Molecules that emulate in part the remarkable capabilities of protein motors were recently chemically synthesized. A promising approach is based on physically interlocked macromolecular complexes such as rotaxanes and catenanes. Using the latter, Leigh et al. [Leigh, D. A., Wong, J. K. Y., Dehez, F. & Zerbetto, F. (2003) Nature 424, 174–179] constructed a molecular rotor in which two small rings are induced by pulses of light to move unidirectionally around a third, larger ring. The mechanism is similar to that by which a peristaltic pump operates. Unlike macroscopic peristalsis, however, in which a traveling wave forces material through a series of one-way valves, the chemical peristaltic mechanism does not directly cause the small rings to move but only alters the energetics, with the motion itself arising by thermal activation over energy barriers. Engines operating by this mechanism are “Brownian” motors. Here we describe a minimal two-state mechanism for a catenane-based motor. Although transitions caused by equilibrium processes cannot drive directed motion, nonequilibrium fluctuations, whether generated externally or by a far-from-equilibrium chemical reaction, can drive rotation even against an external torque. We discuss a possible architecture for input and output of information and energy between the motor and its environment and give a simple expression for the maximum thermodynamic efficiency. The proposed Brownian motor mechanism is consistent with the high efficiency observed by Yasuda et al. [Yasuda, Y., Noji, H., Kinoshita, K. & Yoshida, M. (1998) Cell 93, 1117–1124] for the F$_1$-ATP synthase operating as an ATP-powered molecular rotor.

Brownian motors | ratchets | supramolecular machines

Physically interlocked macromolecular complexes such as rotaxanes and catenanes (1) were used recently by Leigh et al. (2) to construct a molecular rotor in which two small rings are induced by pulses of light to move unidirectionally around a third, larger ring. The mechanism is based on a “Brownian motor” concept (3) in which the motion occurs by thermally activated transitions between chemical states that are in local equilibrium rather than by a “power stroke.” Here we describe a minimal two-state mechanism for a catenane-based motor.

Consider a simple [2]catenane (shown in Fig. 1) in which a small ring moves between two stations, A and B, located on a larger ring. There is an asymmetrically located binding site for some ligand, e.g., Ca$^{2+}$, that controls the relative stability of the two states of localization, A and B. For simplicity we call that half of the ring without the calcium-binding site the top half and that half with the calcium-binding site the bottom half, as shown in the Fig. 1. Let binding of Ca$^{2+}$ destabilize the small ring at station A, causing almost certain transition to station B, and also render kinetically impassable that part of the large ring on which the calcium-binding site is located. Then any transitions between the two stations when calcium is bound pass over the top of the ring.

Detailed Balance

It would be easy to convince ourselves by verbal arguments that even at equilibrium the dynamic association–dissociation of calcium to the binding site of an individual macromolecular complex should lead to a situation in which the majority of transitions from A to B occur when calcium is bound and, hence (because the bottom half is blocked), across the top half of the large ring and that the majority of transitions from B to A occur when calcium is not bound, with equal likelihood across both halves of the large ring. This combination would imply net cyclic flux, where the small ring preferentially sees the order A → B → binding site → A rather than the reverse. Such unidirectional cycling would be a violation of detailed balance and of the second law of thermodynamics. What is the catch?

In the discussion above we implicitly assumed that the binding and dissociation of calcium occurs with a likelihood that is independent of the position of the small ring and that the ring then moves in response. The calcium binding is the “cause” and the ring movement is the “effect” in this description. At equilibrium, however, any given sequence of events is exactly as probable as the microscopic reverse of that sequence: it is as likely for the ring to spontaneously switch from A to B, causing the binding of calcium, as it is for the calcium to first bind and cause the ring to switch from A to B. To maintain thermodynamic consistency we must formulate our model based on thermodynamic linkage between the probability for calcium to be bound and the probability for the small ring to be localized at station A (4). Each cycle that describes motion in one direction around the large ring is exactly counterbalanced by its microscopic reverse at equilibrium. This picture is formalized in the kinetic cycle diagram (5) shown in Fig. 1b.

Consider the two sequences a and b below, each of which is the microscopic reverse of the other. Starting with the small ring at station A, sequence a is: (i) associate calcium; (ii) ring moves from A to B by the top branch of the large ring; (iii) dissociate calcium; and (iv) ring moves from B to A by the bottom branch, which completes a clockwise circuit. At equilibrium, this cycle is exactly as likely as the microscopic reverse sequence b: (i) ring moves from A to B by the bottom branch; (ii) associate calcium; (iii) ring moves from B to A by the top branch; and (iv) dissociate calcium, which completes a counterclockwise cycle. Thus, we see that at equilibrium the carefully designed asymmetry of the molecule is not sufficient to allow directed motion.

However, the input of energy that in itself is not at all directional (e.g., a nonequilibrium scalar chemical reaction) can combine with the asymmetry of the rotor to allow directional cycling. For example, oscillation (or driven fluctuation) of the calcium concentration, induced either externally or by a separate far-from-equilibrium Ca$^{2+}$ oscillator, can drive directed motion (6), and the velocity of the rotor can be controlled by varying the frequency of the external stimulus (7). Alternatively, a catalytic site (8) for a nonequilibrium reaction could be added to the ring.

Now we focus on how the principles of a Brownian motor mechanism (3), the combination of external energy input with broken symmetry and with thermal motion, can allow an oscillating or fluctuating electric field to drive rotation of two rings about one another with an architecture that also provides for the microscopically broken detailed balance to be translated into macroscopic rotation of many individual molecules.

**Electrical Driving**

Oscillating electric fields of 0.35 V/μm have been used to stimulate intramolecular motion in rotaxanes (9). This field
The large ring, this is not true, as seen from the mechanistic diagram in a circumference: 

Field. The electric component of the free energy at a given interlocked with a smaller ring that is immobilized perpendicular can significantly larger fields can be applied to catenanes in a surface of ions by electroconformational coupling (10, 11). Significantly such as the Na,K ATPase and to drive directed transport shown to induce intramolecular motions in membrane proteins which the constraints of thermodynamics are explicit: the interaction 1844/H20841/Symmetry Breaking. 

Fig. 1. Two-station model for a catenane-based molecular rotor. (a) Binding of a ligand (Ca\(^{++}\) in the case shown) destabilizes binding of the small ring at station A and also kinetically blocks the half of the ring on which the ligand-binding site is located. Although at first it might seem that dynamic association–dissociation of Ca\(^{++}\) alone could drive cycling of the small ring relative to the large ring, this is not true, as seen from the mechanistic diagram in b, in which the constraints of thermodynamics are explicit: the interaction  \( K_{int}/K_{eq} \) term reciprocally influences both the binding of Ca\(^{++}\) and the localization of the small ring between stations A and B. When rate constants consistent with the equilibrium constants are used, the flux through any cycle is zero. Oscillations, however (e.g., of the Ca\(^{++}\) concentration), do drive clockwise cycling.

Strength is similar in magnitude to the ac electric fields in cells (approximately \( ±10 \text{ mV} \) across an \( 10^{-8}\text{-m-thick membrane} \) shown to induce intramolecular motions in membrane proteins such as the Na,K ATPase and to drive directed transport of ions by electroconformational coupling (10, 11). Significantly larger fields can be applied to catenanes in a surface monolayer (12).

Symmetry Breaking. Consider a catenane in which a large ring is interlocked with a smaller ring that is immobilized perpendicular to a surface in the presence of a time-dependent external electric field. The electric component of the free energy at a given orientation \( \theta^* \) of the large ring relative to the product of the charge density on the ring \( \rho(\theta - \theta^*) \) and the electric potential \( \Phi(\theta) \) integrated over \( \theta \) (i.e., over the large ring circumference):

\[
U_{\text{electric}}(\theta^*, t) = \int_0^{2\pi} \Phi(\theta, t) \rho(\theta - \theta^*) d\theta. \tag{1}
\]

For a homogeneous field, this electric potential energy is invariant to changing the sign of the field and reflecting each charge about a line drawn through the center of the ring perpendicular to the field (inversion). In a system with negligible inertia (such as all molecular motors in aqueous solution), an applied ac field can drive rotational motion only if this symmetry is broken.

One approach is to use a second field orthogonal to the first. If the second field is temporally out of phase with the first, the overall field rotates and can drive rotation of a simple dipole (13) in the plane of the two fields.

A second approach is to use a needle electrode, e.g., the stylus of an atomic force microscope, that produces components of the field in all three Cartesian coordinates. In this setup, the field is not homogeneous and the electric potential energy of a charge depends approximately on the inverse of the distance from the electrode. It is straightforward to imagine an asymmetric distribution of charges that would give a sawtooth ratchet potential in an electric field. The amplitude of the potential could be controlled by the external field, giving rise to directed motion by a flashing ratchet mechanism (14–16).

The approach on which we focus here is based on adding a second, nonelectrical component to the potential energy by manipulating the chemical interactions between the small ring and two stations on the large ring that interact specifically with the small ring. Even if the chemical and the electrical potential energies individually have inversion symmetry, the combination \( U(\theta^*) = U_{\text{chem}}(\theta^*) + U_{\text{electric}}(\theta^*, t) \) generally does not.

In the simple model ring system shown in Fig. 2a, there are two bases, chosen for simplicity to be directly opposite one another, and an electric dipole at 45° relative to the imaginary line connecting the two bases. The electrical potential energy due to a homogeneous field in the \( z \) direction, \( \pm E_{z0}^* \), is \( U_{\text{el}} = (\sqrt{2}/2)k_BT\cos(\theta^* - \pi/4) \), where \( p \) is the dipole moment and \( \epsilon = 2E_{z0}^*/(\sqrt{2}k_BT) \). The quantity \( \epsilon \) is the difference in the electric potential energy of configuration A relative to B due to the applied field.

Now let us consider the effect of a square-wave oscillating field. Switching from one polarity to the other, the field alternately favors configuration A then B. When the field is positive, molecules in configuration A feel a clockwise torque. After a \( 3\pi/4 \) clockwise rotation, the molecule is at a minimum of the electric potential energy. A diffusive search then allows the specific chemical interaction between the small ring and base to lock B. Now, when the sign of the field reverses, the molecule once again experiences a clockwise torque and thus undergoes a clockwise rotation by \( 3\pi/4 \) followed by a diffusive search to lock into configuration A. The sense of rotation is governed solely by the angle of the dipole relative to the chemical axis. If the amplitude of the field is large relative to the amplitude of the “chemical” part of the potential, as shown in Fig. 2b the motion of the ring is approximately deterministic and the “stoichiometry” is nearly one rotation per cycle of the field. The relaxation to the new stable configuration when the field switches sign is well described as a power stroke, because thermal noise is not required. An oscillating or fluctuating field can do work against an externally applied torque \( \tau \) that opposes the field driven rotation. The rotation stalls when \( \tau = k_BT\epsilon/\pi \).

Two-State Model. For typical experimental field strengths, however, the amplitude of the electric potential energy is often much smaller than that of the chemical part of the potential energy. The effect of the field can then be treated as a perturbation. If the field frequency is not too high, the dynamics can be approximately described in terms of a two-state chemical kinetic model (Fig. 2c) with rate coefficients that depend on the field and the external torque (6, 17). For simplicity we take the chemical part of the potential to be symmetric so the unperturbed rate coefficients all equal the same constant \( k \).

As the field cycles between + and −, the dimensionless energy
The dimensionless energy output is $f - b$ that go backward (counterclockwise) minus the number $b$ that go forward (clockwise). There is also a slip current balance to hold. This is not true: it is a necessary condition, but it is not sufficient (3, 6).

The mechanism by which a fluctuating or oscillating field causes net cycling is illustrated in Fig. 3. Each time the field switches sign, the system relaxes from the high to low energy state, with a number of molecules $f$ undergoing clockwise transition and a different number of molecules $b$ undergoing counterclockwise rotation. The dimensionless electric input work on each stroke is $\varepsilon$ multiplied by the total number of molecules ($f + b$) that relax to the new energetic ground state. The dimensionless energy output is $\mu$ multiplied by the number of molecules $f$ that go forward (clockwise) minus the number $b$ that go backward (counterclockwise). There is also a slip current
in the direction of the torque that tends to lose energy, and thus this energy loss must be subtracted from the energy gain to get the net output work:

\[ W_{\text{in}} = \varepsilon (f + b) \]
\[ W_{\text{out}} = \mu (f - b) - W_{\text{slip}}. \]  

The ratio \((f - b)/(f + b)\) can be evaluated by considering the splitting probabilities. When a molecule undergoes a transition from configuration A to configuration B, the difference in the probability for a clockwise transition vs. a counterclockwise transition is \(r_{\text{AB}} = (\sigma_{\text{AB}} - \beta_{\text{AB}})/((\sigma_{\text{AB}} + \beta_{\text{AB}}) = \pm \tanh((e + \mu)/2)\), and when it changes back the probability for a clockwise transition vs. a counterclockwise transition is \(r_{\text{BA}} = (\sigma_{\text{BA}} - \beta_{\text{BA}})/((\sigma_{\text{BA}} + \beta_{\text{BA}}) = \mp \tanh((e - \mu)/2)/2\). The upper sign is taken when the field is positive, and the lower sign is taken when the field is negative. Nearly all of the pumped A-to-B transitions occur when the field is positive, and nearly all of the pumped B-to-A transitions occur when the field is negative, and thus the ratio is \((f - b)/(f + b) = \tanh((e - \mu)/2)\) for either positive or negative field. Because the “slip” work is dissipative, the maximum efficiency is

\[ \eta_{\text{max}} = \frac{\mu}{\varepsilon} \tanh\left(\frac{e - \mu}{2}\right). \]  

Although this simple expression was derived specifically for the case that the dipole is at an angle \(\pi/2\) relative to the line connecting the two bases, it is easily seen by symmetry that this optimizes the efficiency. The ratio \(\mu/\varepsilon\) is the absolute first-law (energy conservation) maximum, and the postfactor \(\tanh((e - \mu)/2)\) reflects the fact that for a Brownian motor mechanism the system can relax either forward or backward, where the difference, which gives the directionality, is controlled by the relative barrier heights.

A plot of efficiency vs. applied torque is shown in Fig. 4. The dimensionless input work was set at 22, corresponding to \(\sim 90\) pN nm driving at room temperature. The maximal efficiency is \(>80\%\) and occurs at a dimensionless output work of \(\sim 20\) (i.e., \(\sim 80\) pN nm), which is in good agreement with the results of Yasuda et al. (19), who showed that the F_{o}F_{1} ATP synthase can do \(80\) pN nm of work with an input of \(90\) pN nm at an efficiency of nearly 90%. It is important to remember that their “efficiency” is in fact a generalized efficiency (20) that includes the work done on the viscous medium.

In contrast to many macroscopic machines, which are most efficient in the quasistatic limit, the maximal efficiency (Eq. 3) for Brownian motors can be attained only if the cycle time is short compared to the time constant for slip \([k^{-1}\exp(-\mu/2)]\), some amount of which is unavoidable in microscopic systems.

The stoichiometry (cycles of the ring per cycle of the field) is close to unity only when the cycle time is long compared to the relaxation time from the high-energy to low-energy configuration [governed by \(k^{-1}\exp(-\varepsilon + \mu/2)\)].

For the values of \(\varepsilon = 22\) and \(\mu = 20\) and an intrinsic rate constant \(k = 10^{-2}/\text{sec}\), this constraint means that to achieve a situation in which the ring completes one cycle per cycle of the field and the efficiency is near the maximum value, we need \(\sim 100/\text{sec} < T^{-1} < \sim 1000/\text{sec}\), where \(T\) is the period of the square-wave field. Typical values for the rate of ATP hydrolysis by molecular motors and pumps are generally within this range.

**Discussion**

Unlike rotors driven by rotating fields described by Horinek and Michl (21) in which thermal noise and chemical binding are to be avoided to maximize efficiency, chemical binding is essential for symmetry breaking in the Brownian motor mechanism described here. Thermal noise is also required unless the field amplitude is very large. Note that the catenane-based rotor is not chiral and requires symmetry breaking only in the plane perpendicular to the applied field, which is in contrast to several other approaches for designing molecular rotors that have focused on chemical chirality (22, 23).

The mechanism for chemical peristalsis described here is remarkably simple: a small ring physically interlocked on a larger ring interacts chemically at two specific stations, A and B, on the larger ring. By modulating the relative interaction energies at the two stations and the relative heights of the barriers on either side separating them, directed cycling of one ring about the other is achieved even though at any “frozen” value of the external field there would be no tendency for persistent cycling. Increasing the number of chemical localization stations around the larger mobile ring generates more complicated potentials, which can give rise to a rotor with a finely tuned frequency response and possibly even to a motor that can reverse direction as frequency is changed (7).

The main feature distinguishing Brownian motor mechanisms from power-stroke and other macroscopically inspired models for molecular motors is the fact that in Brownian motors, the input energy is used to change the relative energies of different stable conformations of the motor, but motion arises by thermal activation over barriers separating the different conformations. In the model discussed in this article, the amplitude of the external field controls whether the chemical rotor follows a Brownian motor or a power-stroke mechanism. Even in the very simple, minimal model of a Brownian motor, the efficiency and stepping frequency are in good agreement with values measured in single-molecule studies of biological motors.

Certainly there is much left to do in terms of engineering chemical motors that can be put to use in practical applications. For example, the alignment of the rotors on the surface is critical in any application requiring an array of motors, but it is not obvious how to arrange a preferential binding. Additionally, coupling the rotors described here to some load allowing performance of useful work has still not been experimentally accomplished and offers many additional challenges. Here we focused on the fundamental aspects of the constraints placed by detailed balance on single rotors and showed how chemical or electrical energy, coupled with thermal activation, can be used to drive directed motion of these nanoscale devices efficiently.

I thank Charles Smith, Tom Hess, Jim McClymer, and especially Ken Brownstein for very useful discussions and Tom Witten for suggesting, more than a decade ago, the term “peristalsis” as applied to mechanisms such as that described in this article. This work was supported in part by the Mobile Manufacturers Forum.