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Microscopic reversibility and reciprocal relations for Brownian molecular machines

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ABSTRACT

Chemists have made great progress in synthesizing molecules that emulate in part the remarkable properties of biological molecular motors, most especially the ability to use chemical energy to drive directed motion and do mechanical work. Here the mechanism of a molecular motor is treated as a renewal process in which the motor molecule fluctuates away from, and then returns to some arbitrary initial configurational state. During this excursion, some number of fuel molecules will have been catalytically converted to product, and the motor will have undergone some number of mechanical cycles in which work is done on the environment. The dependences of the number of catalytic and mechanical processes per renewal obey reciprocal relations for arbitrarily strong load force and chemical driving force. These relations characterize the behavior of the system far from thermodynamic equilibrium in the same way that the Onsager reciprocal relations characterize the system close to thermodynamic equilibrium.

1. Introduction

Molecular motors[1–3] convert chemical energy into directional motion. Chemists have recently had great success in synthesizing molecules that carry out many of the same functions as biomolecular motors, most notably the ability to use chemical[4,5] and light[6,7] energy to drive directed motion (for reviews see Refs. 8–10). In this paper, a general theoretical analysis of energy conversion by molecular machines is given, and reciprocal relations are derived for the conversion between chemical and mechanical energy that hold even far from thermodynamic equilibrium.

Consider the three-ring catenane shown in Figure 1a. The larger gray ring has three distinct recognition stations, labeled 1, 2, and 3, for the two identical yellow rings. The yellow rings cannot pass one another, nor can they occupy the same station, as they make thermally activated transitions from one station to another. Thus there are a total of three configurational states, labeled A, B, and C. Leigh described a similar [3]catenane[11] with all the characteristics listed above. Here, we add a catalyst (the black dot on the gray ring) that facilitates the conversion between some chemical substrate S and a product molecule P. In principle, if the interaction energies between the yellow rings and the recognition stations depend on whether the catalytic site is occupied or not, free-energy released by a non-equilibrium reaction $S \rightleftharpoons P$ can drive directed rotation (e.g., where $A \rightarrow B \rightarrow C \rightarrow A$ dominates) through the states.

Figure 1b illustrates one topology by which immobilization of the catenane on a surface can allow directional rotation through the states to do work on the external environment. The sequence $A \rightarrow B \rightarrow C \rightarrow A$ results in lifting the 'fly', and the sequence $A \rightarrow C \rightarrow B \rightarrow A$ results in lowering the 'fly'. The weight of the fly exerts a torque X_1 that tends to drive the catenane to undergo the sequence $A \rightarrow C \rightarrow B \rightarrow A$ and hence to rotate counterclockwise.

The triangle reaction in Fig. 1a is identical to that used by Onsager to highlight the connection between chemical 'detailed balance' or microscopic reversibility and his reciprocal relations for

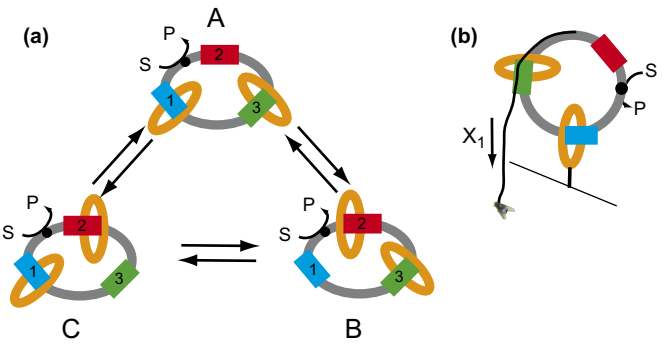

Figure 1. a) Triangle reaction for a three-ring catenane. A catalytic site is incorporated on the larger gray ring as a possible mechanism for chemical energy to drive directed rotation of the yellow rings about the gray ring. (b) One topology in which directional rotation can be used to do work. Clockwise cycling through the states lifts, and counterclockwise cycling lowers the 'fly'. The fly is not drawn to scale.

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coupled transport[12] valid close to equilibrium. A similar mechanism has been proposed by Lehn for a light-driven imine based molecular motor.[13] Near thermodynamic equilibrium, the generalized transport currents J_i usually depend nearly linearly on the 'thermodynamic forces' X_i,

$$J_1 \approx L_{11}X_1 + L_{12}X_2 + \mathcal{O}(2)$$
$$J_2 \approx L_{21}X_1 + L_{22}X_2 + \mathcal{O}(2) \quad (1)$$

where $\mathcal{O}(2)$ indicates terms of second and higher order in the expansion of the generalized currents in powers of the thermodynamic forces. Note that the term 'thermodynamic force', while standard, is perhaps a bit misleading. The X_α have units of energy, and for chemical reactions are in fact chemical potential differences that in and of themselves have no spatial direction. For the catenane shown in Fig. 1 we let J_1 be the net rate at which the catenane cycles directionally through its states A→B→C→A (and hence the rate at which the fly is lifted), X_1 is the load (the external torque, e.g., due to the fly) on the ring, J_2 is the rate at which the substrate is converted to product and $X_2=\mu_S-\mu_P$ is the chemical potential difference between substrate and product. Each rate J_α depends of course on the force X_α (where α=1, 2), and also, in general, on the force $X_{\text{not}\alpha}$, where notα=2 when α=1 and vice versa. Onsager showed by very general arguments that the cross-coupling coefficients are equal $L_{12}=L_{21}$. Thus, for small forces, the magnitude of the flow J_1 caused by the force X_2 (with X_1=0) is identical to the magnitude of the flow J_2 caused by the force X_1 (with X_2=0) if the magnitude of X_2 in the former case is equal the magnitude of X_1 in the latter case. Examples for which the reciprocal relations have been usefully applied include physical devices such as coupled quantum dots and quantum point contacts,[14,15] biological systems such as membrane transporters and ion pumps,[16] coupled enzyme systems,[17–19] and bio-molecular motors.[20,21]

Reciprocity of the flows and forces does not hold for larger forces where higher order terms become important. Further, under some circumstances, $L_{12}=L_{21}\equiv 0$ by symmetry. It is still possible that the flows are coupled at higher order,[22] but no general relationship describing the cross-coupling has been given even for very small forces. Here I show that with a slight change of perspective it is possible to derive reciprocal relations for molecular machines that hold for arbitrary magnitude thermodynamic forces X_α, i.e., that hold arbitrarily far from thermodynamic equilibrium.

2. Reciprocal relations far from equilibrium

The simplest perspective from which to consider the exchange of energy between the chemical reaction S⇌P and the lifting/lowering of the fly in Figure 1 is to treat the motion of the catenane as a renewal process[23] in which the catenane fluctuates away from, and then returns to some arbitrary initial state. The focus on completion of excursions away from, and return to some initial state is reminiscent of the approach developed by Hill[18,24] for analyzing biological energy transduction in terms of the cycles of the proteins responsible for these conversion processes.

Starting at any state, e.g., A (without substrate at the active site), the catenane will, by thermal noise, inevitably undergo a transition to some other state, and after wandering amongst the other states, will eventually return to the original state A. During this excursion, the catenane will have completed some number (possibly zero) of rotations of the ring, N_1, through the states A, B, and C. We take positive N_1 to indicate rotations in the order A→B→C→A and negative N_1 to indicate rotations in the order A→C→B→A. The catenane will also have catalyzed the conversion between some number N_2 (possibly zero) of molecules of S and P. We take positive N_2 to indicate S→P and negative N_2 to indicate P→S. For any sequence of states, e.g., A→……→A that leads to N_1 rotations and N_2 chemical conversions there is an exact (microscopically) reverse sequence $\mathcal{R}$, A→…$\mathcal{R}$…→A, in which the states appear in reverse order and hence, which leads to $-N_1$ rotations and $-N_2$ chemical conversions. The ratio of the probabilities for any such forward and microscopic reverse cycle depends only on the changes brought about in the environment—i.e., on N_1,N_2, and on the generalized forces X_1 and X_2. Thus, in units where the thermal energy k_BT=1 where T is the temperature and k_B is Boltzmann's constant, the ratio of the probability, $P(N_1,N_2)$, for a sequence that results in N_1 rotations and N_2 chemical conversions to the probability, $P(-N_1,-N_2)$, for a sequence that results in $-N_1$ rotations and $-N_2$ chemical conversions is

$$\frac{P(N_1,N_2)}{P(-N_1,-N_2)} = e^{N_1X_1+N_2X_2} \quad (2)$$

This equation follows from microscopic reversibility. For a review of the applications of microscopic reversibility to molecular motors see the recent article on design principles of Brownian machines.[25] Note that the ratio $P(N_1,N_2)/P(-N_1,N_2)$ is not thermodynamically constrained and can take any value from 0 to ∞ depending on the structure of the molecule and irrespective of the values of X_1 and X_2. This is because a sequence in which $-N_1$ rotations and N_2 chemical conversions occur is not the microscopic reverse of any sequence in which N_1 rotations and N_2 chemical conversions occur. Indeed, the ratios $P(-N_1,N_2)/P(N_1,N_2)$ are the key quantitative descriptors of coupling between the chemical process of catalysis of S→P and the cycling of the catenane through its states.

The average numbers of rotations, $\langle N_1\rangle$ and of chemical conversions $\langle N_2\rangle$ during each excursion away from and return to the initial state averaged over many such excursions are

$$\langle N_\alpha\rangle = \sum_{N_1=-\infty}^{+\infty}\sum_{N_2=-\infty}^{+\infty} N_\alpha P(N_1,N_2), \quad \alpha = 1,2 \quad (3)$$

Using Eq. 2 the averages in Eq. 3 can be rewritten,

$$\langle N_\alpha\rangle - \langle N_{\alpha,d}\rangle = \sum_{N_1=1}^{+\infty}\sum_{N_2=1}^{+\infty} N_\alpha\Big[P(N_1,N_2)\left(1-e^{-N_1X_1-N_2X_2}\right) \mp P(-N_1,N_2)\left(1-e^{+N_1X_1-N_2X_2}\right)\Big] \quad (4)$$

where $\langle N_{\alpha,d}\rangle = \sum_{N_\alpha=1}^{+\infty} N_\alpha P(N_\alpha,0)(1-e^{-N_\alpha X_\alpha})$ is the average 'direct' number of uncoupled rotations or chemical conversions per renewal, and we used $P(-N_1,N_2) = P(N_1,-N_2)e^{-N_1X_1+N_2X_2}$ in the expression for $\langle N_\alpha\rangle$ and hence we take '−' for α=1 and '+' for α=2 in the symbol ∓ in Eq. 4. What we accomplished by writing Eq. 3 in this way is to separate the thermodynamic dependence—that dependence mandated by the second law of thermodynamics—of the coupled transport on X_1 and X_2 in the exponential factors in Eq. 4, from the kinetic dependence of the coupled transport on the generalized 'forces', which resides in the X_1 and X_2 dependence of $P(-N_1,N_2)$ and $P(N_1,N_2)$. The ratio $P(-N_1,N_2)/P(N_1,N_2)$ determines the strength of the coupling—i.e., how effectively a chemical potential gradient X_2 can drive directed rotation and vice versa. This ratio is the target for design of synthetic molecular motors, and of evolution for bio-molecular motors. In the limiting cases, it is easy to see that when $P(-N_1,N_2)/P(N_1,N_2)\to 0$, $\langle N_1\rangle-\langle N_{\alpha,d}\rangle=0$ when $X_1=-X_2$, but when $P(-N_1,N_2)/P(N_1,N_2)\to 1$, rotation is uncoupled to chemical reaction and $\langle N_1\rangle-\langle N_{\alpha,d}\rangle=0$ only when X_1=0, irrespective of the value of X_2.

Expanding Eq. 4 in powers of X_1 and X_2 we write

$$\langle N_\alpha\rangle - \langle N_{\alpha,d}\rangle = \sum_{i=0}^{\infty}\sum_{j=1}^{\infty}\frac{1}{i!j!}G_{i,j}^{(\alpha)}X_\alpha^i X_{\text{not}\alpha}^j \tag{5}$$

where 'notα' indicates 2 if α=1 and 1 if α=2. In the expression $G_{i,j}^{(\alpha)}$ the superscript (α) indicates that the term appears in the equation for $\langle N_\alpha\rangle$ and the subscripts indicate that the coefficient multiplies $X_\alpha^i X_{\text{not}\alpha}^j$ in the expansion in powers of X_1 and X_2. The coefficients are

$$G_{i,j}^{(\alpha)} = \sum_{N_1=1}^{+\infty}\sum_{N_2=1}^{+\infty}N_\alpha^{i+1}N_{\text{not}\alpha}^{j}\left[(-1)^{j+i+1}P(N_1,N_2)\pm P(-N_1,N_2)\right]. \tag{6}$$

When α=1 we take for the symbol $\pm$ in the second term '+' when j=even and '−' when j=odd, and when α=2 we take '+' when i=odd and '−' when i=even. The reciprocal relations are manifest

$$G_{m,m+1}^{(1)} = G_{m,m+1}^{(2)}, \quad m\geq 0 \tag{7}$$

and

$$\begin{aligned} G_{m,m}^{(1)} &= G_{m-1,m+1}^{(2)} \\ G_{m-1,m+1}^{(1)} &= G_{m,m}^{(2)}, \quad m>0 \end{aligned} \tag{8}$$

Eqs. 7 and 8 are exact relations that follow deductively from Eq. 2. These equations include the 'linear' reciprocal relation $G_{0,1}^{(1)} = G_{0,1}^{(2)}$ that quantifies the first order effect of X_2 on $\langle N_1\rangle$ to the effect of X_1 on $\langle N_2\rangle$, and also quadratic reciprocal relations $G_{1,1}^{(1)} = G_{0,2}^{(2)}$ and $G_{0,2}^{(1)} = G_{1,1}^{(2)}$ coupling the joint (bilinear) effect of X_1X_2 on $\langle N_1\rangle$ to the 'quadratic' effect of X_1^2 on $\langle N_2\rangle$ and vice versa. These low order terms (m<2) are likely to be the terms of greatest experimental significance. Nevertheless, the reciprocal relations for higher order terms ($m\geq$2) are also valid. The reciprocal relations Eqs. 7 and 8 quantify the symmetry of the interactions between the particles in the two channels and how this leads to interference between the two transport processes.

The factors $G_{i,j}^{(\alpha)}$ are themselves functions of X_1 and X_2, which makes it difficult to use these reciprocal relations for interpreting experiments since it is impossible to separate the X_1 and X_2 dependencies due to the $G_{i,j}^{(\alpha)}$ from the dependencies arising from the exponential weighting factors in Eq. 4. However, we can expand the $G_{i,j}^{(\alpha)}$ in powers of X_1 and X_2,

$$G_{i,j}^{(\alpha)} = \sum_{k=0}^{\infty}\sum_{l=0}^{\infty}g_{i,j;k,l}^{(\alpha)}X_\alpha^k X_{\text{not}\alpha}^l \quad \alpha = 1,2 \tag{9}$$

The $g_{i,j;k,l}$ are constant (X_1 and X_2 independent) coefficients. From Eq. 7 we have $g_{m,m+1;k,l}^{(1)} = g_{m,m+1;k,l}^{(2)}$ and from Eq. 8 we have $g_{m,m;k,l}^{(1)} = g_{m-1,m+1;k,l}^{(2)}$ and $g_{m-1,m+1;k,l}^{(1)} = g_{m,m;k,l}^{(2)}$ for all k, $l\geq$0. By inserting the expansion for the $G_{i,j}$ in Eq. 5 we find, to second order

$$\begin{aligned} \langle N_1\rangle &\approx \langle N_{1,d}\rangle + L_{12}X_2 + (C_{12}+c_{12})X_1X_2 + (Q_{12}+q_{12})X_2^2 + \mathcal{O}(3) \\ \langle N_2\rangle &\approx \langle N_{2,d}\rangle + L_{21}X_1 + (C_{21}+c_{21})X_1X_2 + (Q_{21}+q_{21})X_1^2 + \mathcal{O}(3) \end{aligned} \tag{10}$$

The coefficients denoted by capital letters L_{ij} (L for linear), C_{ij} (C for cross), and Q_{ij} (Q for quadratic) are constants that come from relation Eq. 7, and c_{ij} and q_{ij} are constants that come from Eq. 8. All coefficients in Eq. 10 are independent of X_1 and X_2. Beyond the linear term $L_{12} = g_{0,1;0,0}^{(1)} = g_{0,1;0,0}^{(2)} = L_{21}$ the new reciprocal relations are

$$\begin{aligned} C_{12} &= g_{0,1;1,0}^{(1)} = g_{0,1;1,0}^{(2)} = C_{21} \\ Q_{12} &= g_{0,1;0,1}^{(1)} = g_{0,1;0,1}^{(2)} = Q_{21} \\ c_{12} &= g_{1,1;0,0}^{(1)} = g_{0,2;0,0}^{(2)} = q_{21} \\ q_{12} &= g_{1,1;0,0}^{(1)} = g_{0,2;0,0}^{(2)} = c_{12} \end{aligned} \tag{11}$$

It is interesting to note that we can have all $G_{m,m+1}^{(\alpha)} = 0$ and still have coupling through the $G_{m,m}^{(\alpha)}$ and $G_{m-1,m+1}^{(\alpha)}$ terms as shown for several heuristic models.[22,26]

In many cases, the number of rotations and the number of chemical conversions per excursion from and return to the initial state can be approximately limited to N_1=−1, 0, or +1 and to N_2=−1, 0, or +1, respectively. In this case, the sum in Eq. 4, and in Eq. 6, has only one term, and the reciprocal relations between the kinetic factors are

$$\begin{aligned} G_{e,o}^{(1)} &= G_{e,o}^{(2)} = -G_{e,e}^{(2)} = -G_{o,o}^{(1)} = P(1,1)-P(-1,1) \\ G_{o,e}^{(1)} &= G_{o,e}^{(2)} = -G_{o,o}^{(2)} = -G_{e,e}^{(1)} = P(1,1)+P(-1,1) \end{aligned} \tag{12}$$

where 'e' and 'o' are any non-negative even or odd integers, respectively, and the second position in each subscript is greater the 0. The constraint that N_1=−1, 0, or +1 and N_2=−1, 0, or +1 arises in many tightly coupled transport processes, including biological motors and pumps, and represents an important design goal for synthetic molecular machines.

The generalized currents J_α=$\langle N_\alpha\rangle/\langle\tau\rangle$ are the average numbers of cycles or chemical conversions per excursion from and return to the initial state divided by the average time for an excursion from and return to the initial state. The average time can be calculated in the standard way using the distribution $P(N_1,N_2)$,

$$\langle\tau\rangle = \sum_{N_1=-\infty}^{+\infty}\sum_{N_2=-\infty}^{+\infty}\tau(N_1,N_2)P(N_1,N_1) \quad \alpha = 1,2 \tag{13}$$

Bier et al.[27] showed that the times for specific trajectories are direction independent and hence that $\tau(-N_1,-N_2)$=$\tau(N_1,N_2)$. This identity can be used to generate an expression for τ similar to that for the averages $\langle N_\alpha\rangle$ shown in Eq. 4. However, the expansion of $\langle N_\alpha\rangle/\langle\tau\rangle$ in powers of X_1 and X_2 is an absolute algebraic nightmare because of the ineluctable presence of exponentials of the generalized forces in both the numerator and denominator.

Onsager, in deriving the reciprocal relations[12] for which he won the Nobel prize for chemistry (1968), was limited by the experimental capabilities of his day, in which it was generally only possible to measure currents and voltages or other similar quantities—thermodynamic flows and forces. Now that experiments measuring discrete processes—transfer of individual charges,[28] single steps along a polymer lattice,[29] and single chemical conversions between a substrate and product pair by an enzyme[30]—are routinely accomplished it is possible to focus on the numbers of these elementary events in any time interval. We then see that the deep symmetry relations uncovered by Onsager well over half a century ago are applicable well beyond the 'near to thermodynamic equilibrium' regime.

The reciprocal relations, of course, do not guarantee coupling. For a totally symmetric system we would expect all coefficients for cross-coupling to be zero. However, if the binding of substrate influences the relative interaction energies of the yellow rings for the

different recognition stations, we do expect the catalysis of the reaction S⇌P to interfere with the cycling process of the rings and vice versa. Hence the cross-coupling terms will not, in general, be zero. This allows the downhill catalysis S→P of the chemical reaction to drive directional cycling. Two specific mechanisms by which this may occur are the energy (flashing) ratchet[33] and the information ratchet.[34] Synthetic examples of both the energy ratchet[4] and information ratchet,[5] in which the stabilities of the states and labilities of the transitions have been engineered to optimize coupling have been given.

Just as a mechanical engineer can use the six simple machines—pulleys, wedges, levers, inclined planes, screws, and wheels—to design wonderful and intricate devices that carry out a variety of functions in the macroscopic world, molecular engineers can use the tools of chemistry, the ability to manipulate the labilities of transitions and stabilities of chemical states, to design molecular machines to carry out tasks in the microscopic world. Most of the molecular motors synthesized to date have used external changes in the environment—temperature, light intensity, electric field, pH, redox potential, etc.—to effect the changes in lability and stability by which a molecule can be driven to undergo directional cycling. A major goal remains to incorporate a catalytic function so that the binding of substrate (fuel) and release of product can autonomously drive directed motion much as adenosine triphosphate hydrolysis drive directed motion of biomolecular motors such as kinesins and myosins.

3. Conclusion

It is commonly suggested that the chemically driven motion of molecular motors is a far-from-equilibrium phenomenon that can be described by analogy with macroscopic machines and processes—turbines, cars, steam engines, judo throws, rowing cross-bridges, etc. This point of view is simply not consistent with what we know about the physics of molecules. The *only* non-equilibrium aspect arises from the difference in chemical potentials of substrate and product, $\mu_S >> \mu_P$ and the presence of any external force or torque. The motor molecule itself can be viewed as a 'conduit' for energy to flow between these two macroscopic sources (i.e., the free energy difference of fuel and product, and the viscous bath and any external applied force), but is itself in mechanical equilibrium at every instant.[25,31] Indeed, it has recently been shown how a molecular machine can be operated arbitrarily close also to chemical equilibrium and still perform significant work at an appreciable rate—μm/s velocities against pN loads.[32]

We can gain insight into the question of whether a mechanical or a statistical picture is most appropriate for describing biomolecular motors by comparing a very small macroscopic motor with a biomolecular motor. In his now famous after dinner talk, 'Plenty of Room at the Bottom' Richard Feynman issued a challenge to build a motor that, not counting the power supply and connecting wires, would fit into a cube 1/64th of an inch (a bit less than 1/2 a millimeter) on a side. This challenge was successfully accomplished by an engineer, William McClellan, only a year later. It is reported that Feynman was disappointed that no new principles were applied, McClellan's motor was simply a *tour de force* of miniaturization. When viewed under a microscope without any source of external energy the motor does absolutely nothing—it simply sits there, totally still.

Imagine, now, that we look at a single molecule of the motor in Figure 1 at chemical equilibrium ($\mu_S=\mu_P$). We see a very different picture than that for the mechanical motor. The molecule (Fig. 1) is vigorously moving because of thermal noise, sometimes completing a cycle A→B→C→A, sometimes completing the reverse cycle A→C→B→A, sometimes binding S, sometimes binding P, sometimes converting S to P, sometimes making S from P. The chemical equilibrium is maintained not by a static opposition of equal magnitude forces, but by dynamic processes in which every forward motion is exactly as likely as the microscopic reverse of that motion.

What changes when we add more S, so that the system is no longer at chemical equilibrium? Are the accessible states of the molecular motor different? Certainly not, there is no way for the motor molecule to know what the chemical potential of S in the bulk solution is, it senses only whether S is or is not bound at the catalytic active site. Do the transitions between the states of the molecule have a different character when the chemical potential of S is higher than that of P in the bulk solution? For the same reason—the motor molecule cannot be directly influenced by the chemical potentials of reactants in the bulk—the answer is also certainly no, the character of a transition between two states of the molecule when the chemical reaction is away from equilibrium is exactly the same as the character of that transition when S is at equilibrium with P. Logically, the *only* difference in the presence of excess S is that a motor molecule that is not bound to S has a greater chance of binding to S.

From this understanding we see that we should not expect any mechanical description of how conversion of S to P 'causes' a force or torque that drives a molecular motor. We are left with the perhaps unsatisfying, but nonetheless accurate statement, that conversion of S to P drives directed motion by mass action rather than by exerting any vectorial force.

It is worth noting that there is an interesting class of mechanism operative on a length scale between that of McLellan's motor and the molecular motors discussed here. On the micron scale it is possible to use chemical reactions at the surface of particles to induce locally nonhomogeneous concentrations large enough that there is an imbalance of a concentration over the surface of a particle that leads to a net mechanical force and hence to directed motion.[35,36] Such systems are subject to significant thermal noise, but, in contrast to the catenane based motor discussed here, do move under the action of a vector force, and do not require thermal noise as an essential feature of their operation.

Brownian molecular machines are first and foremost *molecules* and are governed by the laws of chemistry rather than of mechanics. The dynamical behavior of machines based on chemical principles can be described as a random walk on a network of states. A key insight is that a nanoscale system in solution explores all possible motions and configurations. By using chemical design and input energy to constrain Brownian motion, and to prevent motion that is not wanted, what is left behind is the motion that is desired.[37]

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