Welcome to the machine

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Hardly an issue of any major chemistry journal passes today without reporting some new molecular 'machine' or 'device'. They are often staggering in their ingenuity and capabilities: they can crawl over surfaces, flex like muscles, open and shut like sluice gates, mesh like gears, even perform arithmetic and computation. Some, like the molecular box with lockable lid reported by Jørgen Kjems of Aarhus University in Denmark and colleagues last May,[1] are delightfully playful, while at the same time promising genuine technological value (in this case, perhaps for controlled delivery of drugs). They seem to tell us that chemistry has become a kind of scaled-down mechanical engineering.

But how far does that analogy really apply? And are these molecular machines anything more than just whimsical demonstrations of technical prowess, the equivalent of eighteenth-century automata? Indeed, are they truly machines at all? In a field that is arguably now at least two decades old, it may be time to take stock of what has been achieved, what the limitations are, and where the work is all headed.

Moving parts

In his *Principles of Philosophy* (1644), René Descartes wrote that

> the only distinction I recognise between artefacts and natural bodies is that, for the most part, the functions of artefacts are carried out by mechanisms big enough to be easily perceived by sensations. This is necessary, otherwise human beings would not be able to construct them. By contrast, natural effects nearly always depend on mechanisms too small to be sensed.

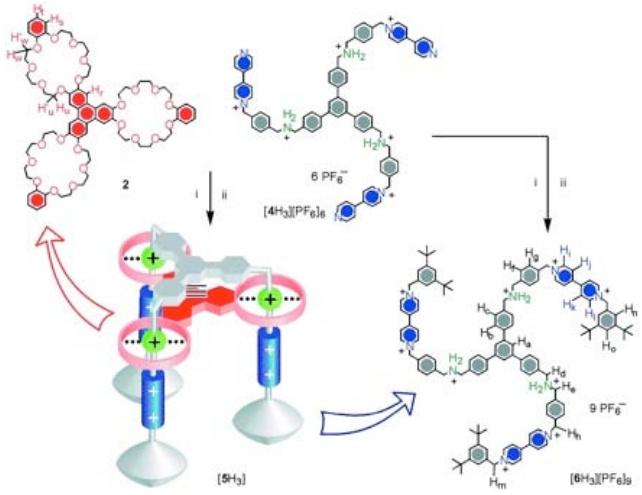
Thus – and somewhat notoriously – Descartes turned the human body into a collection of microscopic machines.

Whether or not this materialistic vision is accepted today, it certainly supplies the metaphor for how we think about the chemistry of life. Cells are 'molecular factories', packed with 'molecular machines' such as the ribosome on which proteins are 'manufactured'. Motor proteins bear molecular cargo along the traffic networks of the cytoskeleton, while membranes are peppered with valves and pumps for regulating biochemical flows. Despite its long pedigree, however, the vision of a machine-like molecular biology is relatively recent – not so long ago, molecular biologists themselves would have deemed it a little fanciful, and for the best part of the twentieth century biochemists tended to describe life's molecular processes in the terms of traditional physical chemistry: referring to energetics and kinetics, with little thought about the shapes and mechanical operation of biomolecules. When Richard Feynman applied machine terminology to the biological microworld in his famous 1959 talk 'There's plenty of room at the bottom', this was as much the result of a naïve physicist's mechanical conception of chemistry as it was a truly prescient vision of nanotechnology.

It's worth remembering this when surveying modern research on so-called molecular machines, not least because it's a reminder that the machine metaphor is precisely that, and not to be confused with what really goes on at the molecular scale. When chemists talk of making molecular cars, elevators, windmills, trains and abacuses, they are using language that provides a convenient and intuitive picture of what they have devised; it doesn't mean that they have exact, miniature analogues of these familiar macroscale devices.

The reason Descartes' imagery has come back into vogue at all is probably mostly that we can now see into the molecular world. Before the emergence of protein crystallography in the 1940s and 50s, it was common to regard proteins as components of a vaguely 'colloidal' life-substance, not as entities in which shape determined function. Electron microscopy, and then scanning probe microscopes, helped to bring the cell's molecular machinery literally into focus, and the geometric, robot-like forms of some viruses particularly encouraged a view of life as driven by ingenious devices. When Erwin Schrödinger wrote *What Is Life?* in 1944, chemistry was about the average behaviour of statistical ensembles of molecules, and it would have seemed absurd to speak in terms of what any individual molecule was up to, let alone imagine we might see it.

But now we need to remind ourselves that Schrödinger had a point. Take the molecular elevator devised by Fraser Stoddart, now at Northwestern University in Evanston, Illinois, in collaboration with Vincenzo Balzani, Alberto Credi and colleagues at the University of Bologna in Italy.[2] In this device, three hoops on the elevator stage are threaded by the tripod legs of the frame. Each hoop may be switched between two docking stages by protonation: by adding acid. It's tempting to think that this means the elevator can be sent from one 'floor' to another on command. That's kind of true, but only in the same sense as any molecular shape change: it is statistical, an equilibrium ruffled by thermal fluctuations. At any moment, most of the elevators are at the bottom floor in acid and the top in basic conditions. But any specific elevator is liable to switch at any moment. Imagine that on the 33rd floor of the Hilton.



The molecular elevator: a triple rotaxane switched by acid.

This points to the key distinction between molecular and macroscopic machines. Without fuel or power, the latter lie inert. But molecules are never inert: under the influence of thermal noise and molecular collisions, they are constantly in motion, always changing shape. They are, in effect, striving to work in a maelstrom. Even proteins, the canonical molecular machines, are constantly and spontaneously unravelling and then refolding. Again: who'd want a car which does that?

Clearly, this needn't prevent things from getting done: in the cell, motor-borne cargo reaches its destination, valves and gates succeed in regulating transmembrane traffic, life goes on. But it does so in a rather noisy fashion: there are typically significant differences in performance and behaviour among 'identical' cells. So what, then, can we expect of molecular machines, and what can we realistically do with them? And how can we design them to be reliable in the buzzing world of the molecule?

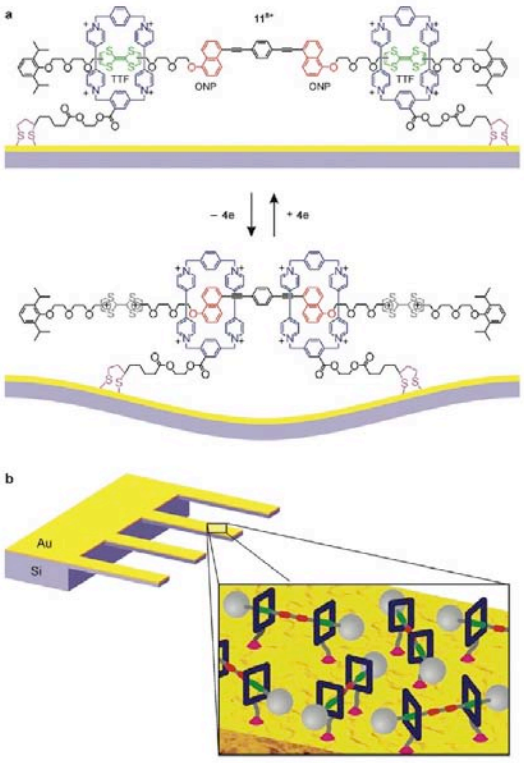
Shuttle service

The molecular elevator stems from one of the first molecular constructions to be presented as a mechanical device: the molecular shuttle, which Stoddart and his coworkers made in 1991 while he was at the University of Sheffield.[3] Having pioneered the synthesis of rotaxanes – hoop-and-axle molecules kept threaded by bulky end caps on the axle – Stoddart figured that a hoop that was offered two potential docking points on the axle might jump between them. These 'stations' provided stable resting places by engaging in 'pi-stacking' interactions with benzene rings on the hoop. With two equivalent stations, the hoop merely flipped between them at random, so that the shuttle couldn't be used to extract useful work: it wasn't really a machine at all. But if the stations were chemically different, and if the propensity of the shuttle to stop there were modulated by, say, changing the charge state using electrochemistry or acid-base reactions, then the motion could be controlled. Stoddart and his collaborators demonstrated such things in the early 1990s.[4]

If a molecular machine of this sort is going to be of practical value, the controllable motion has somehow to be coupled to the rest of the world. That needn't be for strictly mechanical purposes: the very act of switching, for example, suggests applications for binary data storage, and indeed Stoddart has teamed up with nanotech expert Jim Heath at UCLA and collaborators at the California Institute of Technology to make molecular memories based on switchable rotaxanes, in which electric fields applied to electrodes induce switching in a monolayer of the molecules and the readout comes from a consequent change in conductivity across the molecular film.[5] But machines are typically defined as 'things that impart motion'. And to turn molecular into large-scale motion, Stoddart and colleagues have coupled bistable rotaxanes to microscopic cantilevers so that the switching makes the levers bend: a sort of molecular muscle.[6,7]

The researchers strung two hoops on an axle with four stations, and chemical oxidation promoted movement of the hoops from the two end stations to the two in the middle. Because the hoops were themselves covalently tethered to the cantilever surfaces,

bringing the hoops closer together in this way tugged on the cantilevers and made them bend upwards by about 35 nm at the end – a much larger displacement than that of the hoops themselves.



Bending a cantilever with rotaxane ‘molecular muscles’.

Jean-Pierre Sauvage, another expert on rotaxanes at the University of Strasbourg in France, has explored a related ‘molecular muscle’ concept in which two hoops are mutually threaded onto shafts attached to the hoop of the other molecule. The two hoops are pulled towards one another when the device is supplied with metal ions which bind the hoops to the stations.[8] This metal-triggered sliding mimics the way muscles contract by interdigitation of protein strands in the presence of calcium ions. Robert Grubbs and coworkers at the California Institute of Technology has recently made ‘daisy-chain’ polymers in which a whole series of these units is linked together.[9] In theory, Grubbs and colleagues estimate that a perfectly linear polymer of this sort should be 58 percent longer in the extended state than when contracted by docking of the hoops to stations on the arms. Over many monomer units, that difference will add up to an appreciable absolute displacement of the ends. The polymers won’t in fact be fully extended in solution in practice, and the researchers haven’t in any case yet managed to induce reversible switching. But they found that an analogous polymer forced to adopt the extended state is, on average, 48 percent longer than the same polymer where the contracted form is stabilized – a length difference in this case of about 8 nm.

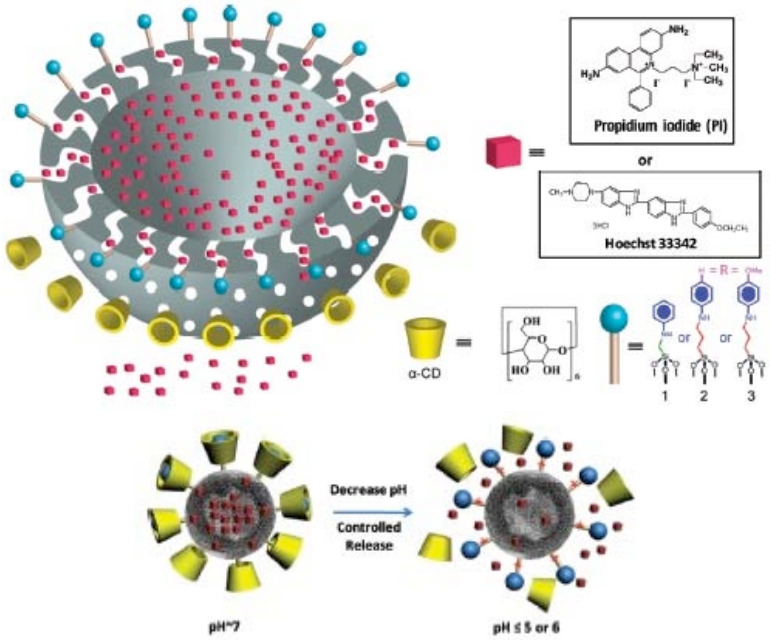
Open on command

It's sometimes hard to decide what warrants description as a molecular machine. Clearly, it's not enough to say that any molecule that moves is a machine, because molecules move thermally all the time: their component parts vibrate, spin and wave about. In general these movements are random: a methyl side-group is as likely to rotate one way as the other. To make a useful machine, this motion needs to go in a preferred direction, at least on average. And ideally, it will do so in a controlled way: the motion can be switched on or off to command.

That kind of control might sound challenging, but it's actually pretty old hat: transitions between isomeric forms of a molecule involve a change in shape that might be induced by heat or light. For example, chemists have known for many decades that a carbon-carbon or nitrogen-nitrogen double bond can be rotated by 180° by ultraviolet light or heat, such that chemical groups at each end of the bond can be switched between opposite sides (the *trans* isomer) and the same side (*cis* isomer). In this way, the two groups are brought closer together or further apart. Does that make *cis-trans* isomerism a kind of mechanical operation? Few researchers would once have thought this way. But the process can be used to bring about controllably mechanical motion. For example, Jeffrey Brinker and coworkers at Sandia National Laboratories in Albuquerque, New Mexico, made light-switchable valves for opening and closing the channels of a porous form of silica by coating the pore walls with azobenzene molecules, which have photoisomerizable N=N bonds. In the *cis* form, produced by UV irradiation, the pendant molecules are shorter and leave an open channel in the centre of the pores, whereas restoring the *trans* form using heat or green light switches the molecules back to a pore-blocking state.[10] It seems reasonable to call this a 'molecular valve', even though the basic chemistry is nothing new. But the same kind of channel-blocking can be induced, in pores and microfluidic channels, by polymers that swell or shrink reversibly in response to environmental stimuli such as pH or heat. Useful, yes; a kind of valve, yes; but still a 'molecular machine'? Hmm.

There are many ways to alter, reversibly, the size and shape of molecules, and many ways to put that change to good use. Whether we designate these things 'machines' or devices may be a matter of taste more than anything else. All the same, the principles of reversible mechanics in Brinker's valves are shared with rotaxane devices, and as though to emphasize that point, Stoddart teamed up several years ago with Jeffrey Zink at UCLA to devise molecular valves based on pseudorotaxanes, where the hoop is not sterically trapped on the thread. They found that nanoscale pores could be blocked by a pseudorotaxane at the pore mouth, and opened by triggering release of the hoop.[11] Stoddart and Zink have very recently made a more bio-friendly version: hollow nanocapsules with porous walls through which the release of encapsulated molecules can be triggered by pH-dependent formation of threaded molecular complexes in which the hoops are bucket-shaped sugar molecules called α-cyclodextrin (α-CD).[12] These will sit on short stalks topped with aniline groups at neutral pH. The stalks are attached at the mouth of pores in spherical shells of porous silica. With the α-CDs appended, the pores are blocked, preventing dye molecules inside from escaping. When the solution is made acid, the aniline groups are protonated, which kicks off the α-CD caps and opens the

pores, letting out the dye. This sort of controlled release might be used to deliver drugs to specific targets in the body, such as cancer cells.



Controlled release of drugs from hollow nanoparticles triggered by molecular valves could be the key to smart drug delivery.

Molecular ratchets

One thing that does seem to distinguish these simple gates and valves from our common conception of a machine is that they don't *get anywhere*. The moving parts simply flip back and forth. In everyday engineering, however, we can turn that sort of repetitive movement into unidirectional motion: it's what happens in a pendulum clock, for example, where the pendulum's oscillation drives one-way rotation of the hands. The key there is the rack-and-pinion mechanism, which is a kind of ratchet in which asymmetric, sawtooth-shaped teeth allow rotation only in one direction. In other words, symmetric motion is made directional by an *asymmetric* geometry. The same is true of a crankshaft driven by the in-out movement of a piston. In swimming, the stroke itself is asymmetric: if you just moved your arms symmetrically back and forward, you'd get nowhere.

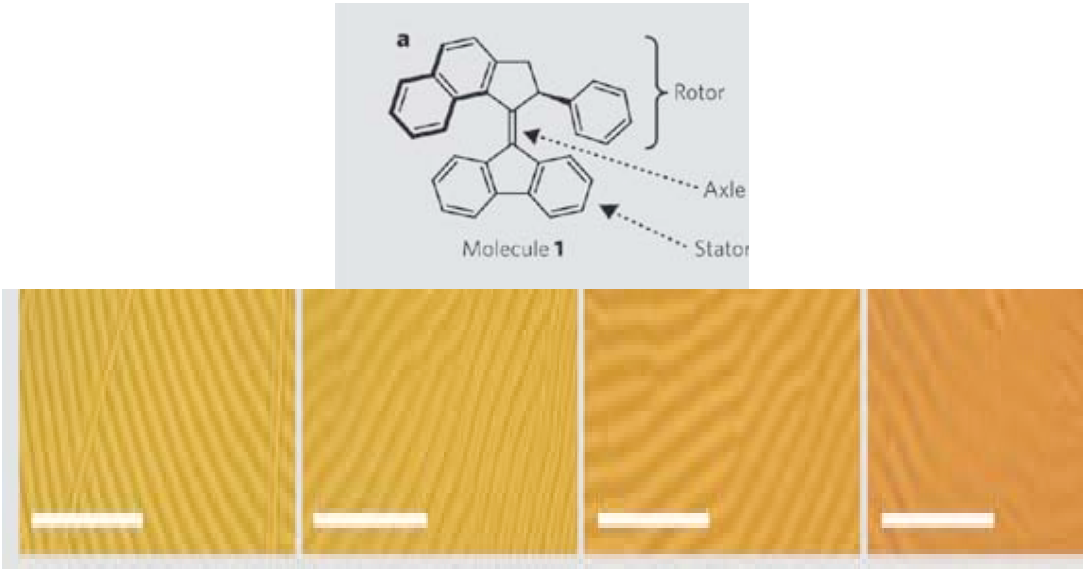
Ten years ago, Ben Feringa at Groningen University in the Netherlands realised that the rotation of molecular groups entailed by *cis-trans* isomerization could also be made directional by coupling it to an asymmetric structure. This enabled him to make the first unidirectional artificial molecular rotor.[13]

Negating the old adage that nature has no use for the wheel, molecular rotors play central roles in biology. One such – a large assembly of many protein parts – spins the whiplike appendages called flagella that enable bacteria to 'swim', while another is the enzyme called ATP synthase which revolves around a spindle embedded in cell membranes as it manufactures the energy-storage molecule ATP. This latter molecule has been

commandeered in artificial devices by Carlo Montemagno and his coworkers at Cornell University, who nine years ago attached tiny metal blades, about 150 by 1500 nm, to the spindle of purified ATP synthase and then fixed the rotary unit head-down onto nickel posts. Powered with ATP to drive the enzymatic reaction in reverse, the motors spun at five revolutions per second, stirring up little eddies in the surrounding fluid.[14]

Spinning molecules are easy to make – for example, the two carbon rings that sandwich an iron ion in ferrocene spin spontaneously as if the ion is a ball bearing. But making a directional molecular rotor from scratch has proved challenging. Feringa's first design was a molecule containing two identical propeller-like blades linked by a C=C bond. The key was that the blades had to twist slightly to avoid bumping into each other at their ends, and this gave the whole molecule a twist: it was chiral. This biased the isomerization process, so that continual irradiation with UV light could, if accompanied by enough heat to trigger conformational changes, allow the molecule to rotate continuously in one direction. Feringa and his colleagues subsequently made rotors like this in which the two blades had different structures, allowing them to be chemically targeted independently so that other components could be attached. In particular, they could fix one blade to a gold surface, making it a stator, while the other blade was left to freely rotate. Fine-tuning of this design has led to molecular rotors that will spin at nearly ten million revs a second at room temperature.[15]

Can this motor do anything useful? Already Feringa and colleagues have used it to rotate much larger objects. They found that the light-triggered rotation could influence the molecular organization of a liquid-crystal film when the motors were added as a dilute (1% concentration) dopant. This allowed them to rotate the fingerprint-like furrows that appear on the surface of the film. And a microscopic glass rod, 5 micrometres across and 28 micrometres long, floating on the top of the film, would 'surf' these undulations and thus be rotated with them.[16]



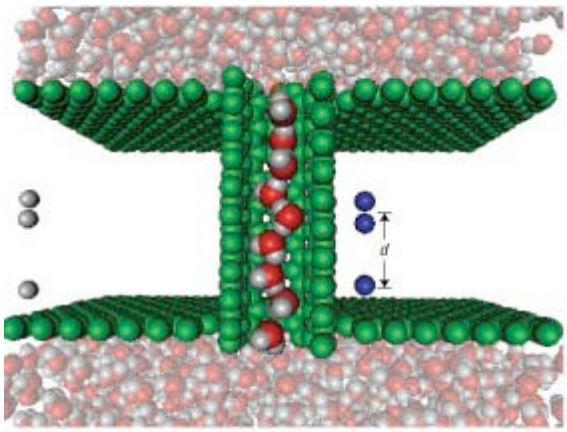
This light-driven molecular motor (top) will rotate the texture of a liquid-crystal film into which it is doped, causing a floating glass rod to rotate with it (bottom).

Feringa's motors exemplify the principles for achieving unidirectional behaviour at the molecular scale: some energy source, such as light or chemical fuel, provides the impetus, and geometric asymmetry defines the direction. The classic example of this kind of process invokes a particle diffusing by random, Brownian motion over a landscape of parallel ridges. If the ridge profiles have an asymmetric, sawtooth form, then it is easier for the particle to move down the shallower slope than to surmount the steep one, and so the random motions are 'rectified' into a net motion in one direction. This is called a Brownian ratchet.[17]

The directional motion can't be driven by thermal or Brownian fluctuations alone, however, since that would violate the second law of thermodynamics. Brownian ratchets need some external energy source to drive the system away from equilibrium. A thermal gradient will suffice, or a fluctuating fluid flow or electric field. At the molecular scale, chemical reactions can supply the necessary energy input, and this is how molecular motors and propulsion devices typically take advantage of the ratchet principle.

Brownian molecular ratchets are found in nature.[18] The movement of RNA polymerase on DNA during replication seems to work this way, progressing steadily in the same direction. The movement of cells is typically driven by a kind of ratcheting, as a network of actin fibres assembles to push the cell membrane forward. As Brownian fluctuations open up a gap between the membrane and the actin fibres propped against it, a new actin monomer may insert itself, preventing the membrane from returning to its original position. (Here the chemical binding energy supplies the driving force.) And the rotary ATP synthase is also a kind of Brownian ratchet in which the asymmetric binding and release of protons flowing through it introduces a bias into the rotational diffusion of the head.

Brownian ratcheting has been used by Haiping Fang and colleagues at the Shanghai Institute of Applied Physics in China to propose a kind of molecular pump made from a carbon nanotube.[19] They considered a nanotube embedded in some membrane matrix, through which water molecules can pass in a hydrogen-bonded chain. Because water is a polarized molecule, three positive charges placed asymmetrically just outside a carbon nanotube at various positions along its length can bias the random motion of the water molecules so as to pump them through the tube preferentially in one direction. These charges might be provided by chemical groups attached to the outside of the nanotube, or by tiny electrodes in the membrane matrix. The pump doesn't require any external hydrostatic or osmotic pressure gradient to drive the water through. However, energy is needed to keep the charges in place, because otherwise water molecules would drag them out of position as they pass through, eventually nullifying the electric field that produces flow. Because the nanotube is so narrow, salt ions can't pass through without losing their shell of hydration water – and this costs too much energy, so salt is essentially excluded from the flow, making the theoretical design a potential nanoscale desalinator.



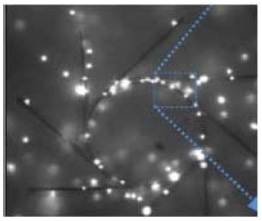
A molecular water pump driven by an asymmetric structure.

Whether motor proteins harness Brownian ratcheting for their directional motion has been much debated, but that now seems likely. For example, the motor protein kinesin which tows organelles as it 'walks' along microtubules, uses the binding of one of its two 'legs' to the track to bias the diffusional search of the other leg for a binding site in the forward direction. Such motor proteins are the paradigms of real molecular machines, both driven by ATP fuel. Rather than trying to rival such devices through synthesis, some researchers have decided simply to adapt them to technological use.

This approach was pioneered by Hitoshi Suzuki of the Kansai Advanced Reserarch Centre in Kobe, Japan, who used immobilized myosin molecules to transport actin filaments in a directional manner.[20] In muscle, myosin proteins ratchet along actin filaments with a pivoting head movement to shorten the tissue. But when myosin molecules are anchored on a solid surface, they can pass strands of actin around as though the strands are crowd-surfing. Viola Vogel, now at ETH in Zurich, Henry Hess at the University of Washington in Seattle, and their co-workers, elected instead to work with the kinesin/microtubule system. Vogel and coworkers first demonstrated the directional movement of microtubules across kinesin-coated surfaces in 1999.[21] They bound the kinesin to shear-oriented films of polytetrafluoroethylene, containing striated grooves and ridges on which the proteins bind preferentially at low concentrations. This sets up linear tracks of motors for propelling adsorbed microtubules. Vogel, Hess and colleagues later demonstrated the transport of 'cargo' (nanoparticles) attached to microtubules propelled in this way.[22] And they made the process light-activated by using 'caged' ATP as the fuel, which became available for use only when photochemically freed from the cage.

The researchers have been putting this molecular transport system to some ingenious uses. They exploited the random motions of fluorescently labelled microtubules to generate images of surface topography with a resolution of less than 50 nm:[23] the idea here is that, because the microtubules can't climb up sharp inclines, embossed patterns on the surface stay dark in time-averaged images. Hess and Vogel, working with Robert Doot, have managed to grow microtubules from the component tubulin proteins within microfabricated polymer channels on glass, thereby creating patterned tracks on which

they could use kinesin to transport fluorescent nanoparticles in a directional manner.[24] (This time the microtubules revert to their biological role as the tracks, while the mobile elements are the kinesin-coated nanoparticles.) In this way they made molecular roundabouts which, with their glowing procession of vehicles, look for all the world like highway roundabouts seen from above at night (image). And at the beginning of 2009 Hess and his coworkers described a 'smart dust' sensor device in which microtubules would capture an analyte in one region and carry it over a kinesin-coated surface to another region for fluorescent labeling, and then finally to another for detection with light.[25] This removes the need for separate washing (to remove unattached analyte), tagging and detection steps in conventional assays of this kind: the molecular machinery does it all.



A nano-roundabout with fluorescent traffic.

DNA on the move

So if we are interested in getting the job done – shifting cargo, pumping and gating flows, turning propellers – rather than in exploring and extending the limits of synthetic chemistry, it might make a lot of sense to use nature's molecular machines. 'Motors are involved in nearly every key process in the cell and living organism', says Feringa: for example, in cell division, motion, signal transduction and mass transport. And they are efficient devices. 'I can do things with kinesin motors which are orders of magnitude faster, more specific and more powerful than what one can do with rotaxanes', says Hess. However, he admits that 'my hybrid solutions are still far away from application-ready, due to their limited stability.'

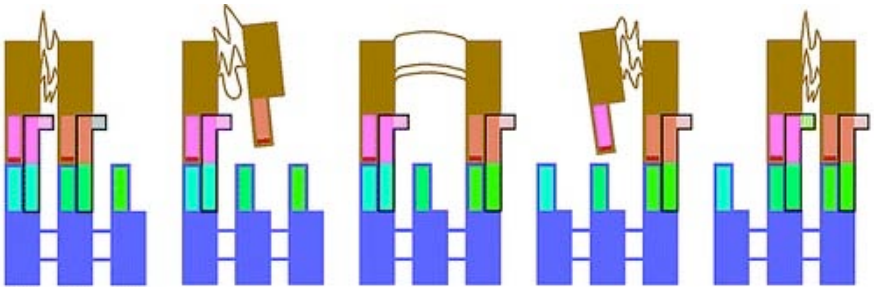
There's another biological fabric that offers perhaps the best of both worlds: DNA. This can be assembled, manipulated and even replicated with existing biological components, but also exhibits transparent design principles that enable us to dream up our own designs. By exploiting the selectivity with which strands of nucleic acid can be linked together via sequence-specific base pairing, DNA can be twisted and bent and looped into all manner of shapes. It has already been used to make a wide variety of molecular machines.

There are two main ways in which reversible movement has been achieved in DNA assemblies. Perhaps the first synthetic DNA machine, created in 1999 by Nadrian Seeman at New York University and his coworkers, made use of the fact that double-stranded DNA undergoes a transition between two different types of double-helical conformation, called the B form (the usual state that it adopts in cells) and the Z form. The switch between them can be induced by metal ions, and involves a torsional twist around the strand axis. Seeman's team used this to reversibly alter the distance between

two ‘reporter’ groups (organic dyes) attached to a synthetic strand composed of two rigid arms linked by a short double-helical ‘hinge’.[26] These groups exchanged energy to emit a telltale fluorescence when close together but could not do so when further separated.

More versatile than movement induced by such conformational change, however, is the use of DNA ‘fuel’ strands, which will bind to parts of a machine to which their sequence is complementary, producing a shape change. Typically, these strands may then be peeled off again by a second strand, a kind of ‘anti-fuel’ – for example, the attached fuel strand might have a few bases left dangling, on which the anti-fuel strand can get a foothold to start stripping it away. This approach was developed by Bernard Yurke of Bell Laboratories in Murray Hill, New Jersey, Andrew Turberfield of Oxford University and their coworkers, who made a DNA machine shaped like a pair of tweezers that could be switched in this way between a compact and open form by adding the two strands in succession.[27] The researchers subsequently figured out how to make DNA machines that switched their conformation repeatedly in a ‘free-running’ manner when provided with the fuel and anti-fuel strands, without the need for the experimenter to intervene constantly to complete the cycle.[28]

Seeman and his colleague William Sherman have used the same principles to make a DNA biped – two double helical legs connected by flexible linkers and ending in single-stranded feet – that ‘walks’ along another DNA strand.[29] The ‘footpath’ contains a series of toeholds with dangling single strands, to which one of the bipeds feet can be bound by adding a ‘set’ strand on which half the sequence is complementary to the free strand on a particular toehold and the other half is complementary to the dangling ‘foot’ sequence. The foot is released again by adding an ‘unset’ strand that peels off the set strand, starting from a region left unpaired at the end of the foot.



The DNA biped in action, walking along a track of three footholds.

If, however, the toeholds of the path are all equivalent, then a walker of this sort will simply move at random along it. And if the detachment of one leg is not coordinated with the detachment of the other, there’s no guarantee that the walker will remain fixed to the path at all.[30] These limitations have now been overcome by Seeman’s group, who designed a walker in which the motion of the legs is coordinated: the leading leg catalyses the release of the trailing leg.[31] This stepping cycle is triggered by fuel strands, and it relies on the track itself being asymmetric, with non-equivalent toeholds. In this way the DNA walker becomes a Brownian ratchet, executing unidirectional motion thanks to the asymmetric environment in which it moves. It’s an ‘expensive’ stroll,

however, because each toehold is in effect destroyed when stepped on: the walker burns its bridges. This shows that we have a way to go yet before we can mimic the coordinated motion exhibited by kinesin on conserved microtubule tracks.

Working together

'Motors are everywhere at the macrolevel in our world', says Feringa. But in chemistry and nanoscience in general sofar we do not make use of motors (or movement) in any process. He sees a 'dramatic shift' coming in chemistry and microphysics from static, equilibrium systems to dynamic ones. 'Out-of-equilibrium, kinetically driven, dynamic systems governed by switches, triggers, response elements and motors will change drastically our approach to smart, responsive and adaptive materials, devices and sensors, computation, and so on.'

Now that molecular engineers are almost spoilt for choice,[32,33] however, they need to consider their options carefully. What are the most robust and reliable fabrics for making these devices, and how might they best be powered? Balzani thinks that light-driven systems have several advantages.[34] 'All living organisms rely on sunlight as the primary energy source', he points out. Light is clean and abundant. In contrast, 'a device that utilizes chemical energy will need addition of fresh reactants at any step of its working cycle, with the concomitant formation of waste products.' What's more, he says, the energy input can be carefully controlled by the wavelength and intensity of the exciting photons. And this energy 'can be transmitted to molecules without physically connecting them to the source – no 'wiring' is necessary.' Lasers can 'address' very small regions and very short time periods, while conversely, 'the irradiation of large areas and volumes enables the parallel addressing of a very high number of individual nanomachines.'

Stoddart thinks that the most useful machines may be ones that, while perhaps inspired by nature, do not follow their design too slavishly. 'My chemist's view is that we need to go down a road involving construction that is much more robust in a skeletal sense than we see in nature', he says. Compare it with the case of flight, for example. 'We ended up keeping wings some of the time but not all of the time – in rockets, say. By and large, we opted for robustness and strength and then added on sources of motive power in a manner that is largely (but not entirely) foreign to the natural world.'

And how might we want to use such machines? In biology, they may power macroscopic devices, such as an arm or leg. Burt for applications like that, three key questions arise: how much force can they produce, and how quickly, and at what energy cost? Initial rough estimates don't bode well. For example, a polymer molecule containing 20 light-switchable azobenzene pivots can perform only about 4.5×10^{-20} J of work per azobenzene, which is comparable to the thermal noise.[35] However, other devices pack more of a punch: a switchable rotaxane might produce a factor of several tens of the thermal energy per molecule. And if large arrays of molecules can be organized so that they all act in concert – as they do in muscle, moved by bundles of many myosin heads – then the collective force can be substantial. Stoddart and his colleagues have recently estimated that a 1-cm^2 monolayer of close-packed rotaxane switches might in principle move 100

kg. The problem there is that they move it only about 1 nm. The answer might be, as in the case of Hess's kinesin tracks, to set up a bucket brigade of motor molecules that act in succession.

The switching might also be slow: if the movement happens by diffusion, it can take between seconds and hours. That can be an advantage in applications geared towards switchable memories, where the lifetime needs to be as long as possible. But for moving things around, it will need to be faster. This can be done by triggering the switching with some impulse – electrochemically or photonically, say – rather than just allowing the system to equilibrate of its own accord.

Considerations like this have led Stoddart to think that molecular machines whose purpose is to induce motion at scales much larger than themselves will have to be organized into large assemblies. 'Single artificial motors swimming around aimlessly in solution are going nowhere fast', he says. 'We have really got to move on into new arenas, into extended structures, into one- and multi-dimensional polymers, onto surfaces, into interfaces, and so on. Intuitively, one feels as the cooperative systems grow in size, the thermal fluctuations that undoubtedly dominate the small molecular world will surely start to become less important, and ultimately will more or less peter out.' Then we'll really be getting somewhere.

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