Fig. 4a). Importantly, the sense of rotary motion is governed by the choice of chemical reagents that control the rotor movement through four distinct stations. Within each station the rotor’s brownian motion relative to the stator is restricted by structural features. Although the principle of a unidirectional rotary motor driven by a chemical fuel has been demonstrated, the requirement of a sequence of non-compatible chemical steps precludes continuous rotary motion with these systems thus far.

In a multicomponent approach to a combined chemically and photochemically driven unidirectional rotary motor, Leigh and co-workers have designed a complex [3]catenane-based molecular system comprising a large ring bearing four different stations and two smaller rings (Fig. 4b). Sequential changes in position of the small rings along the four stations is achieved by applying light, chemical stimuli or heat, resulting in a unidirectional movement of the small rings along the larger one. In this process the backward brownian movement of one ring is prevented by the presence of the second ring. This system has also been engineered to make backward rotation possible by judicious choice of the components used.

By using light as fuel, however, continuous unidirectional rotary motion can be achieved. The photochemical step in these systems is the cis to trans isomerization of a carbon–carbon double bond (an alkene), which allows for a 180° rotation of one part of the molecule relative to another (Fig. 5a). This isomerization results in the movement of bulky groups into unstable positions, which relax thermally. The first generation of a light-driven unidirectional rotary motor comprises a central alkene unit that functions as the axis of rotation, and a chiral helical structure (Fig. 5b). The orientation of the methyl (Me) group determines the most stable shape that the molecule prefers to adopt and hence dictates if clockwise or anticlockwise rotary motion of one half of the molecule (the propeller) with respect to the other (the stator) occurs. By applying light and heat, unidirectional rotation proceeds as a sequential four-step process. The first generation of this approach to a molecular motor was extended in the second-generation motors, where the stator and rotor parts are quite different in molecular structure, enabling additional components to be attached to either the top or the bottom half and surface attachment of the stator (Fig. 5c).

In order to apply these molecular motors, however, rotation at an appreciable speed — that is, 360° rotations per second — is desirable, if not essential. The structure of the second-generation motor is perfectly amenable to a whole range of structural modifications, which allow for fine tuning of the motor’s properties, both photochemical and thermal. The speed of the photochemical step (cis–trans isomerization, Fig. 5) is of the
order of 1 or 2 ps (ref. 55). Hence the rate of rotation is controlled by the thermally induced relaxation of the unstable to the stable state, which requires bulky groups (for example, the methyl and phenyl rings) to pass each other. Structural modification of the bridging atoms and substituents allows for reduction of the energy barrier of the thermal steps, which has led to a 1.2-million-fold increase in the rotation speeds achievable with the second-generation motors$^{66}$. These improved motors allow the propeller to rotate unidirectionally on irradiation at up to 80 revolutions per second at 20 °C.

LINEAR MOLECULAR Motors

Rotaxane-based systems have dominated the field of artificial molecular machines designed to achieve translational motion$^{30,37,38}$. Typically, such systems contain a ring component that shuttles reversibly between stations on the shaft (Fig. 6) with the movement controlled by redox chemistry$^{39-45}$, pH changes$^{46}$ or light$^{42}$.

The development of increasingly sophisticated photochemically active rotaxanes has culminated recently in linear motors powered by light$^{43}$, which allow for movement of a shuttle up to 1.5 nm with a frequency of 10 kHz. These systems operate with a quantum efficiency of up to 20%. Translating the light-driven motion in these molecules into useful work remains a challenge$^{41}$, however, the recent development by Balzani, Stoddart and co-workers$^{45}$ of an autonomous photo-driven rotaxane is a significant step forward in achieving this goal.

A design for an artificial molecular muscle based on the sliding motions of the ring along the shaft of rotaxanes was also reported$^{42}$. Two interlocked rotaxanes allow for elongation and contraction...
by binding different metal ions, a system reminiscent of the Ca\(^{2+}\)-
driven processes that occur during muscle contraction. An example
of a chemically driven system designed to mimic processive
enzymes has been reported recently and is a significant step in
the development of synthetic processive molecular machines akin
to those found in nature.

**MULTICOMPONENT MECHANICAL MACHINES**

The construction of molecular machines, in which mechanical
motion of different units operate in concert, for example when
rotation motion of one part is coupled to linear motion of another
part, requires the design of integrated multicomponent systems.
A system denoted as a 'molecular elevator' composed of three rotaxane
units interlocked mechanically to a platform was reported recently
(Fig. 7a)\(^{30,39}\). The charge of one of the two stations is sensitive to
pH changes and as a result the platform can move between two
levels by adding acid or base.

Although large changes in physical properties can be brought
about using cis–trans isomerization, the direct conversion of light
energy into 'mechanical work', that is, significant motion, is a
more challenging goal. Following an earlier design of molecular
scissors\(^{8}\), the coupling of several molecular motions was achieved in
a light-powered 'molecular pedal'\(^{8}\). A change in molecular
shape on cis–trans photoisomerization of an azobenzene unit is
transmitted via a pivot point (a ferrocene unit) and a pedal-like
motion of large flat zinc porphyrin units to induce a clockwise or
anticlockwise rotary motion in a bound rotor guest. This system
demonstrates that small changes in molecular structure can be
used to drive much larger mechanical changes, remote from the
point of initial mechanical motion.

Recently, the light-driven molecular motors, shown in Fig. 5,
were used by Tour and co-workers to construct a prototype
light-powered "nanocar"\(^{77}\). In this approach carborane 'wheels'
were attached covalently to a molecular rotor 'engine' (Fig. 7b).
Although this multicomponent system did not compromise the
functionality of the motor unit itself, light-driven movement
across a surface awaits demonstration.

**MOTORS ON SURFACES**

The molecular motors discussed above that convert chemical or
light energy into directional rotary or linear motion all operate
in solution, and although brownian motion can be overcome
by building micrometre-dimension devices, another approach
to overcoming brownian motion and bringing about order is to
immobilize machines on a surface. However for nanomachines
to be able to operate in devices or to perform useful work it
will be essential that the motors do not lose functionality when
immobilized. Anchoring and subsequently addressing molecular
machines on surfaces is critical to the successful interfacing of
nanomechanical systems with the macroscopic world.

Altitudinal molecular rotors (the rotor axe is parallel to the
surface), which exhibit a strong dipole moment, have been
immobilized on Au(111) surfaces\(^{14}\). Barrier-height imaging using
scanning tunnelling microscopy measurements revealed that the
direction of the dipole of the rotor unit turns in response to a static
electric field imposed by the tip of the microscope. On the basis
of molecular dynamics calculations, it was suggested that limited
directionality in their motion should be possible using oscillating
electrical fields normal to the surface\(^{25}\). A similar approach has
been reported very recently by Miyake and co-workers using
lanthanide complexes, in which the large metal ion is sandwiched
between two flat porphyrins, the speed of rotation of which can
be modified by varying the lanthanide metal used\(^{77}\).

The second-generation light-driven unidirectional molecular
rotors discussed above (Fig. 5c) have been immobilized
successfully on nanoparticle gold surfaces to yield an azimuthal
(rotor axe normal to the surface) motor. In these systems
the stator component carries two thiol-functionalized 'legs'
that connect the entire motor to the surface\(^{86}\). Repetitive and
unidirectional 360° rotary motion with respect to a surface was
observed to occur on irradiation. The use of two attachment
points per molecule prevents uncontrolled thermal rotation of
the entire motor system with respect to the surface. However,
this study also demonstrates the difficulties that may be
encountered in such immobilization\(^{44}\). The length and nature of
the connecting units (legs) is frequently a critical issue in the
attachment of photoactive compounds to metal surfaces as it can
affect excited-state processes dramatically\(^{26}\).

The tetrathiafulvene unit has proven to be a mainstay in the
design of electrochemically driven rotaxane-based molecular
machines, as it can be converted between two stable states
(bistable), that is, the neutral and oxidized forms, which show
markedly different behaviour when interacting with other
molecular components\(^{87}\). Analogous to cis–trans isomerization,
facile reversible oxidation to the mono- or dicaticionic states of
the tetrathiafulvene unit can be used to effect large changes in the
position of rings along the shaft unit of rotaxanes\(^{86}\). These redox-
switchable 'bistable' rotaxanes have been applied as monolayers
in molecular switch tunnel junction devices\(^{81,82}\). Importantly,
the position of the shuttle can be controlled by either reduction or
oxidation but the conductance of the system is measured only as a
function of the position of the shuttle on the rotaxane. In contrast
to more conventional approaches to redox-switchable systems
where a change in redox state is used to control conductivity, in
this example the redox changes are used to move a molecular
component only.

Whereas demonstration of linear and rotary motion on the
nanometre scale is apparent in the synthetic molecular machines
described above, realizing the summation of motion at the
molecular level to achieve macroscopic motion, for instance
mimicking the operation of myosin/actin-driven movement of
muscles, is more challenging\(^{46}\). Nevertheless, it has been
demonstrated that such translation of work can be achieved\(^{84,85}\).
The approaches taken include: (i) changes in molecular properties
such as surface tension, (ii) indirect macroscopic movement through
amplification of molecular motion and (iii) direct translation of
molecular to macroscopic motion.

**MOLECULAR MOTORS AT WORK**

In the individual steps of the artificial molecular motors
constructed so far, the system acts as a mechanical switch.
Molecular switches have found widespread application in the
dynamic control of bulk materials and single-molecule properties,
as well as molecular devices that take advantage of the ability to
trigger functions through external signals\(^{21}\). Molecular switches
can be used to modulate properties such as surface wettability\(^{46}\),
polymer elasticity\(^{47}\), lateral pressure profile of bilayers\(^{48}\), host–
guest recognition\(^{49}\), supramolecular organization\(^{50}\), catalysis\(^{51}\),
colour\(^{52}\), fluorescence\(^{53}\), conductance\(^{54}\) and enzyme activity\(^{55–57}\).
The use of photochemical molecular switches has the advantage
of short response times, clean and tuneable energy input, and
the ability to convert an optical input into a variety of useful
output signals.

It is therefore unsurprising that indirect translation of changes
in molecular properties to achieve macroscopic movement has
used the reversible photochemical switching of bistable molecules,
such as azobenzenes, mounted on surfaces\(^{98,99}\). Photochemical
isomerization of azobenzenes attached to surfaces was used to induce wetting/dewetting by changing the surface energy of the monolayers and allowing for the transport of liquid droplets across surfaces. Similar millimetre-scale directional transport of droplets on a surface with light was achieved with a photoactive rotaxane operating as a linear nanomechanical switch (Fig. 6a). The system comprises a shuttle (the ring that moves along the shaft) on a thread with a fluoralkane station and a photo-responsive fumaromide station, which has a high binding affinity for the shuttle. The entire system was anchored through physisorption on a modified gold surface.

Photochemical trans–cis isomerization of a fumaromide unit in the thread reduces the binding affinity to the shuttle drastically and, as a consequence, the equilibrium position of the shuttle changes in favour of the fluoralkane station. The shuttle movement is therefore used to expose or conceal the fluoralkane part, which results in a change in surface energy and, as a consequence, the movement of liquid. The collective action of a monolayer of these molecular shuttles makes them operate as a motor and has sufficient power to move a microlitre droplet of diiodomethane on a millimetre scale up a 12° incline (Fig. 6a).

**Figure 6** Synthetic molecular systems designed to achieve translational motion. These linear molecular motors are so-called rotaxanes in which one (or more) rings can move from one binding site to another along a shaft. The change in equilibrium position is triggered by an external signal. a, Macroscopic transport of liquids by surface-bound rotaxanes as a synthetic molecular machine. The position of the ring exposes or conceals a fluoralkane component and concomitantly changes the surface energy. The ring is moved by shining light on the surface coated with motor molecules. When the area above the droplet of liquid is ‘switched’, the liquid is attracted to the irradiated zone, and in this way is transported across the surface and, in this case, up a slope (with 12° incline). Scale bars = 100 mm. Reproduced with permission from ref. 101. b, Design of a molecular muscle and the bending of cantilever beams by the cooperative action of several linear rotaxane motors. The system is based on a bistable [3]rotaxane structure involving a rotaxane with two positively charged rings and four stations, two of which are redox active units and can be switched between a neutral and positively charged form. The rings are connected to the surface of the cantilever via disulphide containing tethers to form a self-assembled monolayer. The rings are initially sitting on the redox-active stations in their neutral state (structure on the left). Oxidation of the redox-active stations, forces the rings to move to the inner neutral stations and results in contraction of the rotaxane, bending the beam. Adapted with permission from ref. 85. Copyright (2005) American Chemical Society.
Although changes in molecular structure can be used to effect large changes in macroscopic properties, indirect macroscopic movement induced by changes in molecular chirality was demonstrated only recently. The reversible rotation of surface textures and microscale objects can be achieved using specially designed second-generation light-driven rotary molecular motors embedded in a liquid-crystal film (Fig. 5d). This motor has a right-handed helical structure and is very effective at inducing dynamic helical organization when applied as a chiral dopant in a liquid-crystalline film. The energy provided by light (the fuel for the motor) does not effect movement of a macroscopic object by itself. However, change in chirality of the motor is amplified through the liquid-crystalline host matrix. The result is a reorganization of the polygonal texture of the film in a clockwise or anticlockwise rotational fashion following the photochemical or thermal isomerization steps of the motor molecule. The rotation of the motor used as a dopant is ‘transmitted’ to the surface through the reorganization of the liquid crystal. A surface relief of 20 nm was observed by non-contact atomic force microscopy. The orientation of the surface relief alters in response to the topology change in the embedded molecular motor. This reorganization generates a torque sufficient to achieve unidirectional rotation of microscopic objects placed on top of the film. These experiments show that a molecular motor can actually perform work. By harvesting light-energy and the collective action of molecular motors, microscopic objects that exceed the nanomotor in size by a factor of 10,000 can be rotated, with directional control.

The application of synthetic molecular motors in liquid-crystalline systems is not limited to the movement of objects. The change in handedness of the motor molecule during the rotary steps induces a reorganization of the liquid-crystalline film and induces a reversible and, importantly, tuneable change in the colour of the film (Fig. 5e). Therefore the macroscopic properties of a material can also be changed using a molecular rotary motor, and in this specific case, pixel generation with colours covering the entire visible spectrum is achieved readily.

Concerted macroscopic motion induced by changes in molecular structure is the fundamental basis of muscular movement. Hence, the possibility of a direct translation of molecular motion to macroscopic levels is, of course, an important goal. The molecular muscle developed by Stoddart and co-workers is based on linear molecular motors and uses a bistable [3]rotaxane structure with two rings and four stations (Fig. 6b). Tethers attached to each ring anchor the whole rotaxane system as a self-assembled monolayer to the gold surface of microcantilever beams. The array of cantilever beams, decorated with these rotaxane molecules, shows reversible bending through sequential addition of chemical oxidants or reductants. The redox chemistry that drives the process is possible because of the presence of the redox-active units at two of the four stations. Redox-switching of the redox-active units initiates a change in the equilibrium position of the positively charged rings on the rod of the rotaxane, driven by a change in electrostatic repulsion. This change in inter-ring distance induces a change in mechanical stress on one side of the microcantilever. The combined effect of a monolayer of these bistable units operating collectively on a surface is to induce a bending of the cantilever. This demonstrates that controlled molecular motion in a wholly synthetic system can effect macroscopic movement.

In the systems developed by Gaub and co-workers, photochromic azobenzenes have been used as tools to generate large reversible anisotropic changes in linear and stiff crosslinked polymer networks, respectively. The simplicity of these systems and the reversibility of the changes on irradiation with different wavelengths of light holds considerable potential for the future development of molecular-based polymer actuator materials.

**MOLECULAR VALVES**

That biological motors perform work and are engaged in well-defined mechanical tasks such as muscle contraction or the transport of objects is apparent in all living systems. Controlling motion using molecular switches is particularly attractive for the construction of nanomechanical valves. For instance, the affinity of crown-ether type receptors to bind cations can be modulated reversibly by light when azobenzene photo-switches are incorporated in these receptors.

A light-actuated nanovalve derived from a channel protein was constructed in our group to control photochemical transport of solutes across a lipid bilayer. The valve consists of a channel protein modified with a photochemical active spiropyran switch. The reversible molecular photochemical switch acts as a valve control.
for the 3 nm channel (Fig. 8a). The valve can be opened and closed with ultraviolet and visible light, respectively. This is possible because the neutral switch molecule converts to its highly polar zwitterionic form on irradiation with ultraviolet light. The hybrid protein valve is compatible with a liposome encapsulation system and allows for external photo-control of transport through the channel, demonstrated in the controlled release of an encapsulated fluorescent compound.

A different approach to photochemical valve control involves a bio-hybrid system in which movement through a channel is controlled allosterically[10]. A semisynthetic ligand-gated ion channel that can be turned on and off by ultraviolet and visible light irradiation, has been developed using an azobenzene (Fig. 1) optical switch (Fig. 8b). The azobenzene switch is attached both to the protein and the glutamate residue, which is specific for the allosteric site (a signal binding site on the protein, which regulates the operation of a separate remote functional component) responsible for closing the protein channel. The point of attachment is naturally critical to its operation, and in contrast to the previous example, the switching unit is attached to the outside of the channel rather than the inside. Trans-to-cis photoisomerization of the azobenzene unit results in a large geometric change in the molecule and, as a consequence, glutamate binds to the receptor and the channel opens. In this nanomechanical valve, several structural units and functions operate in concert to allow reversible channel gating controlled by light.

Redox processes offer an attractive alternative to light-controlled nanomechanical valves because of the possibility of integration into nano-electronic devices. A quite simple yet elegant example of such a molecular valve is based on cyclophanes (large molecular rings), where oxidation can be used to open and reduction to re-close a cavity[11]. Although the channel itself is very small when compared with the protein-based systems described above, this system does hold potential for the development of fully synthetic molecular valves.

An alternative approach to redox-controllable reversible nanovalves is found in a rotaxane-based valve system[11]. The principle involves reversible blocking of solid pores, which allows controlled release of fluorescent dyes from mesoporous (pore size 1.5–2.0 nm) silica particles.

The construction of functioning nanovalves, with movable molecular control units to regulate flow of substances, is a significant step towards the development of real nanomachines. Such nanovalves are, however, attractive components in themselves, for use in drug delivery systems with controlled release, signal transduction, sensors and nanofluidic systems, for example.

CONCLUSIONS AND OUTLOOK

The exquisite solutions nature has found to control molecular motion, evident in the fascinating biological linear and rotary motors, has served as a major source of inspiration for scientists to conceptualize, design and build — using a bottom-up approach — entirely synthetic molecular machines. The desire, ultimately, to construct and control molecular machines, fuels one of the great endeavours of contemporary science. The first primitive artificial molecular motors have been constructed and it has been demonstrated that energy consumption can be used to induce controlled and unidirectional motion. Linear and rotary molecular motors have been anchored to surfaces without loss of function — a significant step towards future nanomachines and devices. Furthermore, it has been demonstrated unequivocally that both linear and rotary motors can perform work and can move objects. However, although the first applications of molecular motors to the control of other functions have been realized, the whole field is still very much in its infancy and offers ample opportunity in the design of nanomechanical devices.

Major challenges in the development of useful nanomachines remain, such as the development of fast and repetitive movement over longer time frames, directional movement along specified trajectories, integration of fully functional molecular motors in nanomachines and devices, catalytic molecular motors, systems that can transport cargo and so on. As complexity increases in these dynamic nanosystems, mastery of structure, function and communication across the traditional scientific boundaries will prove essential and indeed will serve to stimulate many areas of...
the synthetic, analytical and physical sciences. In view of the wide range of functions that biological motors play in nature and the role that macroscopic motors and machines play in daily life, the current limitation to the development and application of synthetic molecular machines and motors is probably the only imagination of the nanomotorists themselves.

doi:10.1038/nnano.2006.45

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Acknowledgements
The Authors thank M. M. Pollard for many suggestions and reading of the manuscript.