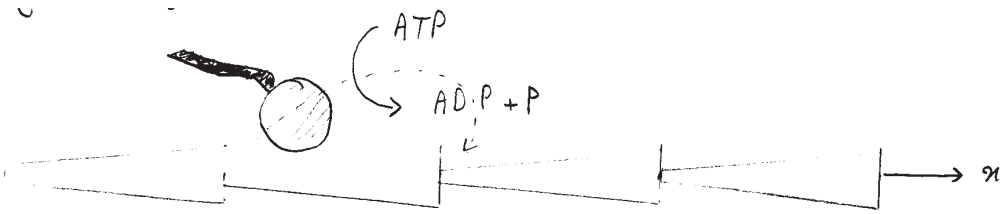
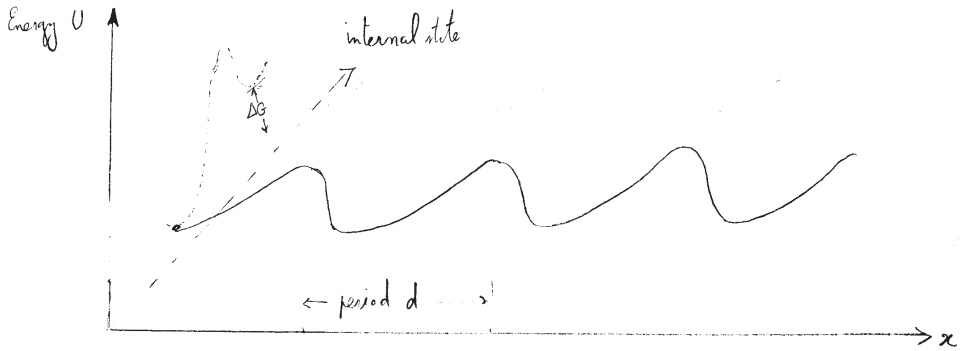
3.2 Molecular Motors

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. In equilibrium there is no directed motion despite asymmetry, and an energy consuming mechanism is needed to rectify motion in a ratchet potential. A general scheme is for the motor to have a number of internal

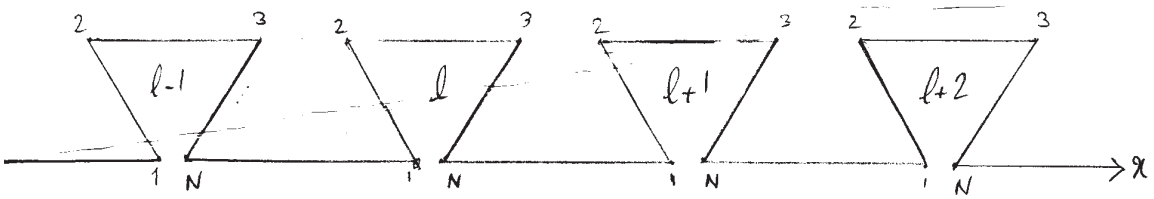


states, e.g. bound to ATP or ADP, each of which experiences a different ratchet potential. As we shall see, moving between the internal states enables trapping and rectifying the fluctuations. We can get a rough estimate of the forces generated by molecular motors as follows: A typical step size for kinesin along a MT is $a \approx 8.2$nm, and the energy released by hydrolysis of one ATP molecule in physilogical conditions is about $\Delta G_h = 12 k_B T$. Assuming

the energy released by hydrolysis of a single ATP is completely used up without any loss, to move an object against a uniform force F, leads to a maximal possible force of $F_{\rm max} = \Delta G_h/a \approx 6.2$ 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 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 appropriate 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. Let us assume that the ADP bound state does not bind too strongly to the microtubule, whilet the ATP bound state is strongly attached to its site, and does not hop. We shall denote the rates for transitions from ADP to and from ATP bound states at the same site by u and d, respectively. Asymmetry is introduced into the model, by allowing jumps to the neighboring sites along the track, but only if accompanied by a change in 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

$$\begin{aligned} \frac{dp_D(n,t)}{dt} &= rp_T(n-1) + dp_T(n) - (u+l)p_D(n)\,, \\ \frac{dp_T(n,t)}{dt} &= lp_D(n+1) + up_D(n) - (d+r)p_T(n)\,. \end{aligned} \tag{3.24}$$

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

$$\begin{aligned} \frac{\partial p_D(x,t)}{\partial t} &= (r+d)p_T(x) - (u+l)p_D(x) - ar\frac{\partial}{\partial x}p_T(x,t) + \frac{a^2 r}{2}\frac{\partial^2}{\partial x^2}p_T(x,t)\,, \\ \frac{\partial p_T(x,t)}{\partial t} &= (l+u)p_D(n) - (d+r)p_T(n) + al\frac{\partial}{\partial x}p_D(x,t) + \frac{a^2 l}{2}\frac{\partial^2}{\partial x^2}p_D(x,t)\,. \end{aligned} \tag{3.25}$$

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

The similarity of the above to Eqs. (3.1) is now apparent. We can thus again 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

$$(l+u)p_D(x) = (r+d)p_T(x)\,, \tag{3.26}$$

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

$$p_T(x) = \frac{u+l}{u+d+r+l}\,p(x) \qquad \text{and} \qquad p_D(x) = \frac{d+r}{u+d+r+l}\,p(x)\,. \tag{3.27}$$

Adding the two Eqs (3.25) and substituting from Eq. (3.27) leads to a standard drift-diffusion equation for $p(x,t)$, with drift velocity

$$v = a\,\frac{ru-ld}{u+d+r+l}\,, \tag{3.28}$$

and diffusion coefficient

$$D = \frac{a^2}{2}\,\frac{ld+ru+2lr}{u+d+r+l}\,. \tag{3.29}$$

Note that a back and forth jump (at rate lr) makes no contribution to the drift, but increases the overall diffusion coefficient.

The requirement of thermal equilibrium places stringent constraints on any pair of forward/backward reaction rates. According to the condition of *detailed balance*, the equilibrium probabilities p_i^* for a set of states $\{i\}$ are related to the transition rates $\{R_{ij}\}$ by

$$R_{ij}p_i^* = R_{ji}p_j^*\,, \tag{3.30}$$

for any pair of states i and j. In the absence of an external potential all sites $\{n\}$ in our model are equivalent in steady state, and the corresponding probabilities must thus satisfy

$$\frac{p_T^*}{p_D^*} = \frac{u_0}{d_0} = \frac{l_0}{r_0}\,, \tag{3.31}$$

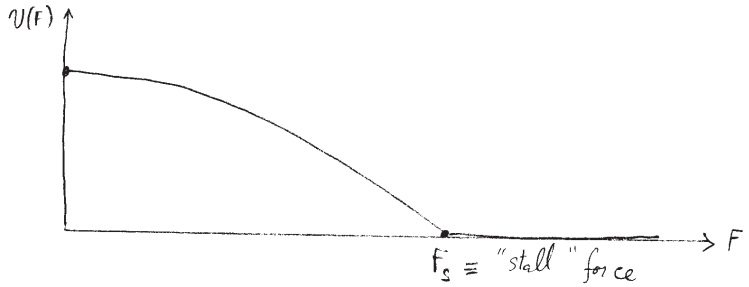
where the zero subscript indicates the rates corresponding to equilibrium. In this case, $r_0u_0 = l_0d_0$, and there is no net velocity, $v = 0$. Thus *asymmetry by itself is not sufficient for directed motion* as expected.

The hydrolysis of ATP provides a (non-equilibrium) source of energy and modifies the transition rates. For example, consider thermal equilibrium between two states of energies U_T and U_D. The transition rates between the two states are then related to the equilibrium probabilities by $p_T^*/p_D^* = \exp[-\beta(U_T - U_D)] = u_0/d_0$. We can imagine that consumption of ATP from the environment provides a boost of energy that reduces the energy required for transition between the two states to $U_T \to U_T - \Delta G_h$, thus increasing the probability flux from D to T such that $u \to u_0 \exp(\beta\Delta G_h)$. If the other rates are unchanged, the drift velocity now becomes

$$v = a\,\frac{ld}{u+d+r+l}\left(\frac{r}{l}\frac{u}{d} - 1\right) = \frac{ald}{u+d+r+l}\left(e^{\beta\Delta G_h} - 1\right) > 0\,. \tag{3.32}$$

3.2.2 Force of a Brownian Motor

To find out how efficiently the energy input from ATP is converted to work, a possible route is to examine 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

$$\left.\frac{r}{l}\right|_F = \left.\frac{r}{l}\right|_0 e^{-\beta F a} \quad \text{and} \quad v = a\,\frac{ld}{u+d+r+l}\left(e^{\beta(\Delta G_h - Fa)} - 1\right) . \tag{3.33}$$

Clearly the motor stalls ($v = 0$) when $F = F_s = F_{\max} = \Delta G_h/a$. This agrees with our previous rough estimate, as there are no frictional forces (and corresponding dissipate losses) for a stationary motor.

The Einstein force is obtained by analogy to Brownian particles from a ratio of velocity and diffusion coefficients. It is possible to image the motion of a motor (more precisely its cargo) along its track. The motion is typically jerky, with back and forth steps, from which a diffusion coefficient can be extracted, along with an average velocity. This is reminiscent of Brownian motion of a small particle in a fluid. A particle in solution experiences a drag force proportional to its velocity, such that $v = \mu F$ where μ is its *mobility*. With or without an external force, the particle also diffuses in solution with diffusion constant D. Diffusion originates in collisions with thermally excited molecules of the fluid, and to ensure proper thermal equilibrium the mobility and diffusion constant must be related by the *Einstein relation*, $D = \mu k_B T$. For our asymmetric hopping model we can similarly postulate an Einstein force

$$F_E = k_B T \frac{v}{D} = \frac{2k_B T}{a}\frac{ru - ld}{rd + lu + 2lr} = \frac{2k_B T}{a}\frac{\frac{ru}{ld} - 1}{1 + \frac{ld}{ru} + 2\frac{r}{d}} , \tag{3.34}$$

where we have used the values for drift and diffusion of the motor along its track from Eqs. (3.28) and (3.29). Since $(ru)/(ld) = e^{\beta \Delta G_h}$, in the limit $\beta \Delta G_h \to 0$

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

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

The force at maximal power provides yet another perspective: Working against a force F, the motor drifts with an average velocity $v(F)$, utilizing a power $\dot{W} = Fv(F)$ from hydrolysis of ATP. $\dot{W}$ is zero at $F = 0$ and also at the stall force where $v(F_s) = 0$, with a maximum at some intermediate F^*. Maximizing the expression for $\dot{W}$, using Eq. (3.28) leads to a transcendental equation for F^*. The equation is simplified in the regime $\beta\Delta G_h \to 0$, which leads to a linear response $v \propto (\Delta G_h - Fa)$ and $\dot{W} \propto Fa(\Delta G_h - Fa)$. Extremizing the above expression clearly leads to

$$F^* = \frac{\Delta G_h}{2a} = \frac{F_{\max}}{2}.$$

3.3 Brownian Motion

To better understand some of features of force and motion at cellular and sub cellular scales, it is worthwhile to step back, and think about Brownian motion. With a simple microscope, in 1827 Robert Brown observed that pollen grains in water move in haphazard manner. From a Newtonian perspective, this is surprising as force is required to initiate motion and cause changes in direction. Where does this force come from; could it be that the observed particles are in some sense active and 'alive,' generating their own motion? The classic 1905 paper by Albert Einstein demonstrates that no active mechanism is necessary, and that the random forces generated by the thermally excited water molecules can account for the motion of the grains. This explanation was confirmed by Jean Perrin in 1908, for which he was awarded the Nobel prize in 1926.

Let us for simplicity indicate the position of the particle by a one-dimensional coordinate x (e.g. its vertical position); extension to more coordinates is trivial. According to Newtonian dynamics, the particle accelerates in response to forces it experience. When the particle at x is immersed in fluid, this includes in addition to external potential forces (e.g. due to gravity), a frictional force due to the fluid viscosity. The deterministic equation governing motion is them

$$m\ddot{x} = -\frac{\partial V}{\partial x} - \frac{1}{\mu}\dot{x}\,. \tag{3.35}$$

For a sphere of radius a, the viscous drag (and corresponding *mobility* μ) is given by

$$\mu = \frac{1}{6\pi a\eta}, \tag{3.36}$$

where η is the specific viscosity of the fluid.

It is important to have a measure of the relative importance of the inertial and viscous terms in the above equation. Let us consider an object (not necessarily a solid sphere) of typical size a and density ρ, moving with velocity v in a fluid. The inertial force necessary to bring to rapidly change its velocity, e.g. to bring it to rest over a distance of the order of its size, is $F_{\text{inertial}} \sim mv(v/a) \sim \rho a^2 v^2$. The dissipative force due to the fluid viscosity is of

order $F_{\text{viscous}} \sim \eta a v$. The relative importance of the two forces is captured by the *Reynolds number*

$$Re = \frac{F_{\text{inertial}}}{F_{\text{viscous}}} = \frac{\rho a v}{\eta}. \tag{3.37}$$

Our physical experiences of motion in fluids relate to the realm of large Reynolds number: We are mostly interested in water and room temperature, which has a *kinematic viscosity* of $\eta/\rho \approx 10^{-6}\text{m}^2\text{s}^{-1}$; and for an animal swimming in water $Re \approx 1\text{m} \times 1\text{ms}^{-1}/10^{-6}\text{m}^2\text{s}^{-1} = 10^6 \gg 1$. Even if the motive force is stopped, the animal will continue to move in the fluid due to its inertia. By contrast, cell and subcellular motion belong to the realm of low Reynolds numbers. For example, a typical bacterium is a few microns is size, and moves at velocities of around $30\mu\text{s}^{-1}$, translating to a Reynolds number of around $10^{-4} \ll 1$. For molecular motors, relevant length scales are of the order of 10nm, with velocities of order of $1\mu\text{s}^{-1}$, leading to even smaller $Re \approx 10^{-8}$. The classic paper "Life at Low Reynolds Number" [*Am. J. Phys.* **45**(1), 1977] by Purcell contains many interesting observations about this limit.

At such small Reynolds numbers we can neglect the left-hand side of Eq. (3.35), concluding that velocity is proportional to external force:

$$\dot{x} = F = -\mu \frac{\partial V}{\partial x}.$$

Of course, by the time we get down to the short scales of microns and below, we should no longer treat water as a continuous fluid; rather, its particulate nature comes into play. The water molecules are constantly moving due to thermal fluctuations, and their impacts on the larger immersed objects results in a random force $\eta(t)$, leading the *stochastic* equation of motion

$$\dot{x} = -\mu \frac{\partial V}{\partial x} + \eta(t). \tag{3.38}$$

A random impacts from all around an immersed object should average to zero over time, but there will be instantaneous fluctuations. We expect the random forces experienced over times longer than typical intervals between collisions to be uncorrelated, leading to

$$\langle \eta(t) \rangle = 0, \tag{3.39}$$

$$\langle \eta(t)\eta(t') \rangle = 2D\delta(t - t'). \tag{3.40}$$

Since the force is the outcome of summing over many impacts, it is reasonable to expect the central limit theorem to hold, leading to Gaussian statistics, i.e.

$$p[\eta(t)] \propto \exp\left[-\frac{1}{2D} \int^t \eta(t')^2 dt' \right]. \tag{3.41}$$

In the absence of external force, the position of the particle evolves as

$$x(t) = x(0) + \int_0^t dt' \eta(t').$$

It is then easy to check that

$$\langle x(t) - x(0) \rangle = 0, \tag{3.42}$$

while the mean-squared dispersion is given by

$$\left\langle [x(t) - x(0)]^2 \right\rangle = \int_0^t dt_1' dt_2' \, \langle \eta(t_1') \eta(t_2') \rangle = 2Dt. \tag{3.43}$$

The above equation thus relates the various of the force to the observed diffusion coefficient of the particle in the fluid.

The stocastic Eq. (3.38) is the *Langevin equation* for the coordinate x. Different realizations of the force $\eta(t)$ lead to different values of $x(t)$; we can also construct a corresponding *Fokker-Planck* equation governing the evolution of the probability $p(x,t)$. In the absence of a potential (as discussed above), this is simply the diffusion equation, with a diffusive *probability current* $J_D = -D\partial p/\partial x$. More generally, we can write the continuity equation

$$\frac{\partial p(x,t)}{\partial t} = -\frac{\partial J}{\partial x}, \tag{3.44}$$

where J now includes an additional drift term such that

$$J = v(x)p(x,t) - D\frac{\partial p}{\partial x}, \tag{3.45}$$

with $v(x) = \mu F = -\mu \partial V/\partial x$. The probability thus satisfies the Fokker-Planck equation:

$$\boxed{\partial_t p(x,t) = -\partial_x (v(x)p) - D\partial_x^2 p}. \tag{3.46}$$

We are discussed the steady state solution for drift-diffusion processes, which in this case leads to

$$p^*(x) \propto \exp\left(-\frac{\mu}{D} V(x)\right). \tag{3.47}$$

However, in the particle is in *thermal equilibrium* at a temperature T, its steady state probability must be related to the potential through Boltzmann weight

$$p^* \propto \exp\left(-\frac{H}{k_B T}\right) \propto \exp\left(-\frac{V(x)}{k_B T}\right). \tag{3.48}$$

. This implies that the diffusion constant (and hence the variance of the random force) is given by

$$\boxed{D = \mu k_B T.} \tag{3.49}$$

This important *Einstein equation* relates noise at microscopic level (D) to macroscopic dissipation (μ) in equilibrium at a temperature T. Its violation could for example indicate that the microscopic trajectory of a particle observed in water is not Brownian, possibly hinting at a live entity. Indeed, since the Hamiltonian in Eq. (3.48) may include several degrees of freedom (other coordinates, kinetic and rotational energies), it can in principle be used to discriminate between passive (equilibrium) and active (non-equilibrium) processes.