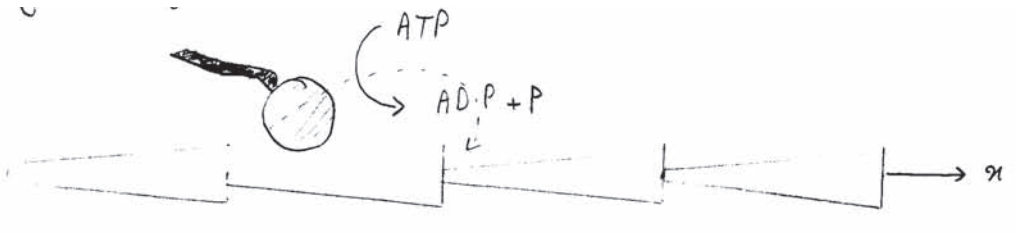
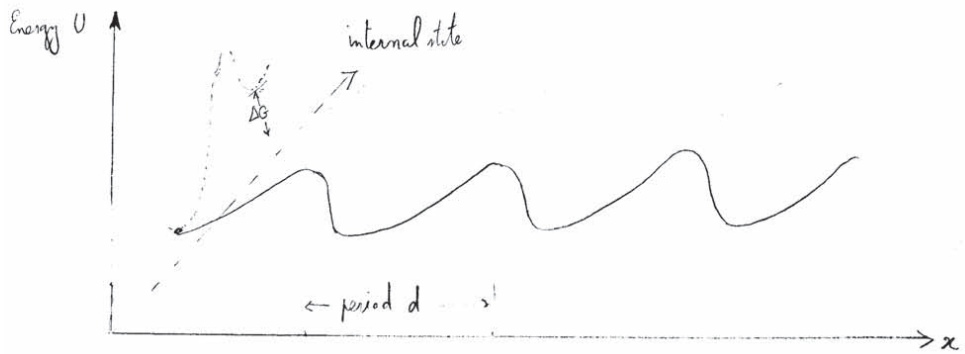
3.2 Molecular Motors

A variety of cellular processes requiring mechanical work, such as movement, transport and packaging material, are performed with the aid of *protein motors*. These molecules consume fuel, typically from conversion of ATP to ADP, to generate force and motion. Unlike macroscopic engines which proceed deterministically through a cycle, the tiny molecular machines are constantly agitated by thermal fluctuations and their operation is inherently stochastic. There are two common elements to most molecular motors:

• An *asymmetry* that determines the direction of motion. In the case of *myosin* this is provided by the polarity of actin filaments along which it moves, e.g. in contracting muscles. *Kinesin* and *dynein* are two motors that transport cargo along microtubules (MTs), but in opposite directions; kinesin moving to the (+) end, and dynein towards the (-) end.

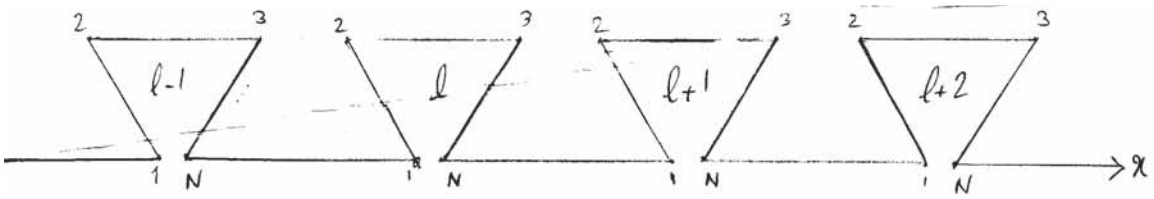


• The asymmetry encountered by motors is reminiscent of ratchets: The motor experiences a periodic but asymmetric potential along its track. However, it is well known that *Brownian ratchets* cannot extract energy from thermal fluctuations, unless an energy consuming mechanism is employed to rectify motion in a ratchet potential. A general scheme is for the motor to have a number of internal states, e.g. bound to ATP or ADP, each of which experiences a different ratchet potential. As we shall see, moving between the internal states enables trapping and rectifying the fluctuations. A typical step size for kinesin along a MT is $a \approx 8.2$nm, and the energy released by hydrolysis of one ATP molecule in physiological conditions is about $\Delta G_h = 12 k_B T$. Assuming the energy released by hydrolysis of a single ATP is completely used up leads to a maximal possible force of $F_{\max} = \Delta G_h / a \approx 6.2$ pN.



3.2.1 Asymmetric Hopping

Rather than working with a continuous ratchet potential, we can capture much of the same physics by examining so called asymmetric hopping models,[3] in which the motor makes discrete jumps along its track. However, at each site along the track, it can be in a discrete number of internal states. For example, in the system depicted below, there are 4 internal states at each site, e.g. corresponding to: MT, MT+ATP, MT+ADP+P, MT+ADP. One



then assigns rates for transitions along the track and between internal states. With proper choice of asymmetric rates the motion can be biased in one direction.

Let us demonstrate the procedure and the constraints involved for a simple model with only two internal states, say representing the motor bound to ATP or ADP. We shall denote the rates for transitions between the two internal states by u and d. As the motor moves to the next site along the track it must change its internal state, and we assign asymmetric rates of r and l for moving to the right (T→D) and the left (D→T) respectively. The Master equations governing the evolution of probabilities for these states are

$$\begin{aligned} \frac{dp_D(n,t)}{dt} &= rp_T(n-1) + dp_T(n) - (u+l)p_D(n) \\ \frac{dp_T(n,t)}{dt} &= lp_D(n+1) + up_D(n) - (d+r)p_T(n)\,. \end{aligned} \tag{3.23}$$

For slowly varying probabilities, the continuum form of these equations is

$$\begin{aligned} \frac{\partial p_D(x,t)}{\partial t} &= (r+d)p_T(x) - (u+l)p_D(x) - ar\frac{\partial}{\partial x}p_T(x,t) + \frac{a^2r}{2}\frac{\partial^2}{\partial x^2}p_T(x,t) \\ \frac{\partial p_T(x,t)}{\partial t} &= (l+u)p_D(n) - (d+r)p_T(n) + al\frac{\partial}{\partial x}p_D(x,t) + \frac{a^2l}{2}\frac{\partial^2}{\partial x^2}p_D(x,t)\,. \end{aligned} \tag{3.24}$$

We can extract the behavior of the above equations for slow and long wavelength variations by first noting that (relatively) rapid interconversion between internal states leads to a local equilibrium in which

$$(r+d)p_T(x) = (u+l)p_D(x)\,, \tag{3.25}$$

or in terms of the net probability, $p(x) = p_T(x) + p_D(x)$,

$$p_T(x) = \frac{u+l}{u+d+r+l}\,p(x) \qquad \text{and} \qquad p_D(x) = \frac{d+r}{u+d+r+l}\,p(x)\,. \tag{3.26}$$

[3] M.E. Fisher and A.B. Kolomeisky, PNAS **96**, 6597 (1999).

Adding the two Eqs (3.24) and substituting from Eq. (3.26) leads to a standard drift-diffusion equation for $p(x,t)$, with drift velocity

$$v = a\,\frac{ru - ld}{u + d + r + l}\,, \tag{3.27}$$

and diffusion coefficient

$$D = \frac{a^2}{2}\,\frac{ru + ld + 2lr}{u + d + r + l}\,. \tag{3.28}$$

The requirement of thermal equilibrium places stringent constraints on any pair of forward/backward reaction rates. In particular, assuming an activation energy ΔU_a between internal states, and an energy difference ΔU_a for the steps along the track, we must have

$$\frac{u}{d} = e^{-\beta \Delta U_a} \quad \text{and} \quad \frac{l}{r} = e^{-\beta \Delta U_s}\,. \tag{3.29}$$

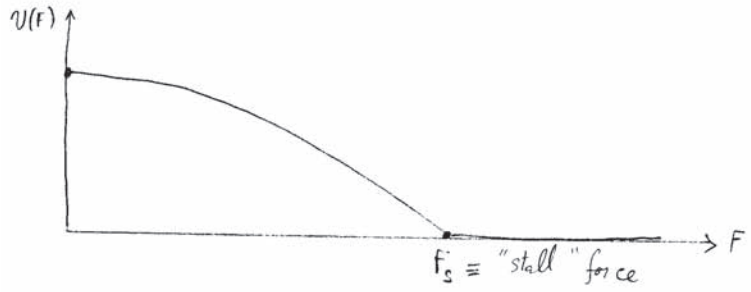
Substituting these forms in the equation for velocity, we find

$$v = a\,\frac{lu}{u + d + r + l}\left(e^{\beta \Delta U_s} - e^{\beta \Delta U_a}\right)\,. \tag{3.30}$$

When there is no input of energy, the two paths to go between T and D states should be equivalent, $\Delta_a = \Delta_s$, and there is no net velocity. The hydrolysis of ATP provides a source of energy, such that $\Delta U_s = \Delta U_a + \Delta G_h$, encouraging steps to the right and a positive velocity.

3.2.2 Force of a Brownian Motor

To find out how efficiently the energy input from ATP is converted to work, we need to know the force exerted by the motor in traveling a distance a at each step. This is not an easy task as it is not possible to directly measure all dissipative and other forces acting on the small molecule. The following procedures have been used to estimate forces on the motor.



The stall force is obtained by pulling the motor back with an optical tweezer. The motor must now also climb up against the potential from the external force F, resulting in

$$\frac{r}{l} = e^{\beta(\Delta U_s - Fa)} \quad \text{and} \quad v = a\,\frac{lu}{u + d + r + l}\left(e^{\beta(\Delta U_a + \Delta G_h - Fa)} - e^{\beta(\Delta U_a)}\right)\,. \tag{3.31}$$

Clearly the motor stalls ($v = 0$) when $F = F_s = F_{\max} = \Delta G_h/a$. This makes sense, as there are no dissipative forces acting on a stationary motor.

The Einstein force is obtained by analogy to Brownian particles from a ratio of velocity and diffusion coefficients. A particle in solution experiences a drag force proportional to its velocity, such that $v = \mu F$ where μ is its *mobility*. In the absence of an external force, the particle diffuses in solution with diffusion constant D. Diffusion originates in collisions with thermally excited atoms in the fluid, and to ensure proper thermal equilibrium the mobility and diffusion constant must be related by the *Einstein relation*, $D = \mu k_B T$. From these relations we can define an Einstein force

$$F_E = k_B T \frac{v}{D} = \frac{2k_B T}{a} \frac{ru - ld}{ru + ld + 2lr} = \frac{2k_B T}{a} \frac{\frac{ru}{ld} - 1}{\frac{ru}{ld} + 1 + 2\frac{r}{d}}\,, \tag{3.32}$$

where we have used the values for drift and diffusion of the motor along its track from the two-state hopping model. Since $(ru)/(ld) = e^{\beta \Delta G_h}$, in the limit $\beta \Delta G_h \to 0$

$$F_E \approx \frac{F_{\max}}{1 + r/d}\,,$$

while for $\beta \Delta G_h \gg 1$, $F_E \approx 2k_B T/a$. Thus the Einstein force is always less than the maximum possible force, and limited by thermal fluctuations.

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