

A Motor Protein Model and How It Relates to Stochastic Resonance, Feynman's Ratchet, and Maxwell's Demon

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Abstract. A motor protein turns chemical energy into motion, but it differs from an ordinary engine in that random Brownian kicks become important. Below we propose a description where the energy input is used to ratchet Brownian motion, i.e. to allow it in one direction and block it in the opposite direction. Our model relates to famous paradoxes like Feynman's Ratchet and Maxwell's Demon, but is thermodynamically consistent.

Motor proteins are large molecules that convert ATP into ADP and use the released energy to make the protein move in one direction along a biopolymer. Turning chemical into motion is also what happens in a car engine. However, there are some very fundamental differences between a car engine and a motor protein.

The operation of a car engine can be fully understood with macroscopic physics. Thermodynamics describes the fuel combustion and Newtonian mechanics describes the ensuing motion. The motor protein operates on a much smaller scale and this means that inertia plays no role in the motion and that, in effect, friction is the only force that has to be overcome. To understand this, think of a piece of chalk. When dropped, gravity will make it accelerate to the ground almost as fast as in vacuum, but when chalk powder is blown out of an eraser it will spread out in a cloud. On the length scale of motor proteins Brownian motion plays an important role, the protein gets random kicks from the molecules of the surrounding medium and the motion will turn out to be not entirely deterministic. Normally noise is thought of as something undesirable; something to filter away, to get rid of or minimize. But in the operating principles that we will describe the Brownian noise will turn out to be essential.

Researchers have already studied systems in different contexts where more noise means a better signal to noise ratio (SNR). The phenomenon has become known under the name "stochastic resonance". The following example is meant to briefly explain stochastic resonance. For a more thorough treatment the reader is referred to the reference by McNamara and Wiesenfeld. Consider the double well in figure 1 as a reaction coordinate for a chemical reaction. The left well corresponds to a species *A* and the right well corresponds to a species *B*. Thermal fluctuations can drive a molecule from *A* to

B or B to A , but when the two wells have the same energy level there will in the long run be a 50-50 distribution in the occupation of the wells. Next we start oscillating the energy difference between the wells, but in such a way that the energy level of both wells will still never exceed the level of the barrier between the wells. As the response of the system we could take the the integral:

$$\text{Signal} = \frac{\omega}{2\pi} \int_0^{\frac{2\pi}{\omega}} J^2 dt \quad (1)$$

where J denotes the flow over the barrier. After calculating the number of noisy, "accidental", Brownian crossings the SNR can be determined. It is not difficult to understand that no signal will occur at zero temperature (i.e. in the absence of thermal noise), the central barrier can never be "taken" in that case and we have $J = 0$. At $T \rightarrow \infty$ the energy profile of the double well is negligible in comparison to kT and all the motion of the molecules will be Brownian. The SNR is therefore a nonmonotonic function of the temperature T . At some temperature T^* the SNR is maximal and, though it is counterintuitive, from $T = 0$ to $T = T^*$ we have a situation where the SNR increases as we increase the amount of noise in the system.

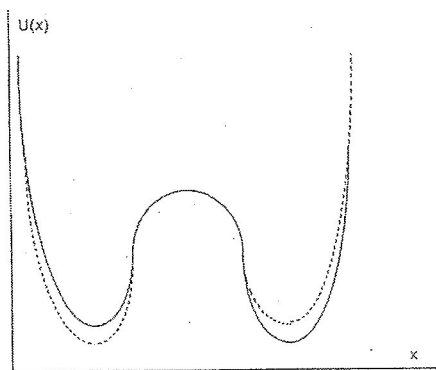


Fig. 1. The oscillating double well. The profile oscillates between the dotted and the solid line. The average energy difference between the wells is zero. The flow over the barrier in response to the oscillation depends nonmonotonically on the temperature.

Next we return to motor proteins and consider figure 2. The figure depicts one period of the biopolymer. The common currency for energy in a living cell is ATP (adenosine triphosphate). The energy that is released when ATP is converted into ADP (adenosine diphosphate) and one inorganic phosphate molecule can be used for the processes that sustain life. On the biopolymer

in figure 2 the reaction rates that rule the $\text{ATP} \rightarrow \text{ADP}$ reaction vary within a period. We will show how this can lead to net transport in a thermodynamically consistent way. Region (i) is where the affinity for binding ATP is largest. ATP is negatively charged and because there is a negative charge at the beginning of region (i) it is impossible for the motor protein to go back to the period to the left after binding ATP. This effectively places a reflecting barrier at the beginning of the period. Through Brownian motion the motor protein will thus inevitably cross region (ii), where neither binding of ATP nor release of ADP is likely, and come to region (iii). In region (iii) the rate for ADP release is large. After such release the passage to the next period is possible and the cycle can start again.

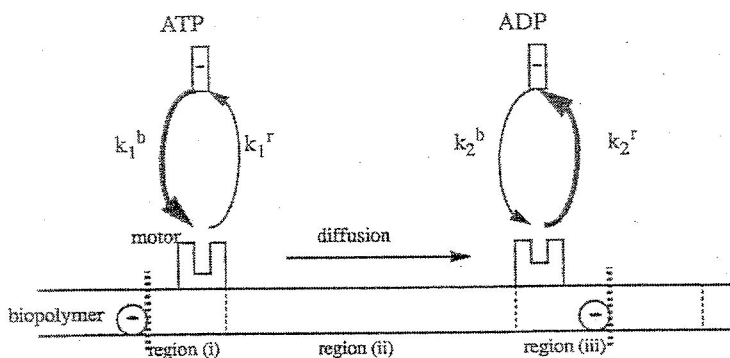


Fig. 2. Our model for a motor protein. One period of the biopolymer is depicted. ATP binding occurs at the beginning of the period (region (i)) and makes backstepping impossible. Through diffusion the protein ends up at the right end of the period (region (iii)), where it releases ADP and moves on to the next period. It is explained in the text how the ATP-ADP chemical gradient is necessary to get net motion.

Suppose that G_{ATP} is the total amount of energy that is released in ATP hydrolysis. G_{ATP} is determined solely by the ratio of the concentrations: $[\text{ATP}]/[\text{ADP}]$. In living cells this ratio is usually about 1 and G_{ATP} is about $20 kT$. G_{ATP} consists of an energy G_1 for ATP binding and an energy G_2 for ADP release. We have the following equations:

$$G_{ATP} = G_1 + G_2 \quad (2)$$

$$\frac{k_1^b[\text{ATP}]}{k_1^r} = \exp\left(\frac{G_1}{kT}\right) \quad (3)$$

and

$$\frac{k_2^r}{k_2^b[\text{ADP}]} = \exp\left(\frac{G_2}{kT}\right) \quad (4)$$

where k_1^b and k_1^r are the reaction rate constants for ATP binding and release and k_2^r and k_2^b are the reaction rate constants for ADP release and binding. G_1 and G_2 are fixed so k_1^b/k_1^r and k_2^r/k_2^b have to be the same all along the biopolymer. But this still leaves a degree of freedom in the sense that the ratios stay the same when the k_1 's are multiplied with C_1 and the k_2 's are multiplied C_2 . We can thus, in region (i), make both the k_1 's very large and make both k_2 's very small. This means that ATP will bind rapidly, but the protein will move to region (ii) before ADP release can occur. In region (ii) all the k_1 's and k_2 's are very small so no chemical conversion takes place. In region (iii) the k_2 's are large and the k_1 's are small, so ADP release will occur but there will be no binding of a new ATP. Staying unbound for a while enables passage to the next period. That C_1 and C_2 vary within one period of the biopolymer is not unlikely and corresponds chemically to larger or smaller reachability of binding sites.

The most efficient way of moving in the above scheme would be if G_1 and G_2 are very large and region (ii) is much longer than region (i) and (iii). This is because the probability for slip (i.e. the turnover of an ATP without passage into the a period) goes down as the length of region (ii) increases. In the limit when the length of region (ii) approaches L , this probability approaches zero. The average time to diffuse from a reflecting barrier to an absorbing barrier at a distance L is $L^2/(2D)$, where D represents the diffusion rate. This means a speed of $2D/L$ for the motor. Notice that taking a smaller period L leads to a higher speed, but that the ATP turnover rate to maintain such a speed goes up quadratically with L . Very accurate measurements have been performed on a motor protein named "kinesin" as it moves along microtubule (Svoboda et al. 1993). Microtubule has a period of 8 nm. At saturating ATP concentration Svoboda et al. observed a speed of 500 nm/sec and a stopping force of 5 pN. A force of 5 pN translates into about 9 kT per period. When the diffusion is not on a flat surface but up a 9 kT ramp it takes about 200 times as long to pass from one period to the next (methods to calculate this are shown in, for instance, the reference (Gardiner, 1985)), which would indeed look like an almost complete standstill. With a diffusion coefficient of $2.0 \cdot 10^{-15} \text{ m}^2/\text{sec}$ our model gives 500 nm/sec for the speed and 60 ATP turnovers per second. Such a value for the diffusion coefficient is realistic, it is, for instance, about an order of magnitude smaller than that for a protein diffusing in a lipid bilayer cell membrane. We assumed a charge distribution such that there is a reflecting barrier at the left end of the period and an absorbing barrier at the right end of the period. It is likely that evolution has created charge distributions more complicated than that to lead to higher speeds and greater efficiency. Also the diffusion coefficient is unlikely to be constant within a period. The most serious shortcoming of our model is that it predicts a smooth drift in one direction, whereas what is observed is the motor protein taking 8 nm steps and standing still for a while between these steps (Svoboda et al. 1993).

It follows very nicely from our model that without an ATP - ADP chemical gradient the motor protein comes to a standstill. When ATP and ADP are in chemical equilibrium we have $G_1 = 0$ and $G_2 = 0$. From (3) and (4) we then derive $k_1^b[ATP] = k_1^r$, which means that ATP is going to be bound half the time in region (i), and $k_2^b[ATP] = k_2^r$, which means that ADP is going to be bound half the time in region (iii). Region (i) and region (iii) do now have a perfect mirror symmetry around the passage point, there is no longer a reflective and an absorbing boundary and no net flux can occur.

At $T = 0$ our motor comes to a standstill because no random motion along the biopolymer will occur. At $T \rightarrow \infty$ our motor comes to a standstill, because a large kT obliterates the chemical gradient. Taking T to be large has the same effect as letting G_1 and G_2 be zero and leads to $k_1^b[ATP] = k_1^r$ and $k_2^b[ADP] = k_2^r$. Like with stochastic resonance there is a finite temperature at which the engine functions optimally.

Our model is essentially a ratchet mechanism, i.e. motion is allowed in one direction and blocked in the opposite direction. In our case the motion is Brownian. The ratcheting of Brownian motion has led to challenging paradoxes. Like most paradoxes these ones come about at the interface of two branches of physics. In this case macroscopic, deterministic, Newtonian mechanics and microscopic, stochastic, Brownian mechanics. Figure 3 is from reference by Feynman (1966) and depicts what is known as "Feynman's ratchet". The left reservoir contains a mechanical device that is similar to one that is found in Sears screwdrivers. 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 peddles in the left reservoir can be moved by the random collisions of the molecules of the medium. Motion in the allowed direction will result and we can in principle pull up a little insect. 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 at the pawl 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 $(T_1 - T_2)/T_1$. In the same way that Feynman's device needs a thermal gradient in order to get functioning reflecting and absorbing boundaries for the Brownian motion our motor protein needs a chemical gradient.

Of a somewhat similar nature is Maxwell's demon. Figure 4 is from the

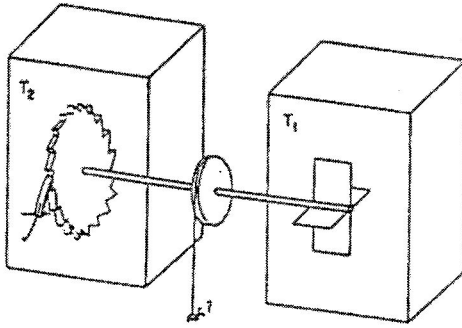


Fig. 3. The thermal ratchet paradox from the reference by Feynman. The device is small enough so the peddles in the right reservoir are moved by collisions of the molecules from the surrounding medium. The ratchet and pawl in the left reservoir block motion in one direction and allow it in the other. Thus, in violation of the Second Law, work can be extracted from thermal fluctuations to lift a little insect. The resolution of the paradox and how it relates to motor proteins is discussed in the text.

introduction in the reference by Leff and Rex (1990). A little “demon” controls a weightless, frictionless gate. The demon observes the molecules that are heading for the gate and opens and closes the gate in response to what he sees. In one direction slow molecules are blocked and fast molecules are allowed to pass and in the opposite direction fast molecules are blocked and only slow ones are let pass. This would result in a temperature difference between the reservoirs. Whereas the demon is doing no work, the ensuing temperature difference could in principle be employed to perform work. Lively discussions are still going on about a way to resolve this paradox (Leff and Rex 1990). Our motor resembles Maxwell’s demon in the sense that it exhibits some rudimentary form of intelligence: it “reads” a situation (whether the protein is in region (i), (ii) or (iii)) and adjusts its behavior (binding and unbinding) accordingly so as to bring about a specific result (forward motion). But unlike Maxwell’s demon, our “intelligence ratchet” requires energy.

The experimental data that are rapidly coming available now on motor proteins have sparked increasing interest in the operating mechanism for motor proteins. A variety of models has been proposed for motor proteins (Magnasco 1993, Astumian and Bier 1994, Peskin et al. 1994). Most of the models are more sophisticated than the one I presented above and concurrently lead to more involved mathematics. Models that take the Brownian nature of the system into account invariably rely on the biasing (blocking motion in one direction and allowing it in the opposite) of Brownian motion that can occur when an external energy dissipating fluctuation (like binding ATP and releasing ADP) is imposed on the system. The above was presented only to

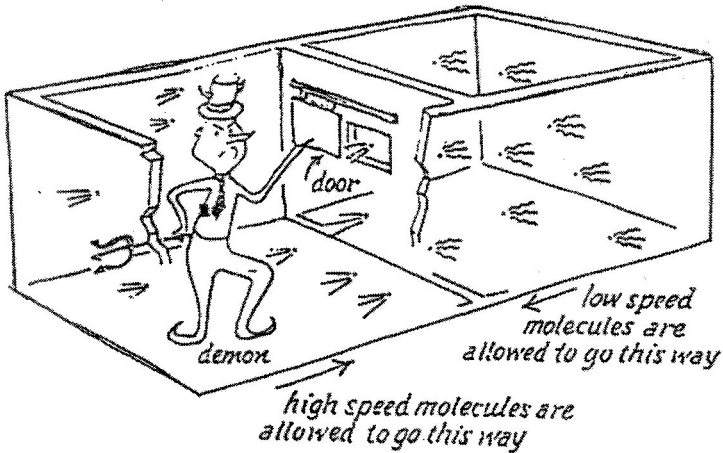


Fig. 4. Maxwell's Demon. From the reference by Leff and Rex (1990). The demon controls a frictionless, weightless gate between two reservoirs. He observes the speed of the approaching molecules and opens and closes the gate so as to get a temperature gradient between the left and right reservoir without any apparent energy input. Our motor protein resembles Maxwell's demon, but it needs energy to observe and select and is thermodynamically sound (see text).

bring out some of the basic features of a consistent model at the interface of microscopic and macroscopic physics.

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