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Brownian ratchets in physics and biology

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Thirty years ago Feynman et al. *presented a paradox in the* Lectures on Physics: *an imagined device could let Brownian motion do work by allowing it in one direction and blocking it in the opposite direction. In the chapter Feynman* et al. *eventually show that such ratcheting can only be achieved if there is, in compliance with the basic conservation laws, some energy input from an external source. Now that technology is going into ever smaller dimensions, ratcheting Brownian motion seems to be a real possibility in nanotechnological applications. Furthermore, Brownian motion plays an essential role in the action of motor proteins (individual molecules that convert chemical energy into motion).*

1. The thermodynamic consistency of a Brownian ratchet

Technology is reaching into ever smaller dimensions nowadays. Many research groups are shrinking labs onto tiny squares of silicon or glass. On these 'labs on chips' individual bacteria viruses and macromolecules (like proteins or DNA strands) are identified and/or manipulated [1]. On the micrometre scale physics is different. For motion in a fluid the Reynolds number (i.e. the ratio of inertia and friction) goes down as the dimension of the involved particles goes down. This means that for a bacteria swimming in water is like swimming in molasses for a human being. Many bacteria therefore have a tail in the shape of a corkscrew and they swim by rotating this tail and moving through the water like a corkscrew through a cork [2]. With microscopic particles in a fluid we are in the overdamped realm, so at any time the velocity $\mathbf{v}$ of a particle is directly proportional to the force $\mathbf{F}$ on that particle, i.e. $\mathbf{F} = \beta\mathbf{v}$, where β is the coefficient of viscous friction [2]. On the micrometre scale the indeterminacies of quantum mechanics are not yet of any consequence. But the effects of Brownian motion do become important. Particles of micrometre scale size do 'feel' the 'kicks' of the molecules of the surrounding medium. The average thermal energy of a particle is kT and for a macromolecule or colloidal particle this is enough to be significant (k is Boltzmann's constant and T is absolute temperature).

An engine is a device that turns any form of energy into mechanical force or motion. Because of the different Reynolds numbers at the micrometre scale, an efficient microscopic engine is not necessarily the microscopic equivalent of an efficient macroscopic engine. At the microscopic level it is possible to 'ratchet' Brownian motion, i.e. to allow Brownian motion in one direction and block it in the opposite direction so net displacement occurs. It appears that a lot of biological systems at the molecular level operate like this [3]. Systems that convert energy in the presence of Brownian motion are complicated: often the associated Langevin or Fokker – Planck equations are not analytically solvable and can only be treated numerically. It is hard to develop an intuition for such systems and some challenging paradoxes, like Maxwell's Demon and Feynman's ratchet, have emerged. Feynman's ratchet is worth examining at this point. It is a device that purports to extract work from thermal fluctuations in violation of the Second Law of Thermodynamics [4, 5].

Like most paradoxes, Feynman's Ratchet comes about at the interface of two branches of physics. In this case macroscopic, deterministic, Newtonian mechanics and microscopic, stochastic, Brownian mechanics. Figure 1 is from the *Lectures on Physics* by Feynman *et al.* [4]. The left reservoir contains a mechanical device that is similar to one that is found in some screwdrivers or in carjacks. Because of the shape of the teeth of the cogwheel and the presence of a pawl that pushes on the cogwheel through a spring, rotation is possible in one direction and blocked in the other. The circumference of the cogwheel effectively consists of a sequence of barriers that are reflecting from one side and absorbing from the other side. If the system is small enough, then the paddle wheel in the left reservoir can be moved by the random collisions of the molecules of the medium against the paddles. Motion in the allowed direction will result and we can in principle pull up the

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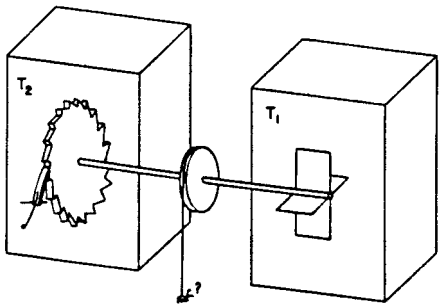

Figure 1. The thermal ratchet from the reference by Feynman *et al.* [4]. T_1 and T_2 are the temperatures of the reservoirs. The device is small enough that the paddle wheel in the right reservoir is moved by collisions of the molecules from the surrounding medium against the paddles. The ratchet and pawl in the left reservoir block motion in one direction and allow it in the other. Thus, in violation of the Second Law of Thermodynamics, at $T_1 = T_2$ equilibrium work can be extracted from thermal fluctuations to lift the little insect at the end of the thread. The resolution of the paradox and how it relates to motor proteins is discussed in the text.

little insect at the end of the thread in figure 1. It is of course in violation of the Second Law of Thermodynamics if work is extracted from thermal fluctuations in a homogeneous medium. The solution of the paradox lies in the realization that when the device is reduced to microscopic size, also the spring that pushes the pawl onto the cogwheel will undergo thermal fluctuations. Feynman showed that the fluctuations of the pawl result in forward and backward motion of the cogwheel being equally likely, i.e. no more functional reflecting or absorbing barriers along the circumference of the cogwheel. Feynman also showed that the system does work when the temperatures of the two reservoirs, T_1 and T_2, are different. He could derive that in that case the device works exactly with the Carnot efficiency $(T_1\text{-}T_2)/T_1$ (although he appears to have cut some corners in his derivation [6]). Feynman's device needs a thermal gradient in order to get functioning reflecting and absorbing boundaries for the Brownian motion. We will see below in detail how, in agreement with the Second Law, working Brownian ratchet engines always require some kind of energy input [7].

2. The motor protein as a Brownian ratchet

A motor protein is one individual nanometre size protein that is connected to a biopolymer. The motor protein catalyses the conversion of ATP (adenosine triphosphate) into ADP (adenosine diphosphate). ATP is the general currency of fuel in a living cell. When ATP is turned into ADP around 20 kT energy is released at normal intracellular concentrations [8]. The motor protein uses this energy to bring about unidirectional motion along the biopolymer. Motor proteins are responsible for muscle action, but also for intracellular transport. Many cells are spanned by networks of microtubules (the so-called cytoskeleton) and the protein kinesin 'travels' along these microtubules carrying vesicles filled with chemicals from the supply site to the demand site. Experiments have been done in which, instead of a vesicle, a silica bead was attached to the kinesin molecule [9]. The motion of this silica bead could be followed under a microscope. The silica bead, moreover, has a dielectric permittivity at high frequencies that is higher than that of the surrounding fluid. This means that the bead will 'pull toward the light'. It is thus possible to manipulate the bead and apply a known counterforce to the motor protein with a laser beam. Such a laser beam is called an 'optical tweezer'. Speeds and stopping forces of the motor protein at different ATP concentrations could thus be measured.

Next I will present a crude and simple model for a motor protein, that shows how ATP binding and ADP release imposes a fluctuation on the system. The effect of this fluctuation is the ratcheting of Brownian motion. Imagine the biopolymer as an array of dipoles (microtubule has a 400 Debye dipole at every period, see figure 2 (*a*)) and suppose that, relative to the biopolymer, the motor protein is a positive point charge which is neutralized when the negatively charged ATP binds (see figure 2 (*b*)). This means that as ATP is being hydrolysed the potential describing the interaction between the motor protein and the biopolymer flips between a flat potential and an anisotropic potential. When no ATP is bound and with large enough barriers the probability density for the motor protein will be concentrated in the minimum as a Dirac delta function. When ATP is bound the potential becomes flat and the motor protein freely diffuses. Upon release of the ADP the barriers pop up again and it is obvious from figure 2 (*b*) that, because of the anisotropy, there is a significant chance that the protein will be caught in the next trench to the right and a much smaller chance that it will be caught in the next trench to the left. Thus net transport to the right occurs as ATP is being hydrolysed. The speed of the motor protein has a nonmonotonic dependence on the flipping frequency. When the flipping is too fast, the protein has no time to diffuse during the time that the potential is flat and no net transport will take place. When the flipping is sufficiently slow there is a fixed amount of net displacement for every ATP that is hydrolysed. So at low flipping frequency the flow increases in direct proportion with the frequency. Svoboda *et al.* [9] found that their kinesin motor moved with a speed of about 500 nm s^{-1} and required a stopping force of 5 pN at saturating ATP concentration. This implies a coefficient of viscous friction of $\beta = 10^{-5}$ N s m^{-1}. The biopolymer involved, microtubule, has a period of $L = 8$ nm. For our model we take a

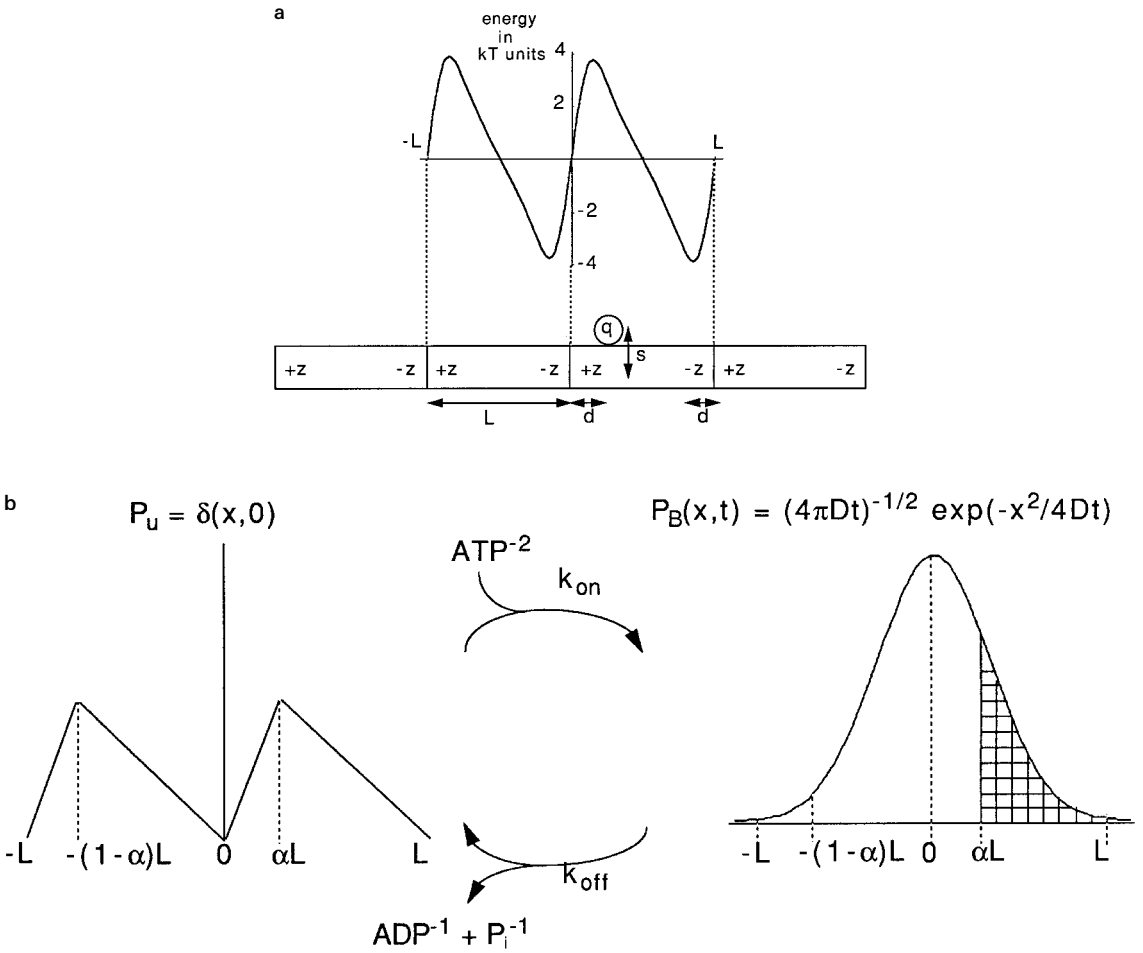

Figure 2. (*a*) **The dimensionless potential of a charged sphere on a linear array of dipoles with period** L**. The involved charges are** $z = 3$ **elementary charges and** $q = 2$ **elementary charges. Going from left to right on the array of dipoles, the distance from** $-z$ **to** $+z$ **is** $2d = L/5$ **and the distance from** $+z$ **to** $-z$ **is** $4L/5$**. For the period we have** $L = 8$ **nm and for the distance from the point charge to the linear array we have** $s = 1{\cdot}5$ **nm. We took for the relative dielectric permittivity** $\varepsilon = 20$**. This setup leads to the depicted anisotropic potential. The energy difference between the maxima and minima comes out to be 8** kT **at** $T = 300$ **K and the horizontal distance between the minimum and the maximum on the right is** $\alpha L = 0{\cdot}3L$**. (*b*) The behaviour of an ATP hydrolysing motor protein in this setup. The repeated binding of** ATP^{-2} **and release of** $ADP^{-} + P_i^{-}$ **(with rate constants** k_{on} **and** k_{off}**, respectively) means that the + 2 charge on the motor protein is repeatedly neutralized and re-established. With ATP unbound the anisotropic potential is 'on' and for high enough barriers the probability density will concentrate in the minima and form a Dirac delta function** P_U**. When** ATP^{-2} **is bound the charge on the motor protein is neutralized, the potential is flat and the probability density distribution will spread like the Gaussian** $P_B(x,t)$**. When, after an average time of** $1/k_{off}$**,** $ADP^{-} + P_i^{-}$ **is released, the anisotropic potential forces the particle to a minimum again. When the release occurs there is a significant probability (the hatched area of the Gaussian) that the particle is to the right of** αL **and will be caught in the well to the right of its original position. The probability to be caught to the left of** $(1-\alpha)L$ **and end up in the well to the left is much smaller. The repeated hydrolysis of ATP thus leads to transport in the positive direction.**

piecewise linear potential, as in figure 2 (*b*), and let the long slope be seven times as long as the short slope. To make everything as simple as possible we take $k_{on}\,[ATP] = k_{off} = \gamma$. We, furthermore, let the energy difference between the minimum and maximum be 8 kT units (this is small enough to be easily 'overcome' by the 20 kT of the ATP hydrolysis). When we substitute $\beta = 10^{-5}$ N s m^{-1} and $L = 8$ nm and solve the system of coupled diffusion-drift equations (see below), we find that we achieve a maximum speed of 100 nm s^{-1} at a turnover of 700 ATPs per second [10]. These numbers are within an order of magnitude of the experimental data. By making elaborations (e.g. making the two transition rates γ different again) higher speeds and better efficiencies can be obtained [11].

Suppose that in Feynman's ratchet we let the teeth on the cogwheel go in and out (figure 3). When the wheel is smooth it does uninhibited diffusive motion under the pawl. When the teeth come out again the pawl will be between the

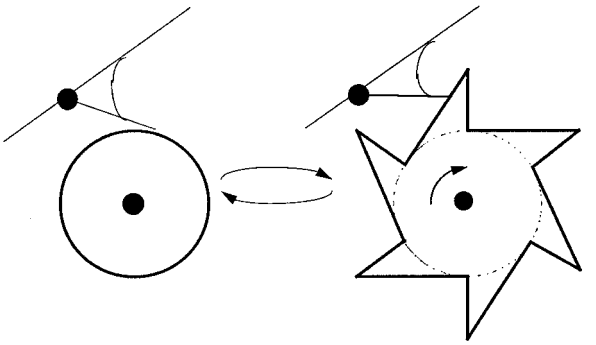

Figure 3. Suppose that the asymmetric teeth of the cogwheel in Feynman's ratchet are pulled in and out. When the teeth are pulled in, the wheel is smoothly diffusing under the pawl. After the teeth come out the force of the spring on the pawl pushes the cogwheel in the clockwise direction and causes an average rotation of $\pi/6$.

top and the bottom of a tooth and will be pushed down to the bottom of that tooth. There will thus be a net rotation of the wheel in the clockwise direction, the average of which is half the length of a tooth. This model is analogous to the fluctuating potential/motor protein model that we presented. There is no violation of the Second Law in this setup. The energy input here occurs whenever the teeth come out again and the pawl is lifted against the force of the spring. Similarly, with the motor protein model of figure 2, the energy input occurs when ADP is released and the energy level of the protein is lifted to a maximum of 8 kT. For our motor protein model to be realistic the 8 kT should be negligible in comparison to the energy drop when ADP is released.

The hydrolysis of one ATP by the motor protein is not a two-step process, but instead has been shown to involve a cascade of many conformational changes of the motor protein [12, 13]. Furthermore, the motor protein is not a point charge and the biopolymer is not a simple dipole. The protein ought to be viewed as a distribution of charges and so should the biopolymer. Nevertheless, to every conformational state of the motor protein there corresponds a periodic $U(x)$, giving the protein–biopolymer interaction energy as a function of the position on the biopolymer. The construction of the actual functions $U(x)$ is a challenge to structural biology. Here we focus on the mechanism. It is obvious that this mechanism is not like a clockwork, i.e. that it is inherently noisy. ATP binding, ADP release and going from one conformational state to another are chemical transitions. Such transitions involve the mounting of an activation barrier through random Brownian fluctuations and for such mounting there is an exponentially distributed waiting time. The hydrolysis of one ATP involves many subsequent chemical transitions. When more

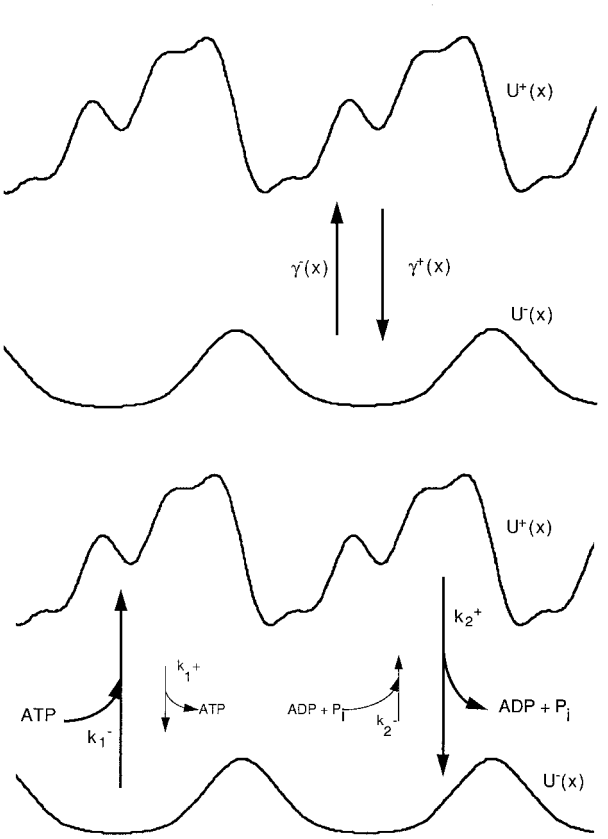

Figure 4. (*a*) A potential fluctuates dichotomously between U^+ (x) and U^- (x). The flipping rates γ^+ (x) and γ^- (x) depend on position x of the particle. The stationary probability density distribution for a Brownian particle can be obtained by solving equations (1). (*b*) When the dichotomous fluctuations involve the dissipation of energy through a chemical reaction, detailed balance can be broken and net transport along the x-axis can result. In the text it is explained how the x-independent flipping rates of figure 2 (*b*) can be achieved in this way.

and more subsequent processes with exponentially distributed waiting times are squeezed in a time interval the system moves toward the deterministic continuum limit. (For an exponentially distributed waiting time the average time T equals the standard deviation. For N subsequent such processes to finish the average total time is NT and its standard deviation is $(N^{1/2})$ T. So for larger N the standard deviation becomes smaller relative to the average.) This is why Svoboda *et al.* found the statistics of motor protein motion to be 'in between' purely clockwork and purely stochastic [14].

Next we will take a system that flips between two arbitrary potentials and we will show how a chemical potential can bring about net flow. Suppose we have two potentials U^+ and U^- (figure 4 (*a*)). U^+ and U^- can now be any continuous periodic function. Also γ^+ and γ^- can

now depend on x. We have the following equations for the joint stationary probability densities $P^{\pm}(x)$ for the particle to be at x and the potential to be U^+ or U^- [7, 15]:

$$\partial_x^2 P^+ + \partial_x(U_x^+ P^+) - \gamma^+ P^+ + \gamma P^- = 0,$$
$$\partial_x^2 P^- + \partial_x(U_x^- P^-) + \gamma^+ P^+ - \gamma^- P^- = 0. \qquad (1)$$

In order to keep the equations as simple as possible we took the energy in kT units and scaled such that the diffusion coefficient and the coefficient of friction equal 1. The terms $\partial_x{}^2 P$ and $\partial_x(U_x P)$ describe the effect of diffusive and deterministic forces, respectively. $\gamma^+ P^+$ is the flow of probability from U^+ to U^-. $\gamma^- P^-$ is the flow of probability from U^- to U^+.

Suppose we have a monomolecular chemical reaction A↔B. Let E_A be the energy of A and E_B the energy of B. At equilibrium the probability for a particle to be in A rather than in B is given by a Boltzmann distribution, i.e. $P_A/P_B = \exp[-(E_A - E_B)/kT]$. The transition rates between A and B always obey the relation $k_{AB}/k_{BA} = \exp[(E_A - E_B)/kT]$.

The system in figure 4 (*a*) is a chemical reaction with an added continuous x ordinate. We express the energy in units of kT. At equilibrium there is a Boltzmann distribution between the + and − state at any point x:

$$\frac{P^+(x)}{P^-(x)} = exp\,[-(U^+ - U^-)],$$
$$\frac{\gamma^+(x)}{\gamma^-(x)} = exp\,[U^+ - U^-]. \qquad (2)$$

This leads to $\gamma^+ P^+ - \gamma^- P^- = 0$ and upon substitution this makes the last two terms in equations (1) disappear. The system then uncouples into two easily solvable equations that prescribe a Boltzmann distribution on the individual potentials U^+ and U^-: $P^{\pm} = C \exp[-U^{\pm}]$. This makes clear how equilibrium between the + and − state leads to equilibrium on each individual potential. At equilibrium the flux $J^{\pm} = (-U_x{}^{\pm} - \partial_x)P^{\pm}$ is zero in both the + and the − state. At equilibrium we, furthermore, have detailed balance, i.e. at every point x there are as many + to − transitions as there are − to + transitions.

If, however, a 'non-Boltzmann' ratio of transition rates is 'forced upon' the system, i.e.

$$\frac{\gamma^+(x)}{\gamma^-(x)} \neq \exp[(U^+ - U^-)], \qquad (3)$$

a non Boltzmann ratio of occupation rates results, i.e.

$$\frac{P^+(x)}{P^-(x)} \neq \exp[-(U^+ - U^-)]. \qquad (4)$$

Diffusive and deterministic forces along the x-axis will 'work' to re-establish the Boltzmann distribution. So breaking the equilibrium between the + and − states by means of (3) leads via (4) to flow along the x ordinate. This will also lead to a breakdown of detailed balance. If at least one of the potentials is anisotropic, there is the possibility of a net flux in one direction.

If the γs are constant and independent of x there will necessarily be a violation of (2) somewhere along the x-axis. It is possible to get such constant and x-independent transition rates by implementing a chemical potential (in most biological systems this means the ATP–ADP potential) in the system. Suppose that the transition from the − state to the + state involves the binding of ATP (figure 4 (*b*)) or, ADP + P_i (where P_i stands for the inorganic phosphate molecule). If the ATP–ADP chemical potential is sufficiently high (i.e. the [ATP]/[ADP] ratio is significantly larger than at equilibrium), then almost all the transitions will be ATP binding and ADP release. ADP binding and ATP release will be extremely rare. The rate constants for ATP binding and release and ADP binding and release, respectively are determined by the following equations:

$$\frac{k_1^-[\mathrm{ATP}]}{k_1^+} = \exp[U^- - U^+]\exp[\Delta G_1],$$
$$\frac{k_2^-[\mathrm{ADP}][P_i]}{k_2^+} = \exp[U^- - U^+]\exp[\Delta G_2], \qquad (5)$$

where ΔG_1 and ΔG_2 are the position independent free energy changes for the binding of ATP and ADP+ P_i to the motor at [ATP] = [ADP] = $[P_i]$ = 1. The total free energy release by ATP hydrolysis equals $\Delta G_{ATP} = \Delta G_1 - \Delta G_2$ at [ATP] = [ADP] = $[P_i]$ = 1. In our system the ΔGs are independent of x and so are the concentrations [ATP], [ADP] and $[P_i]$. So the x dependence of $\exp[U^+ - U^-]$ on the right hand side must be reflected by an x dependence of k_1^-/k_1^+ and k_2^-/k_2^+ on the left hand side. But with a large ATP–ADP chemical potential the k_1^+ and k_2^- transitions are practically unused and its is possible to put the x dependence of the ratios k_1^-/k_1^+ and k_2^-/k_2^+ entirely in these 'unused' k_1^+ and k_2^-. The 'used' transitions k_1^- and k_2^+ are now x independent and for all practical purposes we have created a system like that in figure 4 (*a*) with x-independent transition rates.

The transitions between the + and the − state are stochastic and we can consider them as 'noise'. Often the terms 'white noise' and 'equilibrium noise' are used interchangeably, but our system brings out the difference between these two notions. Equilibrium noise means that (2) is obeyed. Non-equilibrium noise is the situation of (3). Noise is considered white if it has a flat frequency spectrum; in practice this simply means that most of the frequency spectrum is at frequencies much higher than any characteristic frequency of the system. In our system we can make the noise 'white' by simply making both γ^+ and γ^- very large. The ratio of γ^+ and γ^- fixes one degree of freedom in the choice of γ^+ and γ^- and we can make the noise white by leaving the ratio untouched and exploiting the other degree of freedom. Whether equilibrium or non-equili-

brium, white noise will never lead to flux. With non-equilibrium noise the flux is maximal when the average residence times $1/\gamma^+$ and $1/\gamma^-$ are such that after every flip there is an almost complete relaxation to a Boltzmann equilibrium on U^- and U^+, respectively. If the non-equilibrium fluctuations are too fast, the diffusion on the x-ordinate can never 'get started' and the system will simply relax to a stationary Boltzmann distribution on the average potential. So being non-equilibrium (i.e. obeying equation (3)) and having the right time correlation are both necessary conditions for the noise to bring about flux.

3. Man-made Brownian ratchets

Now that technology has come to a level where it is possible to build structures on a micrometre scale, it is actually feasible to drive colloidal particles by ratcheting their Brownian motion. Rousselet *et al.* assembled the device depicted in figure 5 [16]. Two metal walls line the edge of a water bath in which polystyrene or latex beads are suspended. When an electric potential between the two pieces of metal is turned on, the electric field is relatively weak where the 'christmas tree' structure is widest and very strong at the bottlenecks. The beads have a lower value for dielectric permittivity than water, i.e. they 'want to be' where the electric field is low. So when an electric potential is turned on they will concentrate where the distance to the metal is largest. Because of the anisotropy of the 'christmas tree', the potential for the colloidal particle in the vertical direction will resemble the anisotropic potential in figure 2. When the field is turned off the particles diffuse freely. So turning the field on and off will lead to net transport by the mechanism described in figure 2 (*b*).

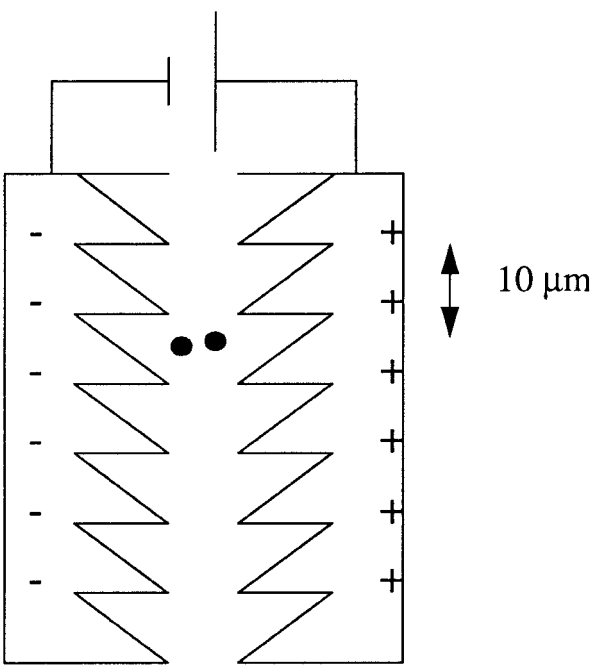

Figure 5. The device of Rousselet *et al.* [16]. When colloidal particles suspended in the fluid have a dielectric permittivity different from that of the surrounding fluid, they 'feel' an anisotropic potential like the one in figure 2. Switching the power on and off results in net drift.

Faucheux *et al.* realized a very elegant optical thermal ratchet [17]. They took a single polystyrene particle with a diameter of 1·5 μm and trapped it in a narrowly focused laser beam, i.e. the forementioned optical tweezer. They let their beam move very fast (much faster than the particle could move) along the circumference of a circle of 7 μm in diameter. The rotation of the beam is so fast that the particle feels the average force due to the beam at any point along the circumference. The particle is thus trapped in the circle. By varying the intensity of the rotating beam with a filter wheel or making the beam rotate with a non-constant speed it is possible to create an anisotropic periodic potential along the circumference of the circle (figure 6). Faucheux *et al.* flipped between such a potential and a flat potential along the circumference and found their particle to rotate in quantitative agreement with the theory.

With the flipping between the two-leg piecewise linear potential and the flat potential as in figure 2 (*b*), the flux is always in the same direction (the direction of the long slope). Adding only slight complications can lead to more involved situations where the flux can change direction as some parameter is varied [18–23].

Suppose, for instance, that the potential fluctuates between three profiles as in figure 7. V_0 is a flat potential and V_- equals $-V_+$. There are a 1000 times as many flips into V_+ as into V_-, but the dwelling time in V_+ is a 1000 times as short as in V_-. A small particle has a small coefficient of friction and consequently a large value of D. Such a small particle diffuses and equilibrates fast and will equilibrate every time after the system flips between V_0 and

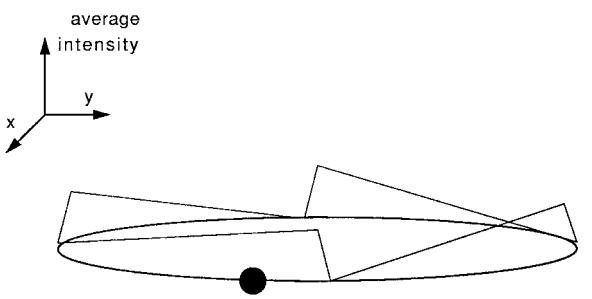

Figure 6. The circular ratchet potential created by Faucheux *et al.* with a rapidly rotating optical tweezer. The variation of the average laser beam intensity along the circle results in an anisotropic potential for a colloidal particle. By flipping between this ratchet potential and a flat potential the particle can be made to undergo a net drift along the circumference of the circle.

V_+. Because there are more flips into V_+ than into V_-, such a small particle will thus be transported to the left. A larger particle has a higher coefficient of friction and diffuses slowly. Such a particle never equilibrates between V_+ and V_0 and effectively 'feels' the average of V_+ and V_0. From this average there are transitions into V_-. Dwelling times in V_- are long enough for complete equilibration. This leads to the larger particle undergoing net transport to the right. Particles of different size, i.e. different coefficients of friction, will thus move in opposite directions.

It is not possible to realize a three-state flipping potential as in figure 7 with the dielectric device of figure 5. A particle will either be attracted to or repelled from a stronger electric field, depending only on whether that particle has a higher or lower dielectric permittivity than the surrounding fluid. The device in figure 8 works with forces that are plainly electric. Modern technology allows very thin electrodes to be spaced such that the period is about 100 μm, i.e. sufficiently small for Brownian motion to be significant. The electrodes should be embedded in the bottom of a glass tray on top of which is the thin film of fluid with the colloidal particles.

Analogously to the mechanism of Faucheux *et al.* it is also possible to create the modulation described in figure 7 with a diffraction pattern from a laser beam. One can take a film of fluid + colloid as in figure 8 and shine narrow lines of laser light, interspaced by the period L, on it. When the lines are moved backward and forward periodically (with spatial amplitude $L/2$) and very fast over the length of the tray, the potential is given by the average intensity. It is possible to create any potential by having the right velocity at any point along the x-axis or varying the intensity of the oscillating pattern with a filter wheel.

The solid line in figure 9 shows the dimensionless flux as a function of the logarithm of γ (cf. figure 7). The variable γ multiplies all the transition rates in figure 7 and, just like β, scales the time. Suppose now, that we plot the flux J again in metres per second and γ in Hz. If the solid line would be the curve for a particle with coefficient of friction β, then it is obvious from the scaling formulae for the dedimensionalized flux and flipping rate that a particle with a coefficient of friction of $\beta' = 3\beta$ has a flux-flipping rate characteristic according to the dotted line. Relative to the solid line the dotted line is translated log 3 to the left and it

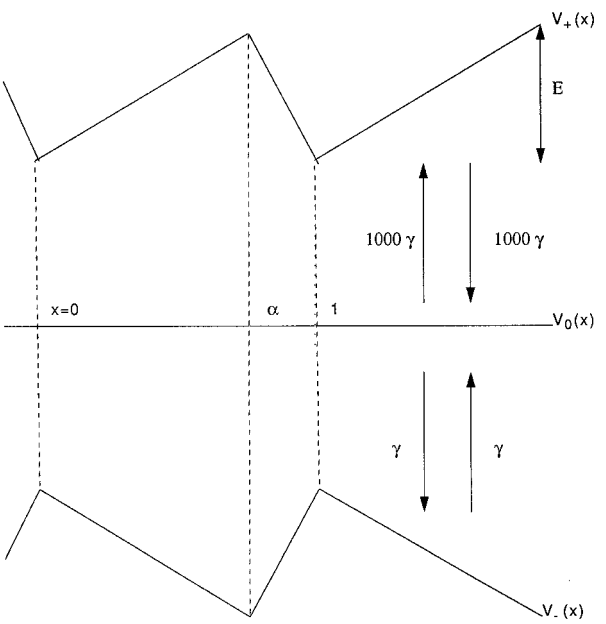

Figure 7. We study diffusive motion along the x-axis as the potential is flipping in a Markovian fashion between V_+ (x), $V_0(x) = 0$ and $V_-(x)$ with the indicated transition rates. We have $V_-(x) = -V_+(x)$ and the transition rates are such that there are a 1000 times as many transitions from $V_0(x)$ into $V_+(x)$ but equal amounts of time are spent in $V_+(x)$ and V_-. In this setup the direction of the induced drift depends on the flip frequency γ.

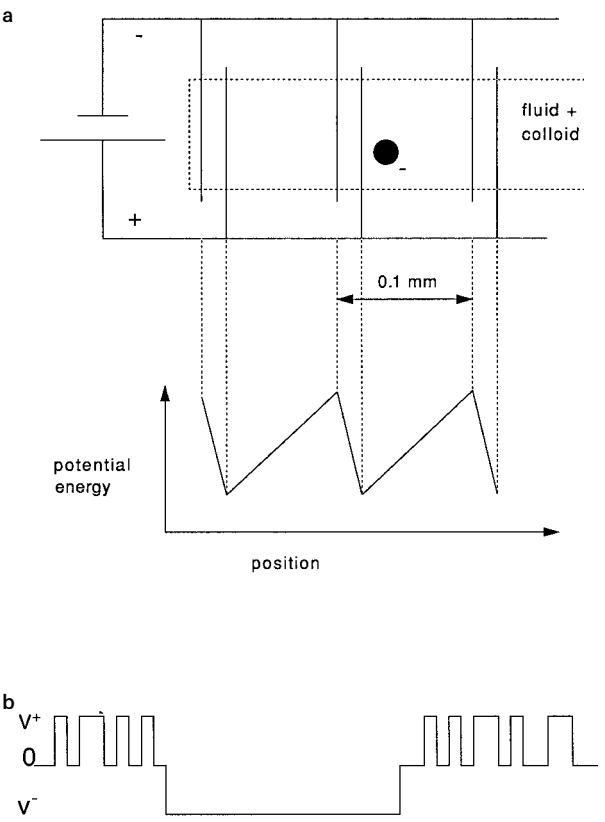

Figure 8. (*a*) A microelectric circuit to realize an anisotropic potential for negatively charged colloidal particles. Interspaced electrodes are embedded in the bottom of a tray on which there is a thin film of fluid with suspended charged colloidal particles. (*b*) When instead of a dc input we apply this 3-state signal to the system in (*a*), the colloidal particles 'feel' the flipping potential of figure 7.

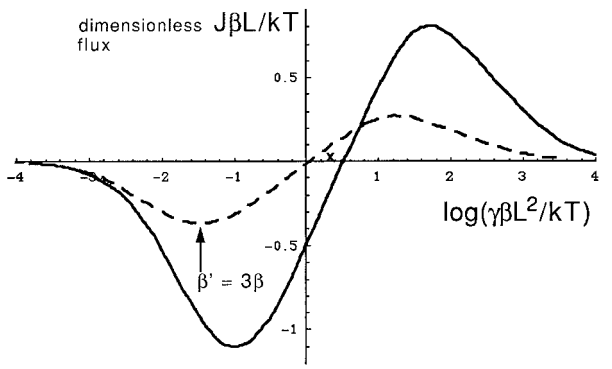

Figure 9. The solid line depicts the dimensionless flux as a function of the logarithm of the dimensionless γ for $E = 10$ and $\alpha = 10/11$ (cf. figure 7). β represents the coefficient of friction of the particle, L is the period of the potential and γ is the flipping frequency of the potential (cf. figure 7). Suppose we have a particle P′ with a β' that is 3 times as high as that of a particle P. After redimensionalization P′ will have a characteristic curve that is vertically contracted by a factor 3 and log 3 shifted to the left (dotted line). The symbol 'x' indicates the value of γ for which P and P′ separate fastest.

is contracted by a factor 1/3 in the vertical direction. The value of the variable γ is under the control of the experimentalist. It is always possible to choose γ such that two particles of different size will flow into different directions. In figure 9 the optimal γ for separation is indicated with a symbol '**x**'. Particles of different size and/or geometrical shape have different values of the coefficient of viscous friction β. The three state flipping thus leads the way to some promising new methods of particle separation [22, 23]. For colloidal particles with a factor 3 difference in their βs and with a period of about 100 μm it takes a few hours to separate the particles over 10 periods [22].

4. Epilogue

Noise is generally thought of as something undesirable, something to get rid of or to filter away. At the microscopic and molecular level, however, when kT is comparable to the involved energies, noise is a fundamental part of the picture. To think of noise as something to exploit is a major shift of paradigm. A lot of research has already been devoted to noise-enhanced signal detection. This phenomenon has been termed 'stochastic resonance'; it has been observed in biological systems [24, 25] and there are possible applications in engineering [26]. Ion pumps and motor proteins are the smallest engines we know and they can no longer be thought of as wind-up toys. They are molecules that 'do their job' by moving from one conformational state to another, thereby following the rules of chemical kinetics. Between two subsequent conformational states there is an activation barrier. When the activation barrier has a height of ΔE, the thermally activated crossing will occur after an exponentially distributed waiting time, the average of which is proportional to $\exp(\Delta E/kT)$. If nano-technological devices are to be as efficient and reliable as biological molecules a good understanding of noise will be indispensable to their design. Brownian motion and diffusion are no longer to be thought of as a problem, but instead to be incorporated as part of the design.

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