MOTOR PROTEINS — MECHANOCHEMICAL ENERGY TRANSDUCTION ON THE MICROSCOPIC SCALE*

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(Received November 11, 2000)

Motor proteins are individual molecules that hydrolyze ATP and use the released energy to move forward along a polymer. These microscopic engines operate in an overdamped regime where Brownian motion is a nonegligible contribution to the physics. We provide a new definition for the efficiency of an engine in the overdamped Brownian realm and discuss how a high efficiency can be reached.

PACS numbers: 05.40.–a, 82.40.–g, 87.15.–v

The first living cells to appear in the course of evolution were the prokaryotes. Bacteria, for instance, are all prokaryotes. The prokaryotic cells are generally only a few micrometers big and all intracellular activity is taking place in the aqueous solution enclosed by the cell membrane. Intracellular transport is taken care of by diffusion. A chemical that is produced on one side of the cell is homogeneously distributed within milliseconds.

Next the algae appeared and finally eukaryotic cells evolved. Multicellular organisms are made up of eukaryotic cells. Eukaryotic cells are around an order of magnitude larger than prokaryotic cells. Furthermore, the eukaryotes have different membrane enclosed organelles within the cell.

Logistic problems arise in large eukaryotes. First there is a problem of quantity: when a cell is ten times as large in all directions a fixed amount of any chemical will eventually be diluted to a concentration that is 1000 times as small. Secondly, there is a transport time problem: diffusion in one dimension is ruled by the equation $\langle x^2 \rangle = 2Dt$. So, if the distance is increased by a factor 10, the time to cover this distance through diffusion is increased by a factor 100.

* Presented at the XXIV International School of Theoretical Physics "Transport Phenomena from Quantum to Classical Regimes", Ustroń, Poland, September 25–October 1, 2000.

Evolution has come up with a solution to these problems. Eukaryotic cells generally have a cytoskeleton, *i.e.* a polymer (microtubule) network that goes through all of the cell. The cytoskeleton provides structural reinforcement, but it is also used as a kind of railroad system. Chemicals that are needed on a location different from where they are produced are packed into a vesicle. The vesicle is then hooked up to a motor protein. Next the motor protein "walks" along the cytoskeletal network and drags the vesicle to its destination. The motor protein catalyzes the hydrolysis of ATP (adenosine triphosphate) and uses some of the released energy of the catalyzed reaction to power itself forward along the biopolymer.

Over the past couple of years a large amount of experimental data has been obtained on motor proteins. With nanotechnological devices, like optical tweezers, it is possible to follow individual molecules and manipulate them [1]. There is no consensus yet about how the action of a motor protein should be looked at and modelled. One could, for instance, legitimately argue that there is no real distinction between chemical energy and kinetic energy on the level of one particular protein. The argument goes as follows. When ATP binds to the protein an internal repositioning of atoms within the protein occurs. ATP hydrolysis involves a number of subsequent conformational changes and after the release of ADP (adenosine diphosphate) and an inorganic phosphate molecule the motor protein returns to its original state. In other words, the protein makes an oscillatory motion which is converted into a forward motion along the polymer to which it is connected. Seen in this way the motor protein is more like a gear; it is like the crank-shaft mechanism in a car that converts the up and down motion of the pistons into the rotation of the crank axle (which is 100% efficient). The motor protein differs from the crank-shaft transmission in that it operates in an environment with Brownian noise and no inertia.

When the efficiency of an engine is discussed, theorists usually assess the efficiency of converting energy from one storable form to another. Many authors have thus estimated the efficiency of a motor protein in models where the chemical energy is used to move the motor protein against a force in a conservative field. Such models, however, do not represent what is really going on. A motor protein faces a task, and that task is to transport a vesicle over a distance l in a time τ in an overdamped medium. On the nanometer scale inertia is negligible in comparison to friction. So all of the energy of ATP hydrolysis is used to "fight" friction. The friction at any moment is directly proportional to the speed v, *i.e.* $F_{\mathrm{fr}} = \gamma v$.

Moving over a distance l in time τ in an overdamped medium is done with least dissipation of energy when a constant speed is maintained. The proof of this is simple. The dissipated energy equals:

$$E_{\mathrm{diss}} = \int_0^l F_{\mathrm{fr}}\, dx = \gamma \int_0^l \dot{x}\, dx = \gamma \int_0^\tau \dot{x}^2\, dt\,. \tag{1}$$

The Euler–Lagrange formula tells us that the integral $\int L(x,\dot{x},t)\, dt$ has a minimum for a trajectory that satisfies $(\partial_x - \frac{d}{dt}\partial_{\dot{x}})L = 0$. Applying this to (1) leads to $\frac{d}{dt}\dot{x} = 0$, *i.e.* constant speed. Suppose the aim would have been to move in time τ over distance l and convert chemical energy into potential energy by moving against a constant force F_{cons} due to a conservative field. In that case the energy necessary to bring the particle uphill would have been $E = \int_0^l F_{\mathrm{cons}}\, dx = F_{\mathrm{cons}} \int_0^\tau \dot{x}\, dt$. With $L = \dot{x}$ we find that the Euler–Lagrange differential equation give zero for every trajectory that leads from $x = 0$ to $x = l$ in time τ. In [2] we propose the following new definition of the efficiency: the efficiency of an engine is $\eta = E_{\mathrm{out}}/E_{\mathrm{in}}$, where E_{in} is the energy input and E_{out} is the minimum amount of energy necessary to accomplish the task of the engine.

As an example consider a bicycle racer. Suppose that in order to qualify for participation in a championship the racer faces the task of doing a 40 km time trial on a flat course without wind within one hour. On a flat course almost all of the energy goes into overcoming air resistance. The most efficient way of accomplishing the task is to keep a speed of 40 km/h all the way. If he rides 41 km/h for half an hour and 39 km/h for the other half hour, he accomplishes his task, but according to our definition he has already lost 5% ($\frac{1}{2}(41^2 - 39^2)/40^2$) in efficiency by spending 1.05 times the minimum necessary amount of energy. Eventually this loss comes on top of the loss that occurs in the conversion from chemical to mechanical energy. For conversion between storable forms of energy our definition reduces to the traditional notion of efficiency. This case would occur if the cyclist would do a 15 km time trial up a 10% slope and again with the task of doing it within an hour. On such a steep incline only a negligible fraction of the energy is invested in fighting air resistance and almost all of the energy goes into overcoming gravity and effectively creating (storing!) potential energy. In this case the cyclist can accelerate and decelerate around his 15 km/h average without spending extra energy and losing efficiency.

Next we will take a simple model of a motor protein and assess the efficiency with the above definition. In Fig. 1 the shaded segment of the biopolymer is accessible to the motor protein only when ATP is unbound. The blank segment is accessible when ATP is bound. In between there are

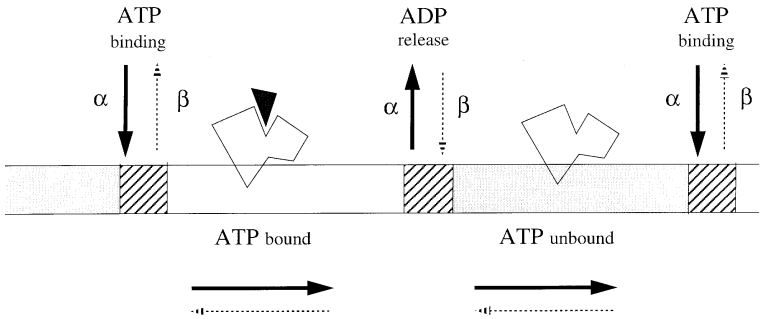

Fig. 1. A simple model to show how a motor protein can transduce chemical energy to mechanical energy with the "help" of diffusion. The shaded segment of the biopolymer is accessible to the motor protein only when ATP is unbound. The blank segment is accessible when ATP is bound. In between there are narrow "transition segments" for ATP binding/release and ADP binding/release, respectively. In the presence of an ATP–ADP chemical gradient the motor protein will move forward as ATP is converted into ADP.

narrow "transition segments." There is one transition segment where ATP can bind or release and another one where ADP can bind or release. Note that the biopolymer has an anisotropy, *i.e.*, it reads differently from left to right than it reads from right to left. The forward moving motor is very much like a Maxwell's Demon in the sense that it really "reads" its position on the biopolymer and adjusts its binding and release behavior accordingly. But the motor protein in this model needs an ATP–ADP chemical potential, *i.e.*, an input of energy, in order to move forward. With a high ATP–ADP chemical potential, release of ATP is very unlikely. So when the motor protein comes from the shaded segment into the ATP binding/release segment it will bind ATP and move forward as if a reflecting barrier were erected behind it. A similar process occurs in the next transition area with the ADP release (where ADP binding is very unlikely). If ATP and ADP are in chemical equilibrium, binding and release are equally likely in both the ATP and the ADP "transition segment" and the motor protein would freely diffuse with an equal likelihood in either direction on each segment.

Fig. 2 shows how this setup can be conceived of as two states, one state where the ATP is bound and another one for ATP unbound. The half of the period that is accessible in one state is inaccessible in the other state. At the reflecting barriers the chemical turnovers take place with transition rates α and β. We assume that the energy ΔG of ATP hydrolysis is equally

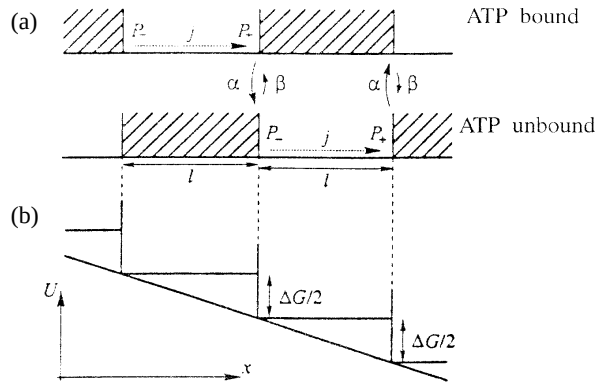

Fig. 2. (a) The model of Fig. 1 cast into a form in which speed and efficiency can be easily evaluated. Only the blank regions are accessible to the protein. At the reflecting barriers chemical transitions occur which bring the protein from one potential (*i.e.* conformational state) to the other. (b) The behavior of this system is like a diffusive descent down a staircase. The vertical "jumps" correspond to the energy releasing chemical transitions. The horizontal segments have to be crossed diffusively.

distributed over the ATP binding and the ADP release:

$$\frac{\alpha}{\beta} = \exp\left[-\frac{1}{2}\Delta G\right] , \tag{2}$$

where ΔG is in kT units. We set the probability density of the protein to be P_- at the right end of the accessible interval and P_+ at the left end of the accessible interval. We then have for the flux j:

$$j = \alpha P_- - \beta P_+ . \tag{3}$$

For a stationary state the horizontal flux on each of the accessible intervals should be the same as the vertical flux between the states. The horizontal flux in each of the segments of length l is governed by Fick's Law, *i.e.*

$$j = \frac{D(P_+ - P-)}{l} , \tag{4}$$

where D is the diffusion coefficient. Finally there is the normalization. One period has length $2l$. In each of the accessible intervals there is a linear decrease of probability along the horizontal axis. The average probability density on a period is therefore $\frac{1}{2}(P_+ + P_-)$. One motor protein per period then boils down to:

$$l(P_+ + P_-) = 1 . \tag{5}$$

Eliminating P_+ and P_- we express j in terms of the system's parameters:

$$j = \frac{D}{l} \, \frac{\alpha - \beta}{2D + (\alpha + \beta)l} \, . \tag{6}$$

For $D/l \ll (\alpha + \beta)$, *i.e.* chemical transitions that are fast relative to the diffusion, we get:

$$j \approx \frac{D}{l^2} \frac{\alpha - \beta}{\alpha + \beta} = \frac{D}{l^2} \tanh\left(\frac{1}{4}\Delta G\right) . \tag{7}$$

For the last step we used (2). With one motor protein per period the power input equals $P_{\text{in}} = j\Delta G$. The average speed of each motor protein is $2lj$ and this results in an effective power dissipation of $P_{\text{out}} = \gamma(2lj)^2$. Taking the ratio and using the fluctuation–dissipation theorem, $\gamma D = 1$ as $kT = 1$, we derive the efficiency:

$$\eta = \frac{P_{\text{out}}}{P_{\text{in}}} = \frac{4\gamma l j}{\Delta G} \approx \frac{\tanh\left(\frac{1}{4}\Delta G\right)}{\frac{1}{4}\Delta G} . \tag{8}$$

We observe that only for $\Delta G \to 0$ can the efficiency approach unity. But it is obvious that the flux j itself also goes to zero in this case. So only when the process takes place infinitesimally close to equilibrium does the efficiency approach unity.

The left to right flow is basically a diffusive descent down a staircase. Every chemical transition corresponds to a downward jump of $\frac{1}{2}\Delta G$. The flat stretches have to be crossed diffusively. It is obvious that at zero temperature, without Brownian motion, the system comes to a standstill. The energy transduction is more efficient if the staircase is more resemblant of a smooth slope. If instead of two steps of $\frac{1}{2}\Delta G$, there were n steps of $\frac{1}{n}\Delta G$ in the catalytic cycle with $nl = 1$, the result would have been:

$$\eta \approx \frac{\tanh\left(\frac{1}{2n}\Delta G\right)}{\frac{1}{2n}\Delta G} , \tag{9}$$

i.e., a greater efficiency as the argument $\frac{1}{2n}\Delta G$ becomes smaller when n gets larger. It should be kept in mind, however, that one cannot make the flat segments arbitrarily small. That would lead to a violation of the $D/l \ll (\alpha + \beta)$ condition that was used for our approximation.

Making the number of steps larger to get a better efficiency is actually something that nature has done. Most biological transductions and conversions occur in many steps [3]. It has been shown that the hydrolysis of ATP by the motor protein *kinesin* involves at least ten individual steps [4]. Most

elementary textbooks on thermodynamics show that also the Carnot engine is optimally efficient when it is operated adiabatically, *i.e.*, all changes are imposed slowly and reversibly such that the system is at all times in equilibrium with its surroundings. In a recent paper by Parrondo [5] the enhanced efficiency for a higher number of smaller steps is derived in a more abstract way for a more general case.

One may argue that even if a Brownian particle is pulled through a fluid by a constant force, it will nevertheless be kicked around by molecules of the medium. Therefore such a molecule is bound to be like the inefficient bicycle racer that covers his flat time trial with varying speeds. But this argument is wrong. The variations in the speed are due to fluctuations coming from the medium. The energy for these fluctuations comes from the medium and the same amount of energy is dissipated back into the medium. Next we will show this rigorously using the Langevin equation. For greater generality we will include inertia.

At any time the pulled Brownian particle has a velocity $V + v$, where V is the drift speed (due to the operation of the engine) and v represents the zero average ($\langle v \rangle = 0$) fluctuations due to Brownian kicks. In its full generality the Langevin equation is:

$$m(\dot{V} + \dot{v}) = \gamma(v + V) + F + \gamma\sqrt{2D}\ \xi(t)\,, \tag{10}$$

where F represents a constant external force. If we multiply each term in the equation with v and next average over a long time, then we obtain for each term the amount of power (energy per unit of time) it exchanges with the "Brownian bath". V is constant in time so $\dot{V} = 0$. Furthermore $\gamma V\langle v \rangle = 0$ and $F\langle v \rangle = 0$ because $\langle v \rangle = 0$. We also have $m\langle v\dot{v} \rangle = \frac{d}{dt}\frac{1}{2}m\langle v^2 \rangle$. The term $\frac{1}{2}m\langle v^2 \rangle$ represents the average kinetic energy of the Brownian particle due to Brownian motion. This equals $\frac{1}{2}kT$ and is constant. Therefore, $\frac{d}{dt}\frac{1}{2}m\langle v^2 \rangle = 0$. So all that remains of the equation is:

$$\gamma\langle v^2 \rangle = \gamma\sqrt{2D}\langle \xi\ v \rangle, . \tag{11}$$

What we basically have here is an energy formulation of the fluctuation–dissipation theorem. The right hand side is the amount of power that our Brownian particle absorbs from the fluctuations in the bath. The left hand side is the amount of Brownian-fluctuations-power that it dissipates back into the bath again. These amounts are equal. It is interesting to note that in a simulation with a discrete Δt the function $\xi(t_i)$ at the i-th timestep is $\xi(t_i) = \theta(i)/\sqrt{\Delta t}$, where $\theta(i)$ is a random number drawn from a Gaussian distribution with a zero average and a variance of one. So with an infinitesimally small timestep, *i.e.* $\Delta t \to 0$, the amplitude of the "kicks" and

the resulting v will become infinite. No contradiction arises for the displacement. In the absence of inertia and with $F = 0$ we get $\Delta x = \sqrt{2D}\,\theta(i)\,\sqrt{\Delta t}$, which goes to zero for $\Delta t \to 0$. What the infinite v means is that for noise that is really "white", *i.e.* uncorrelated at any timescale, an infinite amount of energy goes from the bath into the particle and back into the bath again during any arbitrarily small time interval.

A particle that moves with velocity $v+V$ dissipates $\gamma\langle(v+V)^2\rangle$ of power into the bath. From the fluctuations it receives $\gamma\sqrt{2D}\langle\xi\ (v+V)\rangle$. After working out the averages and using (11) one derives that γV^2 is the difference between what is "dissipated out" and "fluctuated in." This γV^2 is the power that comes from the engine and, as such, the power that is responsible for the drift speed V.

The second law of thermodynamics prohibits the use of Brownian fluctuations for doing work. So the Brownian fluctuations cannot add to the power output of an engine. The above results show that Brownian fluctuations also cannot subtract from the power output. Even though Brownian engines may rely on the presence of thermal noise to deliver any power at all, that noise is of no consequence for the final bookkeeping of incoming and outgoing energy.

None of this work would have been possible, had it not been for the input of Dean Astumian and Imre Derenyi.

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