The University Of Sheffield.

Department of Physics and Astronomy

PHY420

Biological Physics

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Contents

Topic 1

Diffusion and Random walks

1.1 History of Brownian motion

In 1828 a British botanist, Robert Brown, observed pollen grains in water under a microscope. Pollen grains are $\sim 1\,\mu\mathrm{m}$ in size so large enough for Brown to see. He saw them moving - "dancing around". He thought they were moving because they were alive. He tested this hypothesis by looking a pollen from dead plants but that also moved. He went on to look at lots of other small particles including soot and ground metal. All these particles moved in the same random dancing way even particles that had never been alive. Brown did not understand where this motion came from. Today we call this motion "Brownian motion" and we call particles of size $\sim 1\,\mu\mathrm{m}$, colloids. It was not until 1905 that a famous German physicist, Einstein, finally understood Brownian motion.

1.2 Theory of Brownian motion

We often see or sense the effects of diffusion e.g. put a tea bag (or a drop of ink) in water and you see the colour gradually spread out through the water. If someone sprays deodorant in a corner of the room the smell gradually spreads out so it can be smelt further away. This spreading out is caused by the fact that all the particles in the water/air and the ink/tea/deoderant particles are moving about in a random way. They move because they have thermal energy due to their temperature. The hotter the fluid is the more the particles move. Their thermal energy is converted into kinetic energy $k_B T \sim \frac{1}{2} m v^2$. We cannot see the movement of these particles because they are too small but over time we see the macroscopic

effect of the particles we can detect (in/tea/deoderant) spreading out.

But this still does not explain Brownian motion. There are 2 problems:

(i) Colloid particles ($\sim 1\,\mu\mathrm{m}$) are much larger than atoms ($\mathrm{\AA} = 10^{-10}\,\mathrm{m}$) or molecules ($\mathrm{nm}$) so their mass m is too large for their thermal energy to be enough to move them as much as Brown saw in his microscope. As the water molecules move they will bump into the pollen/colloid and transfer momentum "kicking" the colloid. But these kicks will be so small because the water molecules are so much smaller than the pollen - they should be too small to see in the microscope.

(ii) We can calculate how fast the water molecules move: $mv^2 \sim k_B T$ so $v \sim \sqrt{k_B T/m} \sim \sqrt{10^{-21}\,\mathrm{J}/10^{-26}\,\mathrm{kg}} \sim 500\,\mathrm{ms}^{-1} \sim 100\,\mathrm{km/h}$. The collision rate is rate is given by the speed divided by the distance moved before hitting another molecule ($\sim 1\,\mathrm{nm}$) i.e. rate $\sim 10^3/10{-}9 \sim 10^{12}\,\mathrm{s}^{-1}$ - isn't this too much fast to see?

Einstein realised that these 2 problems cancel each other out. Individual kicks are much too small and much too fast for us to see. The water molecules bumping into the colloid come from all directions so usually all the little kicks cancel each other out and we would not see any movement of the colloid. However occasionally there will be many kicks all in the same direction adding up to a big kick that we can see. Since there are 10^{12} little kicks every second, the *rare event* of a big kick will happen a few times a second i.e. on a time scale we can see. So we see the colloid dancing around due to these rare big kicks even though we cannot see the little kicks happening on a faster time scale than we can see.

1.3 Random walks

Diffusion and Brownian motion can be modelled as a "random walk". Imagine a drunk man trying to walk home. He does not walk in a straight line — he takes a step or two in one direction and then a step or two in a totally different direction. His path is a "random walk", which looks like that drawn in Figure 1.1. Figure 1.1a is a close up of a bit of figure 1.1b which shows the path on a larger length scale. Figure 1.1a is like the motion of a colloid and figure 1.1b like the motion of an individual water molecule or diffusing ink particle. The structure looks the same on different length scales - it is a fractal.

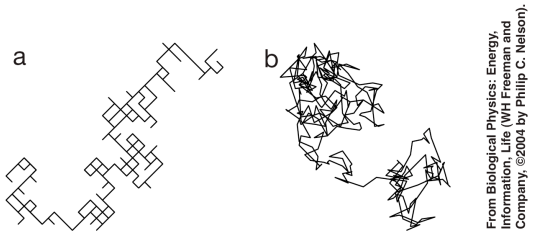

Figure 1.1: A random walk. a) close up and b) on a larger length scale

A random walk is a *Markov process* — the next step is independent of the previous step (it only depends on the current position) i.e. there is no memory of the preceding path. For a random walk of N steps each of length a taking a time Δt the position at time $t = N\Delta t$ is given by

$$\boldsymbol{X} = \sum_{i=1}^{N} \vec{a}_i$$

Since each successive step $\boldsymbol{a}_i$ is in a different direction these vectors average to zero, $\langle \boldsymbol{a}_i \rangle = 0$ (isotropic) this means:

$$\langle \boldsymbol{X} \rangle = 0$$

So on average the random walker goes nowhere - on average the drunk man makes no progress towards his home. The spreading out behaviour of a random walk comes from the variance:

$$\langle X^2 \rangle = Na^2$$

NB the variance of each step $\langle a_i^2 \rangle$ add because each step is independent so $\boldsymbol{a}_i$ are independent random variables. Since $N = t/\Delta t$ we have $\langle X^2 \rangle = a^2 t/\Delta t$ i.e. $\langle X^2 \rangle \sim t = Na^2$ and the size

$$X = \sqrt{\langle X^2 \rangle} = Na^2 \sim t^{1/2}$$

$D = a^2/(2\Delta t)$ is called the *diffusion constant* and for diffusion in d dimensions we have:

$$\langle X^2 \rangle = 2dDt \tag{1.1}$$

1.4 Distribution of positions

Consider a one dimensional ($d = 1$) random walk of total number of steps $N = N_+ + N_-$ made up of N_+ forwards steps and N_- backwards. The position after N steps is then given by $X = (N_+ - N_-)a$. The distribution of positions $P(X)$, which can also be thought of as the probability of being at position X after N steps, is given by the number of possible walks ending at position X divided by the total number of possible walks of N steps. i.e. the number of possible walks with N_+ forwards and N_- backwards steps, Ω, divided by the total number of walks.

$$P(X) = \frac{\Omega}{2^N} = \frac{1}{2^N}\frac{N!}{N_+!N_-!} \tag{1.2}$$

$$= \frac{1}{2^N}\frac{N!}{N_+!(N-N_+)!} = \frac{1}{2^N}\,{}^N C_{N_+} = \frac{1}{2^N}\begin{pmatrix} N \\ N_+ \end{pmatrix} \tag{1.3}$$

This is the Binomial distribution. It can be shown that for large $N \gg 1$ and $\frac{n}{N} \ll 1$ where $n = X/a$ that this becomes a Gaussian distribution:

$$P(X) \sim e^{-\frac{X^2}{2Na^2}}$$

In $d = 3$ dimensions we have $\Omega_x\Omega_y\Omega_z$ giving $P(X) \sim e^{-3\frac{X^2}{2Na^2}}$. In terms of the diffusion constant $Na^2 = 2Dt$ in one dimension so

$$P(X) \sim e^{-\frac{X^2}{4Dt}}.$$

For this to be a probability it must be normalised i.e. $\int_{-\infty}^{\infty} P(X)\mathrm{d}x = 1$. Using the Gaussian integral result $\int_{-\infty}^{\infty} e^{-ax^2}\mathrm{d}x = \sqrt{\pi/a}$ we obtain $\int_{-\infty}^{\infty} P(X)\mathrm{d}x = \sqrt{4\pi Dt}$ and therefore

$$P(X) = \frac{1}{\sqrt{4\pi Dt}}e^{-\frac{X^2}{4Dt}}. \tag{1.4}$$

If we consider many particles $P(X)$ becomes the number density $c(X)$ of particles at point X and the distribution tells us how diffusing particles spread out as shown in figure 1.2.

1.5 Diffusion equation

Consider diffusion in $d = 1$ dimensions. Let the number of particles at point x be $M(x) = Vc(x)$ where V is the volume and $c(x)$ is the concentration

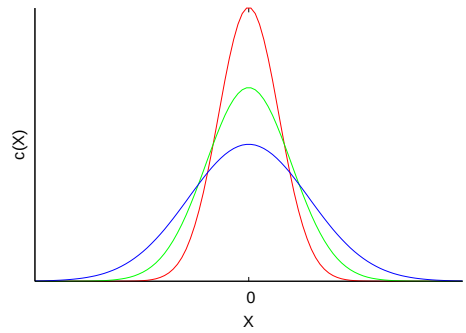

Figure 1.2: Number density distribution of diffusing particles. Red, green, blue curves show the distribution at successive times.

i.e. the number density of particles at point x. The number of particles crossing point (x) from left to right is given by the number of particles at point $(x-\frac{\Delta x}{2})$ that are travelling forwards (to the right) minus the number at point $(x+\frac{\Delta x}{2})$ that are travelling backwards (to the left). If we assume half the particles travel each way this gives $\frac{1}{2}M(x-\frac{\Delta x}{2})-\frac{1}{2}M(x+\frac{\Delta x}{2})$. Taking the continuum limit for small Δx this gives $-\frac{\Delta x}{2}\frac{\mathrm{d}M}{\mathrm{d}x}$. The flux j of particles at position x is given by the number of particles crossing the point per unit area and time:

$$j=-\frac{\Delta x}{2\Delta y\Delta z\Delta t}\frac{\mathrm{d}M}{\mathrm{d}x}=-\frac{\Delta x^2}{2\Delta t}\frac{\mathrm{d}c}{\mathrm{d}x}$$

where we have identified $\Delta x\Delta y\Delta z=V$. Notice that the diffusion constant $D=\frac{a^2}{2\Delta t}$ and we can equate $\Delta x=a$ so

$$j=-D\frac{\mathrm{d}c}{\mathrm{d}x} \tag{1.5}$$

This Fick's law (or Fick's first law). It is also called a "constitutive" equation since it describes how matter responds to an external stimulus (here the concentration gradient). It describes the linear response, i.e. it is correct to linear order. It describes how diffusing particles travel from regions of high concentration to regions of low concentration.

The number of particles $M(x)$ changes over time Δt because particles travelling right from $(x-\frac{\Delta x}{2})$ and particles travelling left from $(x+\frac{\Delta x}{2})$ cross the point x. Therefore,

$$\begin{aligned}\frac{\mathrm{d}M}{\mathrm{d}t}&=\Delta y\Delta z(j(x-\frac{\Delta x}{2})-j(x+\frac{\Delta x}{2}))\\ \frac{\mathrm{d}M}{\mathrm{d}t}&=-\Delta y\Delta z\Delta x\frac{\mathrm{d}j}{\mathrm{d}x}\\ \frac{\mathrm{d}c}{\mathrm{d}t}&=-\frac{\mathrm{d}j}{\mathrm{d}x}\end{aligned} \tag{1.6}$$

This equation is called the "continuity" equation because it ensures the conservation of number of particles.

Combining equations (1.5) and (1.6) gives the diffusion equation:

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}$$

The diffusion equation is sometimes called Fick's second law. The number distribution we obtained before (equation 1.4) is a solution to this partial differential equation. The diffusion equation above is for diffusion in $d = 1$ dimension. In higher dimensions the diffusion equation is given by:

$$\frac{\partial c}{\partial t} = D\nabla^2 c$$

which comes from $\boldsymbol{j} = -D\,\nabla c$ and $\partial_t c + \nabla \cdot \boldsymbol{j} = 0$.

For those interested, see appendix B for details about how to solve the diffusion equation using Green's functions.

1.6 1D random walk using Fourier Modes

We can also consider a 1D random walk using Fourier modes. Consider a particle at point n that can move forwards (right) to point $n+1$ with rate k^+ or backwards (left) to point $n-1$ with rate k^-. The discrete Master equation for this system is then:

$$\frac{\partial P_n}{\partial t} = k^+ P_{n-1} - k^+ P_n + k^- P_{n+1} - k^- P_n$$

If the random walk is unbiased $k^+ = k^- = k$ and therefore

$$\frac{\partial P_n}{\partial t} = k(P_{n-1} - 2P_n + P_{n+1}) \tag{1.7}$$

Remembering that the discrete Fourier Transform is given by $\tilde{P}_q = \sum_n e^{iqn} P_n$ and differentiating this twice gives

$$\left.\frac{\partial^2 \tilde{P}_q}{\partial q^2}\right|_{q=0} = -\sum_n n^2 P_n = -\langle n^2 \rangle \tag{1.8}$$

We now rewrite equation (1.7) in terms of $\tilde{P}_q$, solve it for $\tilde{P}_q$ and differentiate this twice to obtain $\langle n^2 \rangle$ as given in equation (1.8):

$$\begin{aligned}
\frac{\partial \tilde{P}_q}{\partial t} =& k(e^{iq}\tilde{P}_q - 2\tilde{P}_q + e^{-iq}\tilde{P}_q) \\
\frac{\partial \tilde{P}_q}{\partial t} =& -2k(1-\cos q)\tilde{P}_q \\
\tilde{P}_q =& Ae^{-2k(1-\cos q)t} \\
\frac{\partial \tilde{P}_q}{\partial q} =& -2Akt\sin q e^{-2k(1-\cos q)t} \\
\frac{\partial^2 \tilde{P}_q}{\partial q^2} =& -2Akt\cos q e^{-2k(1-\cos q)t} + A(2kt)^2 \sin^2 q e^{-2k(1-\cos q)t} \\
\left.\frac{\partial^2 \tilde{P}_q}{\partial q^2}\right|_{q=0} =& -2kt \\
\langle n^2 \rangle =& 2kt
\end{aligned}$$

which clearly has the same form as equation (1.1).

1.7 Langevin equation

Consider a particle in a fluid with no external force - just the force due to collisions with fluid molecules. The equation of motion is given by

$$m\frac{\mathrm{d}\boldsymbol{v}}{\mathrm{d}t} = \boldsymbol{f}_{\text{fluid}} = \langle \boldsymbol{f}_{\text{fluid}} \rangle + \boldsymbol{f}_L(t) \tag{1.9}$$

where the average force due to the fluid is the friction given by $\langle \boldsymbol{f}_{\text{fluid}} \rangle = -\xi \boldsymbol{v}$ where ξ is the friction coefficient. The fluctuating time varying force $\boldsymbol{f}_L(t)$ is the Langevin force representing the random fluctuations of the fluid particles - often referred to as the noise. Since this force is random we know that it averages to zero i.e. $\langle \boldsymbol{f}_L(t) \rangle = 0$. The correlation function is given by

$$\langle \boldsymbol{f}_L^i(t) \boldsymbol{f}_L^j(t') \rangle = A\delta_{ij}\delta(t-t') \tag{1.10}$$

where the superscripts i and j represent different points in space, $\delta(t-t')$ is the Dirac delta function and δ_{ij} is the Kronecker delta function defined as $\delta_{ij} = 1$ if $i = j$ and $\delta_{ij} = 0$ if $i \neq i$. Equation (1.13) means that the Langevin is totally uncorrelated between different points in space and time.

The Langevin equation is:

$$\boxed{m\frac{\mathrm{d}\boldsymbol{v}}{\mathrm{d}t} = -\xi \boldsymbol{v} + \boldsymbol{f}_L(t)} \tag{1.11}$$

Usually the collision timescale $\tau = m/\xi$ is much shorter than the measurement time. If the Langevin force is zero $\boldsymbol{f}_L(t) = 0$ the solution for the velocity of the particle is $\boldsymbol{v} = \boldsymbol{v}_0 e^{-t/\tau}$. To find a general solution for $\boldsymbol{f}_L(t) \neq 0$ we use the constant variation method: we look for a general solution of the form $\boldsymbol{v} = \boldsymbol{v}_0(t)e^{-t/\tau}$. Substituting this into equation (1.11) gives $m\frac{\mathrm{d}\boldsymbol{v}_0}{\mathrm{d}t}e^{t/\tau} = \boldsymbol{f}_L(t)$. Integrating this gives $\boldsymbol{v}_0 = \int_0^t \frac{\boldsymbol{f}_L(t')}{m} e^{t'/\tau}\mathrm{d}t' + \boldsymbol{v}_1$ where $\boldsymbol{v}_1$ is a constant (the velocity at time $t = 0$). Therefore the general solution to the Langevin equation (1.11) is given by:

$$\boldsymbol{v}(t) = \boldsymbol{v}_1 e^{-t/\tau} + \int_0^t \frac{\boldsymbol{f}_L(t')}{m} e^{-(t-t')/\tau}\mathrm{d}t'$$

On average the Langevin force averages to zero and we have $\langle \boldsymbol{v}(t)\rangle = \boldsymbol{v}_1 e^{-t/\tau}$ i.e. the initial velocity decays to zero over the time τ. For $t \gg \tau$ the average velocity $\langle \boldsymbol{v}(t)\rangle = 0$. This means that if our measurement time is long compared to the collision time we can set $\boldsymbol{v})_1 = 0$ without loss of generality.

The velocity correlation function is then given by:

$$\langle \boldsymbol{v}(t)\boldsymbol{v}(t')\rangle = \frac{1}{m^2}\int_0^t \mathrm{d}t_1 \int_0^{t'} \mathrm{d}t_2 \langle \boldsymbol{f}_L(t_1)\boldsymbol{f}_L(t_2)\rangle e^{-(t-t_1+t'-t_2)/\tau}$$

We use equation (1.13) with a factor of 3 for the 3 components in 3D and integrate twice assuming $t' > t$ so performing the integration over t_2 first:

$$\begin{aligned}
\langle \boldsymbol{v}(t)\boldsymbol{v}(t')\rangle =& \frac{1}{m^2}\int_0^t \mathrm{d}t_1 \int_0^{t'} \mathrm{d}t_2 3A\delta(t_1 - t_2)e^{-(t-t_1+t'-t_2)/\tau} \\
=& \frac{3A}{m^2}\int_0^t \mathrm{d}t_1 e^{-(t-2t_1+t')/\tau} \\
=& \frac{3A\tau}{2m^2} e^{-(t+t')/\tau}(e^{2t/\tau} - 1) \\
=& \frac{3A}{2m\xi}(e^{(t-t')/\tau} - e^{-(t+t')/\tau})
\end{aligned}$$

For $t, t' \gg \tau$ the second term goes to zero and we are left with

$$\langle \boldsymbol{v}(t)\boldsymbol{v}(t')\rangle = \frac{3A}{2m\xi} e^{-|t-t'|/\tau} \tag{1.12}$$

which means that the velocity has a memory that decays over time τ.

1.7.1 Thermodynamic limit

From equation (1.14), if $t = t'$ then $\langle \boldsymbol{v}^2(t) \rangle = \frac{3A}{2m\xi}$. This must be consistent with thermodynamics. The equipartition theorem tells us that the average kinetic energy $\langle \frac{1}{2} m \boldsymbol{v}^2 \rangle = \frac{3}{2} k_B T$ therefore $\frac{3A}{2m\xi} = \frac{3k_B T}{m}$ which defines $A = 2k_B T \xi$ therefore

$$\langle \boldsymbol{f}_L^i(t) \boldsymbol{f}_L^j(t') \rangle = 2k_B T \xi \delta_{ij} \delta(t - t') \tag{1.13}$$

and

$$\langle \boldsymbol{v}(t) \boldsymbol{v}(t') \rangle = \frac{3k_B T}{m} e^{-|t-t'|/\tau} \tag{1.14}$$

1.7.2 Diffusion and the Einstein relation

For a particle at position $\boldsymbol{r} = 0$ at time $t = 0$ diffusing in 3D we know from equation (1.1) that its long time average displacement is $\langle \boldsymbol{r} \rangle = 0$ and $\langle \boldsymbol{r}^2 \rangle = 6Dt$. We can now calculate this from the Langevin equation.

$$\begin{aligned}
\boldsymbol{r}(t) &= \int_0^t \boldsymbol{v}(t') \mathrm{d}t' \\
\langle \boldsymbol{r}^2(t) \rangle &= \langle \int_0^t \mathrm{d}t_1 \boldsymbol{v}(t_1) \int_0^t \mathrm{d}t_2 \boldsymbol{v}(t_2) \rangle = \int_0^t \mathrm{d}t_1 \int_0^t \mathrm{d}t_2 \langle \boldsymbol{v}(t_1) \boldsymbol{v}(t_2) \rangle \\
&= \int_0^t \mathrm{d}t_1 \int_0^t \mathrm{d}t_2 \frac{3k_B T}{m} e^{-|t_1 - t_2|/\tau} \\
&= \int_0^t \mathrm{d}t_1 \int_0^{t_1} \mathrm{d}t_2 \frac{3k_B T}{m} e^{-(t_1 - t_2)/\tau} + \int_0^t \mathrm{d}t_2 \int_0^{t_2} \mathrm{d}t_1 \frac{3k_B T}{m} e^{-(t_2 - t_1)/\tau}
\end{aligned}$$

where we have split the integral up into two terms to deal with the modulus sign. The first term is for $t_1 > t_2$ (integrating first over t_2 between $0 < t_2 < t_1$ and then over $0 < t_1 < t$) and the second term is for $t_2 > t_1$ (integrating first over t_1 for $0 < t_1 < t_2$ and then over $0 < t_2 < t$). This gives

$$\langle \boldsymbol{r}^2(t) \rangle = \frac{6k_B T}{m} t\tau$$

Combined with the diffusion result $\langle \boldsymbol{r}^2 \rangle = 6Dt$ this leads to the Einstein relation (1905):

$$\boxed{D = \frac{k_B T}{\xi}} \tag{1.15}$$

where we have written the timescale $\tau = m/\xi$. This is a special case of the fluctuation dissipation theorem (see 8 for more).

The friction can be estimated using Stokes law for a spherical particle of radius a in a fluid of viscosity η i.e. $\xi = 6\pi\eta a$. For a water molecule $a \sim 1\mathring{A}$ and water has a viscosity of $\eta \sim 1 -^{3}$ Pa s. This gives $D \sim 10^{-9}\,\mathrm{m^2\,s^{-1}}$ which corresponds to $\sim 1\,\mathrm{cm}$ in a day. For a protein $a \sim 10\,\mathrm{nm}$ in water $D \sim 20^{-9}\mu\mathrm{m^2\,s^{-1}}$ so a protein could diffuse across a cell ($\sim 100\mu\mathrm{m}$) in $\sim 100\,\mathrm{s} \sim 2\,\mathrm{mins}$. This is too slow for many biological processes which need transport across a cell in seconds. This is why molecular motors are needed to actively transport things faster around the cell.

1.7.3 Fokker Planck equation *(Optional extra)*

Another approach is to study the probability $p(\boldsymbol{r}, t)$ that the particle is at position $\boldsymbol{r}$ at time t. The probability current (flux) due to diffusion is $\boldsymbol{j} = -D\nabla p$. To conserve particles the probability must obey the conservation equation:

$$\frac{\partial p}{\partial t} + \nabla \cdot \boldsymbol{j} = 0 \tag{1.16}$$

leading to the diffusion equation:

$$\frac{\partial p}{\partial t} = D\nabla^2 p$$

For the initial condition $p(\boldsymbol{r}, t = 0) = \delta(\boldsymbol{r})$ that the particle is at $\boldsymbol{r} = 0$ at $t = 0$ the solution is (see Appendix B):

$$p(\vec{r}, t) = \frac{1}{(4\pi Dt)^{3/2}} e^{-r^2/(4Dt)}$$

From this we can calculate the expectation value $\langle \vec{r}^2 \rangle$ as follows

$$\langle \vec{r}^2 \rangle = \int r^2 p(\vec{r}, t) \mathrm{d}\boldsymbol{r} = \frac{1}{(4\pi Dt)^{3/2}} \int r^2 e^{-r^2/(4Dt)} 4\pi r^2 \mathrm{d}r$$

giving the expected result $\langle \vec{r}^2 \rangle = 6Dt$.

This approach can be extended to diffusion in a potential (biased diffusion) leading to the convection diffusion equation. To calculate the contribution to the probability flux from a potential we generalise the Langevin equation (1.11) to include an external potential V causing a force $-\nabla V$ i.e.

$$m\frac{\mathrm{d}\boldsymbol{v}}{\mathrm{d}t} = -\xi\boldsymbol{v} - \nabla V + \boldsymbol{f}_L(t) \tag{1.17}$$

If we are concerned with long times $t \gg \tau$ and small masses we can neglect the Langevin noise term and the inertial term giving $\xi\boldsymbol{v} = -\nabla V$.

The contribution to the probability flux is $p\boldsymbol{v} = -\frac{1}{\xi}p\nabla V$. Adding this to the flux due to diffusion give the total flux is then:

$$\boldsymbol{j} = -D\nabla p - \frac{1}{\xi}p\nabla V$$

Putting this into the conservation equation (1.16) extends the diffusion equation to the Fokker Planck diffusion-convection equation:

$$\frac{\partial p}{\partial t} = D\nabla^2 p + \frac{1}{\xi}\nabla(p\nabla V) \tag{1.18}$$

where the first term is the diffusion term and the second term the convection term. At steady state $t \to \infty$ in the thermodynamic limit at thermal equilibrium the probability is given by the Boltzman distribution $p(r) = e^{-V(r)/(k_B T)}/Z$ where Z is the partition function. Substituting this into equation (1.18) gives the Einstein relation

$$\boxed{D = \frac{k_B T}{\xi}}$$

1.7.4 1D harmonic potential

Consider as an example a harmonic potential in one dimension $V(x) = \frac{1}{2}kx^2$. The Langevin equation $\xi\boldsymbol{v} = -\nabla V + \boldsymbol{f}_L(t)$ is then:

$$\xi\frac{\mathrm{d}x}{\mathrm{d}t} = -kx + \boldsymbol{f}_L(t)$$

where we have neglected the intertial term ($m \sim 0$). The collision timescale $\tau = \xi/k$. The solution to this equation is given by

$$x = x_0 e^{-t/\tau} + \int_0^t \frac{1}{\xi}\boldsymbol{f}_L(t')e^{-(t-t')}\mathrm{d}t'$$

Let the initial point $x_0 = 0$. The position correlation function is

$$\begin{aligned}
\langle x(t)x(t')\rangle =& \frac{1}{\xi^2}\int_0^t \mathrm{d}t_1 \int_0^{t'} \mathrm{d}t_2 \langle \boldsymbol{f}_L(t_1)\boldsymbol{f}_L(t_2)\rangle e^{-(t-t_1+t'-t_2)/\tau} \\
\langle x(t)x(t')\rangle =& \frac{k_B T\tau}{\xi}(e^{(t-t')/\tau} - e^{-(t+t')/\tau}) \langle x^2(t)\rangle = \qquad \frac{k_B T\tau}{\xi}(1 - e^{-2t/\tau})
\end{aligned}$$

For $t, t' \gg \tau$

$$\begin{aligned}
\langle x(t)x(t')\rangle =& \frac{k_B T\tau}{\xi}e^{-|t-t'|/\tau} = \frac{k_B T}{k}e^{-|t-t'|/\tau} \\
\langle x^2(t)\rangle =& k_B T/k
\end{aligned}$$

and for $t \ll \tau$ we expand the exponential to first order to give

$$\langle x^2(t) \rangle = \frac{2k_B T t}{\xi} = 2Dt$$

recovering the diffusion result.

Topic 2

Biopolymers

2.1 Introduction

Polymers are long thin molecules. Their shape is like string or cable. Chemically they are a chain made up of many repeated units called monomers e.g. -A-A-A-A-A-A- The degree of polymerisation, N, is the number of monomers in a single polymer chain. This can be be very large e.g. $N \sim 10^4$. The mass of the polymer is $M = Nm$ where m is the mass of a monomer. Many every day materials are polymers (e.g. plastics, paints, fabrics, clothes, cosmetics, foods) and biological materials are full of biopolymers. Polyethene (plastic bag) is a common polymer and has a simple chemical structure with monomer (repeat unit) -CH_2- where C is a carbon atom and H is a hydrogen atom i.e. -CH_2-CH_2-CH_2-CH_2-CH_2-

In polymer physics we usually coarse grain this molecular picture of a polymer and represent each carbon atom in the backbone of the polymer with a single point. Or we coarse grain the picture further and draw what looks like a smooth string.

So far we have been thinking about linear polymers - polymers that are one single chain. Some polymers however are branched polymers and make different shapes e.g. star polymers, H-polymers and polymer brushes (or combs).

Polymers like polyethene can have chains of different length. The distribution of lengths of polymer chains in a sample is called the *polydispersity*. The average number of monomers per chain, $N_n = \frac{\sum_n nW_n}{\sum_n W_n}$ where W_n is the number of chains with n monomers.

Polymers can form different states of matter. Polymer melts and polymer solutions are liquids. They are often very viscous liquids and many have viscoelastic properties. At lower temperatures polymers can be in

a glass state (e.g. polystyrene at room temperature). Polymers can also exist in crystalline form with small crystals embedded in amorphous (disordered) material (liquid or gas) e.g. polyethene, starch. Finally some polymers have rod like molecules that can line up forming liquid crystal phases. The molecules in a liquid crystal have disordered positions like a liquid but orientational order.

2.1.1 Flexibility - Persistence length

The contour length of a polymer $L = Na$ where a is the size of a monomer. The *persistence length* l_p tells us about how stiff a polymer is. The persistence length is given by

$$l_p = l_0 e^{\frac{\Delta\epsilon}{k_B T}}$$

If $L \gg l_p$ the polymer is flexible. If $L \ll l_p$ the polymer is stiff and rod-like and can be modelled as an elastic rod. If $L \sim l_p$ the polymer is called semiflexible.

2.2 Ideal chain "Freely jointed chain" model

Flexible polymers can be assumed to be a *freely jointed chain* (assuming each monomer is connected to the next by a connection that can rotate by any angle). Flexible polymers can be modelled by a random walk. Instead of N being the number of steps of length a in a random walk, here N is the number of links/segments in the chain (i.e. the number of monomers) and a is the size of one monomer or one bond/segment in the chain. The end to end distance of the polymer (distance in space between the beginning and end of the polymer chain is $\boldsymbol{R} = \sum_{i=1}^{N} \boldsymbol{a}_i$. The average end to end distance $\langle \boldsymbol{R} \rangle = 0$ just like for diffusion. The size of the polymer is given by $\langle \boldsymbol{R}^2 \rangle = \langle \sum_{i=1}^{N} \sum_{j=1}^{N} \boldsymbol{a}_i \cdot \boldsymbol{a}_j \rangle = \sum_{i=j} \langle \boldsymbol{a}_i \cdot \boldsymbol{a}_j \rangle + \sum_{i \neq j} \langle \boldsymbol{a}_i \cdot \boldsymbol{a}_j \rangle = Na^2 + 0$ since the orientation of each segment is assumed to be independent. Therefore the size of the polymer is given by $R = \sqrt{\langle \boldsymbol{R}^2 \rangle}$

$$R = aN^{1/2}$$

The scaling law is $R \sim N^{\nu}$ where the exponent $\nu = \frac{1}{2}$. We will find that other models of polymers give other values for the exponent ν. N plays the role time did in the diffusion problem where we had $\langle \boldsymbol{R}^2 \rangle = \langle X^2 \rangle \sim t$.

Sometimes in polymer physics we talk about the *radius of gyration* instead of R. The radius of gyration, R_g, is the radius from the centre of mass

of the polymer $\boldsymbol{r}_0 = \frac{1}{N}\sum_{i=1}^{N} \boldsymbol{r}_i$ where $\boldsymbol{r}_i$ is the position vector of monomer i.

$$\begin{aligned} R_g^2 =& \frac{1}{N}\langle \sum_{i=1}^{N} |\boldsymbol{r}_i - \boldsymbol{r}_0|^2 \rangle \\ R_g^2 =& \frac{1}{2N^2}\langle \sum_{i}^{N}\sum_{j}^{N} (\boldsymbol{r}_i - \boldsymbol{r}_j)^2 \rangle = \frac{1}{N}\langle \sum_{i}^{N} |\boldsymbol{r}_i^2 \rangle \end{aligned}$$

For an ideal chain $\langle (\boldsymbol{r}_i - \boldsymbol{r}_j)^2 \rangle = \langle \boldsymbol{R}^2 \rangle = Na^2 = |j-i|a^2$ since here $|j-i| = N$. Therefore

$$\begin{aligned} R_g^2 =& \frac{1}{2N^2}\sum_{i}^{N}\sum_{j}^{N} |j-i|a^2 \\ R_g^2 =& \frac{1}{2N^2}\int_0^N \mathrm{d}i \int_0^N \mathrm{d}j \; |j-i|a^2 \\ R_g^2 =& \frac{1}{2N^2}\int_0^N \mathrm{d}i \int_0^j \mathrm{d}j \; (i-j)a^2 + \frac{1}{2N^2}\int_0^N \mathrm{d}j \int_0^i \mathrm{d}i \; (j-i)a^2 \\ R_g^2 =& Na^2/6 \end{aligned}$$

Therefore $R_g \sim N^{1/2}$ so has the same scaling as R.

The distribution of sizes R is the same as that for diffusion so in the limit of large N is a Gaussian distribution:

$$P(R) \sim e^{-\frac{3R^2}{2Na^2}}$$

in 3 dimensions which when normalised is $P(R) = (\frac{2\pi Na^2}{3})^{-3/2} e^{-\frac{3R^2}{2Na^2}}$. For a freely jointed chain in the limit of large N the distribution is Gaussian so we sometimes call this as *Gaussian chain*.

The configurational entropy of an ideal polymer chain is given by $S = k_B \ln \Omega$ where $\Omega \sim P(R)$ given above. Therefore

$$S(R) = S(0) - \frac{3k_B R^2}{2Na^2}$$

2.2.1 Stretching an ideal polymer

If we apply an external force to stretch an ideal polymer we will increase R^2 and therefore decrease the entropy $S(R)$. This is because there are

fewer configurations possible for a polymer that is stretched compared to an ideal random walk. The free energy F is given by:

$$F = U - TS = F_0 + \frac{3k_BTR^2}{2Na^2}$$
$$F - F_0 = \frac{1}{2}\left(\frac{3k_BT}{Na^2}\right)R^2$$

which has the form of Hooke's law energy $F = \frac{1}{2}kx^2$. Therefore ($\frac{3k_BT}{Na^2}$ is an effective spring constant i.e. the polymer chain behaves like a spring but the restoring force is not from an increase in internal energy U, as for an elastic spring, but is due to a decrease in entropy S, therefore it is an entropic spring.

2.3 Self-avoiding walks & excluded volume *(Optional extra)*

The ideal random walk model assumes successive monomers can be anywhere in space. However in reality 2 monomers cannot be in the same place at the same time. In fact real polymers in solution have repulsive interactions between monomers at short range distances. In other words real polymers cannot intersect or cross themselves. The leads us to modify the random walk model to a self avoiding walk. This can be pictured most easily by a lattice model where successive monomers can only be on lattice sites that do not already have a monomer i.e. each site has ≤ 1 monomer. A self avoiding walk has a larger root mean squared end to end distance, R_F than that for a random walk, R i.e. $R_F > R$. We call it R_F where F stands for Flory who calculated the exponent ν for $R_F \sim N^\nu$ and found $\nu > \frac{1}{2}$. Since $R_F > R$ we call the $\nu > \frac{1}{2}$ the swelling exponent because the polymer is swollen (larger). Initially the scaling laws were found by computer simulations on different lattices. It was found that ν does not depend on the lattice chosen, it depends only on the number of dimensions. It is therefore called a universal exponent.

2.3.1 Flory's theory of excluded volume

In 1971 Flory calculated the swelling exponent ν for all dimensions d. The radius of a self avoiding walk is larger than for an ideal random walk ($R_F > R$) and therefore this costs energy. The elastic energy to stretch a polymer

from R to R_F is

$$F_{\text{elastic}} = \frac{3}{2}k_BT\frac{R_F^2}{R^2} \approx \frac{3}{2}k_BT\frac{R_F^2}{Na^2}$$

The polymer is swollen due to interactions, $U(r)$, between monomers that are repulsive at short range (due to the Pauli exclusion principle). NB the interaction is attractive at long range due to van der Waals interactions. The free energy of a volume V is given by $F_{\text{interaction}} = \frac{1}{2}k_BTVvc^2$ where $c = N/V$ the number density and $v = \int \mathrm{d}\boldsymbol{r}(1 - e^{-U(r)/(k_BT)})$ is the virial expansion and v is called the excluded volume parameter (dimensions of volume). Let us simplify the interaction $U(r)$ by taking a hard core potential (ignored the attraction and $U(r)$ is a delta function at $r = b = 2a$ where a is the size of a monomer. The excluded volume is $v = \frac{4}{3}\pi b^3$ (see figure 2.1). It is the volume a neighbouring monomer cannot penetrate. The volume

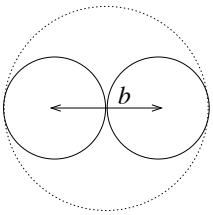

Figure 2.1: The excluded volume is a sphere or radius $b = 2a$.

of the polymer chain $V \approx \frac{4}{3}\pi R_F^3$ and therefore

$$F_{\text{interaction}} = \frac{1}{2}k_BT\frac{vN^2}{\frac{4}{3}\pi R_F^3}$$

The total free energy in d dimensions is given by $F = F_{\text{elastic}} + F_{\text{interaction}}$. Therefore

$$F = \frac{3}{2}k_BT\frac{R_F^2}{Na^2} + \frac{1}{2}k_BT\frac{vN^2}{\kappa_d R_F^d}$$

where κ_d is a constant depending on the dimensions d. To work out the scaling $R_F \sim N^\nu$ we minimise F to find the equilibrium size (NB we don't need to worry about the constants i.e we can take $\frac{F}{k_BT} \sim \frac{R_F^2}{N} + \frac{N^2}{R_F^d}$).

$$\begin{aligned}
\frac{\mathrm{d}F}{\mathrm{d}R_F} =& \frac{2R_F}{N} - \frac{dN^2}{R_F^{d+1}} = 0 \\
R_F^{d+2} \sim& N^3 \\
R_F \sim& N^{\frac{3}{d+2}}
\end{aligned}$$

i.e. the swelling exponent is $\nu = \frac{3}{d+2}$. It depends only on the dimension d and not on the chemical details so it is a universal exponent.

$d=1$	$\nu =$	1	exact (trivial - in 1d chain has to be length N)
$d=2$	$\nu =$	$\frac{3}{4}$	exact (known from full mathematical treatment)
$d=3$	$\nu =$	$\frac{3}{5}$	close to experiments and simulations 0.588
$d=4$	$\nu =$	$\frac{1}{2}$	exact (interactions don't count and chain is ideal)

2.4 Semiflexible polymers

Semiflexible polymers have $L \sim l_p$. In a semiflexible polymer model the polymer is represented as a continuous line (unlike the segments of a flexible polymer model such as an ideal polymer). We denote the position of a point on the polymer at contour length s as $\boldsymbol{r}(s)$. The tangent vector $\boldsymbol{t}(s) = \frac{\partial \boldsymbol{r}}{\partial s}$ is the unit vector tangent to the polymer curve. NB the tangent vector is a unit vector $|\boldsymbol{t}| = 1$ as long as we assume the polymer is inextensible. The unit normal vector $\boldsymbol{n}$ is given by $\frac{\boldsymbol{n}}{R} = \frac{\partial \boldsymbol{t}}{\partial s} = \frac{\partial^2 \boldsymbol{r}}{\partial s^2}$, where $\frac{1}{R}$ is the curvature and R is the radius of curvature.

The free energy is given by the bending energy. For a straight rod $\boldsymbol{t}(s)$ is constant and therefore $\frac{\partial \boldsymbol{t}}{\partial s} = \frac{\partial^2 \boldsymbol{r}}{\partial s^2} = 0$. For a bent rod or a curved semiflexible polymer the bending energy is quadratic in $\frac{\partial \boldsymbol{t}}{\partial s}$ i.e.

$$U_{\text{bend}} = \frac{1}{2}\kappa_b \int_0^L \left(\frac{\partial \boldsymbol{t}}{\partial s}\right)^2 \mathrm{d}s = \frac{1}{2}\kappa_b \int_0^L \left(\frac{\partial^2 \boldsymbol{r}}{\partial s^2}\right)^2 \mathrm{d}s = \frac{1}{2}\kappa_b \int_0^L \frac{1}{R^2}\mathrm{d}s$$

where $\kappa_b = EI$ is the bending modulus/bending rigidity/flexural rigidity, E is the Young's modulus and I is the moment of inertia. For a solid cylinder of radius a the moment of inertia $I = \frac{\pi}{4}a^4$. The persistence length $l_p = \frac{\kappa_b}{k_B T} = \frac{EI}{k_B T} \sim \frac{Ea^4}{k_B T}$.

The conformational distribution is given by

$$\Omega \sim e^{-\frac{U_{\text{bend}}}{k_B T}} = e^{-\frac{1}{2} l_p \int_0^L \left(\frac{\partial^2 \boldsymbol{r}}{\partial s^2}\right)^2 \mathrm{d}s}$$

This model for semiflexible polymers is known as the Kratky-Porod model or the *worm like chain* model. It is a Gaussian random walk in curvature rather than in orientation.

2.4.1 Tangent correlations

Consider the Hamiltonian $H = \frac{1}{2}k_BTl_p\int_0^L \left(\frac{\partial^2 \boldsymbol{r}}{\partial s^2}\right)^2 \mathrm{d}s$ for a semiflexible polymer. We can write this in discrete form of small pieces of length a so the contour length $s = ai$ and the Hamiltonian becomes

$$\begin{aligned} H =& \frac{1}{2}k_BTl_pa\sum_i^N \left(\frac{\boldsymbol{t}_{i+1}-\boldsymbol{t}_i}{a}\right)^2 \\ =& \frac{k_BTl_p}{2a}\sum_i^N (\boldsymbol{t}_{i+1}^2 - 2\boldsymbol{t}_{i+1}\cdot\boldsymbol{t}_i + \boldsymbol{t}_i^2) \\ =& \frac{k_BTl_p}{a}\left(1 - \sum_i^N \boldsymbol{t}_i\cdot\boldsymbol{t}_{i+1}\right) \end{aligned}$$

where $\boldsymbol{t}^2 = 1$ since we have an inextensible string. This Hamiltonian is analogous to the Heisenberg spin model ($H = -J\sum_i S_iS_{i+1}$). Note that

$$\langle \boldsymbol{t}_i\cdot\boldsymbol{t}_{i+1}\rangle = \langle\cos\theta\rangle$$

The partition function $Z = \sum e^{-\frac{H}{k_BT}}$ can be written in continuous form as the integral over a sphere with radius $r = 1$ i.e.

$$\begin{aligned} Z =& \frac{1}{4\pi}\int_0^{2\pi}\mathrm{d}\phi\int_0^{\pi} e^{\frac{l_p}{a}\cos\theta}\sin\theta\,\mathrm{d}\theta \\ =& \frac{a}{2l_p}\left(e^{l_p/a} - e^{-l_p/a}\right) = \frac{a}{l_p}\sinh\left(l_p/a\right) \end{aligned}$$

To calculate $\langle \boldsymbol{t}_i\cdot\boldsymbol{t}_{i+1}\rangle$ we integrate by parts':

$$\begin{aligned} \langle \boldsymbol{t}_i\cdot\boldsymbol{t}_{i+1}\rangle =& \langle\cos\theta\rangle = \frac{1}{Z}\frac{1}{4\pi}\int_0^{2\pi}\mathrm{d}\phi\int_0^{\pi}\cos\theta\, e^{\frac{l_p}{a}\cos\theta}\sin\theta\,\mathrm{d}\theta \\ =& \frac{1}{2\frac{a}{l_p}\sinh\frac{l_p}{a}}\left\{\Big[-\frac{a}{l_p}e^{\frac{l_p}{a}\cos\theta}\cos\theta\Big]_0^{\pi} - \int_0^{\pi}\frac{a}{l_p}e^{\frac{l_p}{a}\cos\theta}\sin\theta\,\mathrm{d}\theta\right\} \\ =& \frac{1}{\sinh\left(l_p/a\right)}\left\{\cosh\left(l_p/a\right) + \frac{a}{l_p}(e^{-l_p/a} - e^{l_p/a})\right\} \\ =& \coth\left(l_p/a\right) - \frac{a}{l_p} = \mathcal{L}(l_p/a) \end{aligned}$$

where $\mathcal{L}(x)$ is the langevin function.

Let $\langle \boldsymbol{t}_N \rangle$ be the average orientation of the end point of the polymer where all the other points $\boldsymbol{t}_0 \ldots \vec{t}_{N-1}$ are fixed. Then

$$\begin{aligned}
\langle \boldsymbol{t}_N \rangle =& \boldsymbol{t}_{N-1} \langle \boldsymbol{t}_N \cdot \boldsymbol{t}_{N-1} \rangle = \boldsymbol{t}_{N-1} \mathcal{L}(l_p/a) = \boldsymbol{t}_{N-2} \mathcal{L}(l_p/a)^2 \\
\langle \boldsymbol{t}_N \rangle =& \boldsymbol{t}_0 \mathcal{L}(l_p/a)^N \\
\langle \boldsymbol{t}_N \cdot \boldsymbol{t}_0 \rangle =& \mathcal{L}(l_p/a)^N = \left(\coth(l_p/a) - \frac{a}{l_p} \right)^N
\end{aligned}$$

For $\frac{a}{l_p} \ll 1$ this gives

$$\langle \boldsymbol{t}_N \cdot \boldsymbol{t}_0 \rangle \approx (1 - \frac{a}{l_p})^N = e^{N \ln 1 - \frac{a}{l_P}} \approx e^{-Na/l_p}$$

Hence

$$\langle \boldsymbol{t}(0) \cdot \boldsymbol{t}(s) \rangle \approx e^{-s/l_p}$$

i.e. the correlation of orientations decreases exponentially. This implies that the persistence length l_p is the distance over which the polymer forgets its orientation. This is another definition of the persistence length l_p as well as our previous definition $l_p = \frac{\kappa_b}{k_B T}$ in terms of the bending modulus.

2.4.2 End to end distance

See problems class.

Topic 3

DNA

3.1 Structure

The famous double helix structure of DNA was discovered thanks to Rosalind Franklin's x-ray crystallography data (1951-2). Her supervisor Maurice Williams showed her data to Watson. Watson (a biologist) and Crick (a physicist) worked out the double helix structure from the x-ray diffraction pattern in Franklin's data. They published their paper in 1953. Watson, Crick and Williams got the Nobel prize.

DNA is a polymer with 4 different types of monomer: A (adenine), G (guanine), T (thymine) and C (cytosine). These monomers are called "bases". We can think of these bases (monomers) as a 4 letter alphabet. 3 of them together code for one "amino acid" which is a monomer of a protein. There are 20 different types of amino acids - we can think of the DNA code for these as 3-letter words. Combinations of these 3-letter words make up what we can think of as sentences composed using the 20 possible words. Each sentence is a *gene* and encodes for a *protein*.

The bases stack into 2 phosphate "backbones" and these hydrogen bond to each other forming a double helix. A pairs only with T and G pairs only with C. This means the DNA can be copied in DNA replication.

The *central dogma of molecular biology* is that DNA can undergo *replication* (by DNA polymerase) and *transcription* (by RNA polymerase) forming messenger *RNA*. RNA can undergo *translation* (by the ribosome) to form *proteins*.

Transcription factors are molecular switches that turn genes of/off by binding to the region of DNA just before a gene. A *promoter* X activates (turns on) a gene Y i.e. $X \to Y$. A repressor X represses (turns off) a gene Y i.e. $X \dashv Y$. Other molecules can activate/deactivate transcription

factors. e.g. the lac repressor binds to DNA only when lactose is absent. When there is no lactose present it binds to DNA and turns off the genes for lactose metabolism thereby saving energy.

3.1.1 Semiflexible polymer

The persistence length of DNA $l_p \sim 50\,\mathrm{nm}$ is much larger than its width ($\sim 2\,\mathrm{nm}$). The whole length of human DNA is $L \sim 2\,\mathrm{m}$. However fragments of DNA that are commonly used in experiments and sequencing have $L \sim l_p$ so behave as semiflexible polymers. Therefore DNA is often modelled as a semiflexible polymer.

3.1.2 Topology of DNA

DNA can behave like a telephone cable in which twist (T_w) transforms into writhe (W_r). This is called *supercoiling*. For constant topology the linking number $L_k = T_w + W_r$ is constant. Writhe is the sum of crossings, $W_r = \frac{1}{2}(\text{number of positive crossings} - \text{number of negative crossings})$. The winding number is found by dividing the total angle by 2π.

To read the bases that form the genetic code (to replicate DNA or make proteins) the double helix has to untwist. As DNA is twisted this leads to over/under twisting, supercoiling, knotting etc. In the case of circular DNA (bacteria) the double helix linking number is $L_k = 1$ and reading the genetic code can lead to knotting.

The enzyme topoisomerase (a protein) comes to the rescue. There are 2 types: Topo 1 binds to a single strand of DNA, cuts the phosphate backbone, allows DNA to relax and untangle and then the DNA reconnects. Topo 2 cuts both strands of DNA, passes another unbroken strand through and reconnects. Both these change the linking number of DNA (i.e. the number of times strands are linked around each other). Topo 1 changes L_k by 1 and Topo 2 changes it by 2.

Relaxed DNA (no twist so $L_k = W_r$) has $L_k(0) =$ number of turns $=$ number of base pairs in nm$/10.4$. The pitch is $3.4\,\mathrm{nm}$ and 1 base pair has length $\sim 0.34\,\mathrm{nm}$. Plectonemes (supercoiled extra loops) can be made experimentally by rotating a single DNA molecule with a magnetic bead on the end and applying a magnetic field.

The twist energy can be written as:

$$F_{\text{twist}} = \frac{1}{2} k_B T l_T \int_0^L (\omega - \omega_0)^2 \mathrm{d}s$$

where l_T is the twist persistence length, $\omega = \frac{\partial \phi}{\partial s}$ and ϕ is the angle. To minimise the energy we need $\frac{\partial^2 \phi}{\partial s^2} = 0$, therefore the form of the angle is $\phi = as + b$. Given $\phi = 0$ for $s = 0$ and $\phi = \omega_0 L + \Delta\phi$ for $s = L$ where $\Delta\phi$ is the extra rotation due to twist, the angle is given by $\phi = (\omega + \Delta\phi/L)s$ so $\omega = \frac{\partial \phi}{\partial s} = \omega_0 + \Delta\phi/L$. Therefore the twist energy can be written as

$$F_{\text{twist}} = \frac{1}{2} k_B T l_T \frac{(\Delta\phi)^2}{L}.$$

The torque needed to produce this twist is then $\Gamma = \frac{\partial F_{\text{twist}}}{\partial \Delta\phi} = k_B T l_T \Delta\phi / L$.

To calculate the energy of a plectoneme we model a plectoneme as a circle of radius R. The work done against force is $2\pi R f$ and the bending energy cost is $\frac{1}{2} k_B T l_p \frac{1}{R^2} 2\pi R$ therefore the total energy cost of a plectoneme is:

$$F_{\text{plect}} = 2\pi R f + \pi k_B T l_p / R$$

We minimise this ($\frac{\partial F_{\text{plect}}}{\partial R} = 0$) to find the radius of a plectoneme:

$$R = \sqrt{\frac{k_B T l_p}{2f}}$$

and therefore the energy cost to make a plectoneme is $F_{\text{plect}} = 2\pi\sqrt{2 f k_B t l_p}$. The energy provided by torque is $2\pi\Gamma$ and therefore plectonemes are formed if the torque $\Gamma > \Gamma_c = \sqrt{2 f k_B T l_p}$. This corresponds to a critical number of turns of overtwist of angle $\Delta\phi$ to get a plectoneme.

Topic 4

Proteins

See slides for pictures.

4.1 Structure

Proteins are biopolymers that are made up of monomers called amino acids (sometimes called residues). Each monomer in a protein can be different (unlike simple polymers like polyethene). Amino acids all contain central carbon atom surrounded by a hydrogen, a carboxyl group, an amino group and a 4th group which is different for each amino acid. There are 20 naturally occurring amino acids. 9 are neutral, nonpolar and hydrophobic. 6 are polar and hydrophilic but overall neutral. 3 are positively charged (basic) and hydrophilic and 2 are negatively charged (acidic) and hydrophilic. Proteins are special polymers since they fold up into unique shapes rather than random walk shapes. Their unique shape is determined by the interactions between different parts of the molecule. The main important interactions are:

- Covalent bonds between atoms (harmonic springs) $U = k(x - x_0)^2$
- Ionic (Coulomb) interactions between charges $U = \frac{q_1 q_2}{\epsilon r}$
- van der Waals interactions between dipoles $U = \frac{A}{r^{12}} - \frac{B}{r^6}$
- Hydrogen bonds between slightly positive hydrogen atoms and slightly negative oxygen atoms (e.g. in water molecules of which there are usually many surrounding a protein)

- Hydrophobic interactions due to the entropic cost of ordering water molecules around the molecules that hate water. These are still poorly understood.

Proteins are often charged like other biopolymers (e.g. DNA is negatively charged). However when in solution oppositely charged ions in the surrounding solution associate near to a charged biopolymer and screen the charges so the biopolymer appears less charged. The ions on the biopolymer are called co-ions and the ions from the solution are called counterions. Counterions minimise the electrostatic energy by being close to the co-ions on the biopolymer. However they maximise entropy by diffusing away. The result of these opposing effects is what is called a "counterion cloud" surrounding the biopolymer. The Poisson-Boltzmann equation $\frac{\mathrm{d}^2V}{\mathrm{d}x^2} = -\frac{ze\rho_0}{\epsilon_r\epsilon_0}e^{-zeV/(k_BT)}$ describes this in more detail, where V is the electrical potential, e is the charge of an electron, z is the number of charges and ρ_0 is the average density of ions.

Protein structure is often described in terms of primary, secondary, tertiary and quaternary structure. The primary structure is simply the sequence of amino acids that make up the protein chain. The secondary structure is the shapes this chain folds up into locally e.g. a helix shape called an alpha-helix or a lined up (parallel or antiparallel) into a flat structure called a beta-sheet. The tertiary structure describes the shape these secondary structure shapes ("motifs") fold into. Finally quaternary structure refers to the shape formed when multiple proteins bind together to form e.g. a dimer, trimer or tetramer or 2, 3 or 4 proteins respectively. Protein filaments that we have already met in this course (e.g. actin) are made up of not just 2 or 3 but many 100s of proteins bound together into a filament.

How proteins fold into their unique shape is not yet understood. One major driving force is the hydrophobic effect. For proteins inside a cell the hydrophobic residues want to hide inside the protein with the hydrophilic residues on the outside next to the surrounding water. However some proteins sit in the membrane and for these the reverse is true - the hydrophobic residues want the be on the outside of the protein next to the lipids (lipids are fats so hydrophobic residues like them in the same way as they like oil). It turns out to be very complicated to calculate the free energy of folding ΔG_{fold}. There are more than 10^{100} different possible configurations (shapes) for an average sized protein. Imagine a protein was to randomly try all of these until it found the best one. It would take longer than the age of the universe to do this! However real proteins fold in milliseconds. This is called Levinthal's paradox. Attempts to explain this paradox describe

protein folding landscapes with valleys and local minima on the way to the global minimum. The protein folding problem is one of the big unsolved problems in biophysics.

4.2 Molecular recognition

Why is the shape of a protein so important? The shape of a protein determines to a large extent the function of a protein, in particular what it can bind to. Other proteins or other molecules can bind to proteins at specific binding sites e.g. by fitting into a particular place like a key fitting into a lock. For example there are many proteins that bind to DNA at specific sites on the DNA. Such binding is determined by the thermodynamics

$$\Delta G = \Delta U - T\Delta S$$

where the ΔU includes the electrostatics, Hydrogen bonds, van der Waals interactions and ΔS includes the vibrational entropy of the molecules and the hydrophobic effects. For binding to occur the free energy $\Delta G < 0$. So the image of a key fitting into a lock is not quite right. Due to thermal motion the key and the lock are wiggling about! If binding 2 molecules together prevents some of this vibration this corresponds to an entropic cost (decrease in entropy, ΔS negative) and the ΔU term must be strong enough (negative enough) to overcome this for binding to occur.

Topic 5

Polymerisation of protein filaments: Actin and microtubules

5.1 Introduction

Please see slides for pictures.

Actin and microtubules are 2 of the most common polymers found in biological cells. They are made up of subunits or monomers that themselves are polymers. These monomer units are proteins made up of thousands of atoms folded up into a particular shape. For our purposes we will treat this shape, which is sometimes called a globule, as a sphere. Thousands of these subunits join together to make a filament. Actin filaments look like 2 strands twisted around each other. Microtubules are bigger (25nm diameter) and stiffer. They are made up of 13 strands forming a tube.

Actin and microtubules play many important roles in cells. The make up what is called the “cytoskeleton” which is the polymer gel that gives animal cells their rigidity (like our bone skeleton does for us). Actin and microtubules assemble into different structures in the cell. For example, when a cell is about to divide microtubules form a structure called the “mitotic spindle”. The DNA is in the centre and the microtubules pull the 2 replicated sets of DNA apart.

5.2 Persistence length

In topic 2 about polymers we introduced the concept of persistence length l_p. Persistence length is a measure of how stiff a polymer is. A stiff rod-like polymer has a long persistence length and a flexible string-like polymer has a short persistence length. Let us consider a polymer as a curved line with arc length coordinate s along its length. At a particular point $\vec{r}$, we can define its local curvature

$$\frac{1}{R} = \frac{\partial\theta}{\partial s} = \frac{\partial^2\vec{r}}{\partial s^2}$$

where R is the radius of curvature and θ is the angle of the curve at point $\vec{r}$. The free energy of such a curved line of total length L is given by:

$$F = \frac{1}{2}k_B T l_p \int_0^L \frac{1}{R^2}\mathrm{d}s \tag{5.1}$$

where $k_B T$ is the thermal energy. We can define the persistence length macroscopically relating it to the Young's modulus E of the material making up the polymer:

$$l_p = \frac{Ea^4}{k_B T} \tag{5.2}$$

where a is the radius of the polymer. We can also define l_p microscopically:

$$l_p = l_0 e^{\Delta\epsilon/k_B T} \tag{5.3}$$

where l_0 is the subunit/monomer size and $\Delta\epsilon$ is the energy cost of a change in angle of the monomers (cis/gauche).

Whether a polymer is flexible or stiff depends on how long it is (L) compared to its persistence length l_p.

$L \gg l_p$	flexible
$L \sim l_p$	semiflexible
$L \ll l_p$	rod like

Examples of l_p for biopolymers are:

$l_p \sim 50\,\mathrm{nm}$	DNA
$l_p \sim 20\,\mu\mathrm{m}$	actin
$l_p \sim 5\,\mathrm{mm}$	microtubules

Compare these values to typical cell sizes: $1 - 10\,\mu\mathrm{m}$ for bacteria and $10 - 100\,\mu\mathrm{m}$ for eukaryote (animal/plant). Therefore for filament lengths of order the cell size (commonly the case), actin is semiflexible and microtubules are rod like.

5.3 Fluctuations of actin

Let us consider a semiflexible actin filament as a straight line along the x axis with deviations u away from horizontal. The free energy is given by

$$F = \frac{1}{2} k_B T l_p \int_0^L \left(\frac{\mathrm{d}^2 u}{\mathrm{d}x^2} \right)^2 \mathrm{d}x \tag{5.4}$$

A small displacement δu will have an energy cost of

$$\begin{aligned} \delta F = F - F_0 &= \frac{1}{2} k_B T l_p \int_0^L \left[\left(\frac{\mathrm{d}^2 u}{\mathrm{d}x^2} + \frac{\mathrm{d}^2 \delta u}{\mathrm{d}x^2} \right)^2 - \left(\frac{\mathrm{d}^2 u}{\mathrm{d}x^2} \right)^2 \right] \mathrm{d}x \\ &\approx k_B T l_p \int_0^L \frac{\mathrm{d}^2 u}{\mathrm{d}x^2} \frac{\mathrm{d}^2 \delta u}{\mathrm{d}x^2} \mathrm{d}x \end{aligned}$$

We integrate this by parts twice assuming that $\delta u(0, L) = \frac{\mathrm{d}\delta u}{\mathrm{d}x}(0, L) = 0$ obtaining

$$\delta F = k_B T l_p \int_0^L \mathrm{d}x \frac{\mathrm{d}^4 u}{\mathrm{d}x^4} \delta u$$

Since energy is force times distance $\delta F = \int_0^L f \delta u \, \mathrm{d}x$ where f is force per unit length. Therefore

$$f = k_B T l_p \frac{\mathrm{d}^4 u}{\mathrm{d}x^4}$$

and the equation of motion for the filament is

$$k_B T l_p \frac{\partial^4 u}{\partial x^4} = -\xi_\perp \frac{\partial u}{\partial t}$$

where $\xi_\perp$ is the friction coefficient for fluctuations perpendicular to the filament and $\frac{\partial u}{\partial t}$ is the velocity perpendicular to the filament.

5.4 Polymerisation of actin

Actin polymerisation is not the usual equilibrium polymerisation of polymers that occurs spontaneously to minimise the energy. Polymerisation of actin costs energy. This energy comes from the biochemical energy stored in the molecule called ATP. ATP is created by the cell from the food (sugar) it takes in. The energy from the food is stored in the molecule ATP and ATP is used in many biochemical reactions in the cell. ATP gives the energy required to pay the cost of biochemical reaction such as polymerisation of

actin. One ATP molecule is needed for every monomer added to an actin filament. Due to this internal source of energy, ATP, many processes in a biological cell are *out of equilibrium*. In biophysics research we call these out of equilibrium processes *active*.

Actin has 2 ends. It can polymerise and depolymerise at both ends. The *barbed end* also called the *plus end* polymerises faster and the *pointed end* also called the *minus end* depolymerises faster. Let $k_p^+ c$ be the rate of polymerisation at the plus end, where c is the concentration of monomers (G-actin). Similarly $k_p^- c$ is the rate of polymerisation at the minus end. Let k_d^+ and k_d^- be the rate of depolymerisation at the plus and minus ends respectively. We can write a *master equation* for this process. A master equation describes the time evolution of probabilities. Here the probability we are interested in is P_n, the probability of a filament having n monomers. The master equation for this process is

$$\frac{\mathrm{d}P_n}{\mathrm{d}t} = (k_p^+ + k_p^-)c(P_{n-1} - P_n) - (k_d^+ + k_d^-)(P_n - P_{n+1})$$

Let us simplify this by assuming that polymerisation only occurs at the plus end and depolymerisation only occurs at the minus end, i.e. $k_p^- = k_d^+ = 0$ and $k_p^+ = k_p$ and $k_d^- = k_d$. The the master equation is

$$\frac{\mathrm{d}P_n}{\mathrm{d}t} = k_p c P_{n-1} - (k_p c + k_d)P_n + k_d P_{n+1}$$

We can find the probability distribution $P_n(n)$ at steady state i.e. when $\frac{\mathrm{d}P_n}{\mathrm{d}t} = 0$. By writing the equation in the from:

$$k_p c(P_{n-1} - 2P_n + P_{n+1}) + (k_d - k_p c)(P_{n+1} - P_n) = 0$$

we can transform this discrete master equation to a continuous for by identifying $(P_{n+1} - P_n) = \frac{\mathrm{d}P_n}{\mathrm{d}n}$ and $(P_{n+1} - 2P_n + P_{n+-1}) = \frac{\mathrm{d}^2 P_n}{\mathrm{d}n^2}$. Therefore

$$\begin{aligned}
\frac{\mathrm{d}^2 P_n}{\mathrm{d}n^2} + \frac{(k_d - k_p c)}{k_p c}\frac{\mathrm{d}P_n}{\mathrm{d}n} &= 0 \\
\frac{\mathrm{d}P_n}{\mathrm{d}n} &= -\frac{(k_d - k_p c)}{k_p c}P_n + A \\
P_n &= Be^{-\frac{(k_d - k_p c)}{k_p c}n} + A'
\end{aligned}$$

where A, and B are constants of integration. Boundary conditions tell us that $A' = 0$ and $B = P_0$ so we have

$$P_n = P_0 e^{-\frac{(k_d - k_p c)}{k_p c}n}$$

If $k_d > k_p c$ the length is bounded and the distribution is an exponential decay. If $k_p c > k_d$ the length is unbounded can become infinitely long, which is not likely physically. In the case of unbounded growth the length will be limited by the number of monomers being used up i.e. to model this correctly we can no longer assume that c is constant. If $k_p c = k_d$ then $P_n = P_0$ and the length is constant. Polymerisation at the plus end is exactly balanced by depolymerisation at the minus end and the length is constant by the actin filament appears to translate in space. This is called *treadmilling*.

5.5 Force generation by polymerisation

A filament polymerising against a barrier can exert a force on the barrier (if the other end of the filament is fixed of tethered in some way). If the polymerising end of a filament is touching a barrier a gap needs to appear in order to insert another monomer. Since the barrier and filament are moving with Brownian motion such a gap will appear. When a gap is present a monomer can bind and then the barrier cannot move back again. This means the barrier cannot perform a random walk - it can only move forwards as the filament stops it moving backwards. In this way the filament exerts a force on the barrier. This mechanism is called a *Brownian ratchet*. The energy (work done) is given by fb where f is the force generated and b is the monomer size. The polymerisation rate k_p is proportional to the probability of attaching a monomer which is a Boltzmann distribution $P \sim e^{-E/(k_B T)}$ where here the energy E is the work done fb i.e.

$$k_p = k_p^0 e^{-\frac{fb}{k_B T}}$$

Rearranging this gives the force generated

$$f = -\frac{k_B T}{b} \ln \frac{k_p}{k_p^0}$$

We can estimate this by assuming that the ration $\frac{k_p}{k_p^0} \sim \frac{1}{10}$ and $b \sim \mathrm{nm}$ and $k_B T \sim 4\,\mathrm{pN\,nm}$ therefore $f \sim 10\,\mathrm{pN}$.

Remember the reason actin polymerisation can exert a force in this way is due to the fact that the system is out of equilibrium due to the internal source of energy in the form of the molecule ATP.

5.6 Microtubule Dynamic Instability

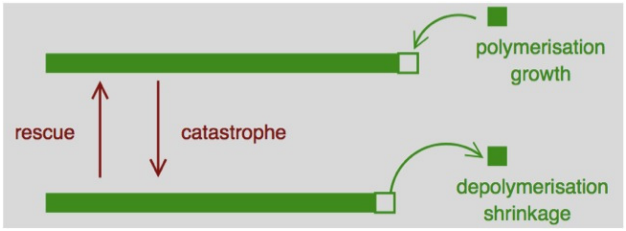

Figure 5.1: A microtubule fixed at one end can be either in a growing or shrinking state. It can switch states stochastically.

Microtubules, like actin, can actively polymerise and depolymerise. Almost all the polymerisation and depolymerisation of microtubules happens at the same end. Microtubules can exist in 2 possible states: a growing state (polymerising) or a shrinking state (depolymerising). Let the growth speed by v^+ and the shrinking speed be v^-. Let the probability of a growing microtubule of length l be denoted by $P^+(l,t)$ and the probability of a shrinking microtubule of length l be denoted by $P^-(l,t)$. Mircotubules in a growing state can spontaneously switch to a shrinking state with a rate k_C. This is known as a "catastrophe". Shrinking microtubules can spontaneously switch to a growing state with a rate k_R. This is know as a "rescue". We can write down coupled master equations for the polymerisation and depolymerisation of microtubules. We can solve these equations in steady state to find the distribution of microtubule lengths $P(l)$. See problems class.

Topic 6

Biopolymer gels - cytoskeleton

6.1 Viscoelasticity in polymers

An elastic solid obeys Hooke's law i.e. the deformation x is linear in the force f i.e. $f = -kx$, where k is the spring constant. Dividing this equation by area we obtain the tensile stress, $\sigma = E\gamma$ where $\gamma = \frac{\Delta x}{x}$ is the extensile strain and E is the Young's modulus. The shear stress $\sigma = G\gamma$ where G is the shear modulus and $\gamma = \frac{\Delta x}{y}$ is the shear strain.

A simple liquid (a Newtonian liquid) flows with a constant strain rate $\dot{\gamma}$ in response to an applied shear stress i.e. $\sigma = \eta\dot{\gamma}$ where η is the viscosity. NB The strain rate $\dot{\gamma}$ is sometimes denoted u.

Viscoelastic materials have viscous and elastic properties: their response depends on time. At short times $t < \tau$ they are elastic and behave like solids. On long times $t > \tau$ they are viscous and behave like liquids. $\tau = \eta/G_0$ is the relaxation time, where G_0 is the instantaneous elastic shear modulus at short times. The Maxwell linear response model:

$$\left(1 + \tau\frac{\mathrm{d}}{\mathrm{d}t}\right)\sigma = \eta\,\dot{\gamma} \tag{6.1}$$

is the simplest model for viscoelasticity. The first term ($\tau \sim 0$) is the viscous term and the second term (large τ) is the elastic term.

Non-Newtonian fluids (complex fluids) can have a viscosity that depends on shear rate i.e. $\sigma = \eta(\dot{\gamma})\dot{\gamma}$. If the viscosity is constant with respect to the shear rate the fluid is Newtonian (e.g. water). If the viscosity decrease with shear rate we call it *shear thinning* (e.g. paint). If the viscosity increases with shear rate we call it *shear thickening* (e.g. cornflour paste).

6.1.1 Rheology measurements

Rheology is the study of how materials flow. In the following we discuss different measurements that can be made.

The *creep compliance* $J(t)$ is measure by applying a constant stress, σ_0, and measuring the strain over time, $\gamma(t) = \sigma_0 J(t)$. Viscoelastic materials respond initially with a fast elastic response, then at long times show a viscous response with a constant strain rate.

The *stress relaxation modulus* $G(t)$ is measured by applying a constant strain, γ_0, and measuring the stress as a function of time, $\sigma(t) = \gamma_0 G(t)$. For a viscoelastic material the initial response at short times is elastic and at longer times as the material starts to flow the stress decreases to zero.

A common rheological measurement is to apply an oscillating strain deformation at a frequency ω i.e. $\gamma(t) = \gamma_0 \cos \omega t$. The stress response is

$$\sigma(t) = \gamma_0 (G'(\omega) \cos \omega t - G''(\omega) \sin \omega t)$$

where $G^*(\omega) = G' + iG''(\omega)$ is the complex modulus given by

$$G^*(\omega) = i\omega \int_0^\infty e^{-i\omega t} G(t) \mathrm{d}t$$

$G^*(\omega)$ tells us about both the elastic and viscous response at a given frequency ω. The real part $G'(\omega)$ is the elastic component and is called the *storage modulus*. The imaginary part $G''(\omega)$ is the viscous component and is called the *loss modulus*.

There is a temperature dependence to rheological measurements. A very viscous polymer solution or melt will become less viscous when the temperature T is increased. The effect of temperature on the stress relaxation modulus G is similar to the effect of time. Experimental evidence shows that we can write $G(t, T) = G(a_T t, T_0)$ where a_T is a shift factor and T_0 is a reference temperature. This is called *time-temperature superposition*. This implies that all microscopic time scales scale with temperature in the same way. This is very useful experimentally as it means we can measure a material at a higher temperature to get the effective longer time behaviour.

At intermediate times $G(t)$ is approximately constant at a value G_p called the plateau modulus, which is independent of the degree of polymerisation N. In the plateau region the polymer behaves like an elastic solid (like a rubber). The plateau ends at the terminal time $\tau_T \sim N^m$ where $m \approx 3.4$ from experiments (see next section for theoretical explanation). At later times $t > \tau_T$ the polymer flows with zero shear viscosity $\eta_0 = \int_0^\infty G(t - \tau) \mathrm{d}\tau \sim \tau_T G_p$.

6.1.2 Entanglements

Viscosity in polymers can be understood by thinking about entanglements. Chains cannot pass through each other so when we try to shear a polymer melt the chains will become entangled. The rubber like plateau is due to entanglements that act as temporary cross links (a rubber is a cross linked polymer). These temporary cross links can disentangle on a timescale of τ_T. Longer chains will take longer to disentangle so τ_T will depend in N.

The *tube model* can explain this dependence $\tau_T(N)$. Imagine a single polymer chain is confined inside a tube. This imaginary tube is due to the other chains surrounding the chain we are interested in. Let τ_T be the time it takes for the polymer to move out of its original tube. We assume the motion inside the tube is purely viscous i.e. velocity, v, is proportional to the resistive force, f, with proportionality constant mobility, μ. The mobility can be written in terms of the diffusion constant D as $\mu = \frac{v}{f} = \frac{D}{k_B T}$. The mobility of the polymer can be written in terms of the mobility of a single segment, $\mu = \mu_{\text{seg}}/N$. The diffusion constant of the polymer is the written as $D = k_B T \mu_{\text{seg}}/N$. We assume the polymer inside the tube performs a random walk $L^2 \sim D\tau_T$. Therefore $\tau_T \sim \frac{L^2 N}{k_B T \mu_{\text{seg}}} \sim N^3$ since $L \sim N$. The exponent $m = 3$ of scaling $\tau_T \sim N^3$ is close to the experimental exponent $m \approx 3.4$. To get a value closer to reality extensions to this tube theory include constraint release and contour length fluctuations.

6.2 Active gel

The cytoskeleton is made up of 3 main protein biopolymers: actin, microtubules and intermediate filaments. These form a soft material. Due to crosslinks between the polymer chains it forms a polymer gel. However, unlike gels like hair gel, it is out of equilibrium. We call such an out of equilibrium material “active” so the cyctoskeleton can be described as an “active gel”. It is continually driven out of equilibrium due to the consumption of biochemical energy. In this course we have already talked about one resulting behaviour — actin and microtubules can use this energy to polymerise. In a cell these protein filaments are very dynamic — they depolymerise and repolymerise. A second out of equilibrium property of the cytoskeleton is due to molecular motors. These are protein molecules that can bind to cytoskeleton filaments and move (“walk”) along them. Molecular motors or clusters of them can also bind to 2 filaments at the same time. If the filaments are parallel the motors can walk along both filaments at the same time. However, since motors will only walk in a particular di-

rection along a filament, if the filaments are not parallel the motors will exert stress. In the case of actin with molecular motors called myosin this results in contractility.

Topic 7

Membranes

7.1 Composition of biomembranes

A biomembrane is a plasma membrane, which is a 2D fluid and therefore has no resistance to in plane shear. The membrane surrounding a cell is a lipid bilayer, which is 2 layers of lipid molecules. Phospholipids (lipids) are amphiphiles meaning they have a polar head group which is hydrophilic (loves water) and a hydrocarbon chain tail which is hydrophobic (hates water). An everyday example of such a molecule is soap. The polar head wants to be next to water and the hydrophobic tail wants to be next to oil. In a lipid bilayer many lipids self assemble into 2 layers of heads with their tails in between the layers. There are other phases possible for lipids such as micelles which are small spheres with head groups on the edge and tails in the middle. Micelles form spontaneously when the concentration of lipids in water is increased above the critical micelle concentration. If the concentration is increased again inverted micelles form in which spherical droplets of water are surrounded by lipid heads and their tails point outwards towards the tails of neighbouring inverted micelles.

7.2 Self assembly

At the critical micelle concentration individual amphiphiles/lipids aggregate into clusters. Energy favours clusters but entropy favours uniform distribution of molecules. To estimate the energy cost of a free molecule we assume that the area of the hydrophobic tail is the surface area of a cylinder of radius R and length nl_{cc} where n is the number of carbons in the hydrocarbon chain and lcc is the length of a carbon-carbon bond. The energy

cost of a free molecule is then this area multiplied by the surface tension γ of the water/hydrocarbon interface i.e. $E = 2\pi R n l_{cc}\gamma$. To estimate the entropy per molecule we assume the molecules are like an ideal gas with $S = k_B(\frac{5}{2} - \ln \frac{\rho h^3}{(2\pi m k_B T)^{5/2}})$ where h is Planck's constant, ρ is the density and m is the mass of a molecule. The free energy per molecule in the solution phase is therefore given my $F = E - TS$ and the cross over between energy dominated and entropy dominated is at $F = 0$. Putting in typical numbers leads to very low density ρ implying that bilayers won't break up easily.

The shape of an aggregate is related to the shape of the amphiphile molecule (for more details see Israelachiviliv 1976). e.g. for a spherical micelle of radius R, surface area $4\pi R^2$ and volume $\frac{4}{3}\pi R^3$ made up of molecules with head surface area a_0 and tail volume v_{hc} we can find the radius R in terms of the molecular shape by equating the surface area and volume ratios i.e. the number of molecules $= \frac{4\pi R^2}{a_0} = \frac{4\pi R^3}{3v_{hc}}$ giving $R = 3v_{hc}/a_0$. In order to have no hole in the middle we need the radius to be less than the tail length i.e. $R \leq n l_{cc}$ where n is the number of carbons and l_{cc} the length of a carbon carbon bond. This gives a shape factor $\frac{v_{hc}}{a_0 n l_{cc}} \leq \frac{1}{3}$ i.e. a large surface area to volume ratio i.e. cone shaped. Similar arguments lead to cylindrical micelles (shape factor $1/3$ to $1/2$), bilayers (shape factor $1/2$ to 1) and inverted micelles (shape factor > 1). Single chain lipids have a shape factor of $\frac{v_{hc}}{a_0 n l_{cc}} \sim 0.4$ and double chain lipids have a shape factor of ~ 0.8 i.e. double chain lipids form lipid bilayers.

7.3 Tension/Compression

Tension in a wire is $\tau =$ force/length and tension in a surface is $\tau = \frac{\partial F}{\partial A}\big|_N$ where F is the free energy, A is area and N is the number of particles in the membrane (constant). Imagine a thin plate of thickness d under tensile stress σ. The stress tensor is given by

$$\sigma_{ik} = K_V u_{ll}\delta_{ik} + 2\mu(u_{ik} - \frac{1}{3}\delta_{ik}u_{ll})$$

where K_V is the bulk (volume compression) modulus and μ is the shear modulus. The strain tensor is given by

$$u_{ik} = \frac{\sigma_{ll}}{9K_v}\delta_{ik} + \frac{1}{2\mu}(\sigma_{ik} - \frac{1}{3}\delta_{ik}\sigma_{ll})$$

Here we assume $\sigma_{xx} = \sigma_{yy} = \sigma$ and therefore

$$u_{xx} = u_{yy} = \left(\frac{2}{9K_V} + \frac{1}{6\mu}\right)\sigma \tag{7.1}$$

For an applied tension (force/length) of $\tau = \sigma d$ leading to a change in area $u_{xx} + u_{yy}$ then $\tau = K_A(u_{xx} + u_{yy})$ where K_A is the area compression modulus. From equation 7.1 $\sigma d = K_A(\frac{4}{9K_V} + \frac{1}{3\mu})\sigma$ and therefore

$$K_A = \frac{dK_V}{\frac{4}{9} + \frac{K_V}{6\mu}}$$

Now let us consider the energy of the molecules at an interface with water. Let the interface area be a per molecule and the surface tension is γ. For small a the molecules are densely packed (crowded) and they repel each other as $1/a$ however for large a the molecules are dilute and there is an energy cost of γa per molecule. We therefore write the energy as $E \sim \alpha/a + \gamma a$. Minimising this we find the preferred surface area per molecule $a_0 = \sqrt{\alpha/\gamma}$. We rewrite the energy in terms of a_0 eliminating α i.e. $E \sim \gamma a_0^2/a + \gamma a$. The energy density change is then $\sim \gamma\left(\frac{a-a_0}{a_0}\right)^2 \sim \frac{K_A}{2}(u_{xx} + u_{yy})^2$ therefore $K_A = 2\gamma$ for a monolayer and $K_A = 4\gamma$ for a bilayer.

7.4 Bending/curvature

In 1D you know that the curvature $\kappa(s) = C(s) = \frac{1}{R(s)}$ where s is the arc length coordinate along the contour of the curve. The curvature of a surface has 2 principle radii of curvature on the 2 directions of maximum and minimum curvature, $C_1 = \frac{1}{R_1}$ and $C_2 = \frac{1}{R_2}$. The curvature tensor (matrix) is then

$$\begin{pmatrix} C_1 & 0 \\ 0 & C_2 \end{pmatrix}$$

e.g. for a sphere $R_1 = R_2 = R$ and a cylinder $R_1 = R$ and $R_2 = \infty$. We define the mean curvature $= \frac{1}{2}(C_1 + C_2)$ and the total curvature as the trace of the curvature tensor i.e. $C_T = (C_1 + C_2) = (\frac{1}{R_1} + \frac{1}{R_2})$ and the Gaussian curvature as the determinant of the curvature tensor i.e. $K = C_1C_2 = \frac{1}{R_1R_2}$. The Gaussian curvature is constant for constant topology. The bending

energy density is then given by

$$\begin{aligned}\frac{E}{A} =& \frac{\kappa_b}{2}\left(\frac{1}{R_1}+\frac{1}{R_2}\right)^2 + \kappa_{_G}\left(\frac{1}{R_1 R_2}\right)\\ =& \frac{\kappa_b}{2}(C_T - C_0)^2 + \kappa_{_G} K\end{aligned}$$

where κ_b is the bending rigidity, C_0 is the spontaneous curvature and $\kappa_{_G}$ is the Gaussian bending rigidity.

The Helfrich Hamiltonian for a membrane is given by:

$$H = \int \mathrm{d}\boldsymbol{S}(\frac{\kappa_b}{2}(C_T - C_0)^2 + \kappa_{_G} K + \gamma) \tag{7.2}$$

where γ is the surface tension and the integral is over the surface area of the membrane.

7.5 Membrane tubes

A common experiment to measure properties of membranes is to pull a tube from a membrane. The vesicle or cell is held in place by a micropipete under suction pressure or by an optical trap and then a bead stuck to the membrane is pulled by (another) optical trap. This pulls a roughly cylindrical tube from the vesicle/cell.

Assuming a negligible pressure difference between the inside and outside of the membrane and a cylindrical shape we can write the free energy using the Helfrich Hamiltonian (7.2) and the work done to pull a tube of length L with a force f:

$$F = A\left(\frac{\kappa_b}{2}(\frac{1}{R_1}+\frac{1}{R_2})^2 + \kappa_G(\frac{1}{R_1 R_2}) + \gamma\right) - fL.$$

For a cylinder of radius r the curved surface area $A = 2\pi r L$ and the radii of curvature are $R_1 = r$ and $R_2 = \infty$ therefore

$$F = \frac{\pi L \kappa_b}{r} + 2\pi r L\gamma - fL.$$

We can calculate the radius of the tube formed by minimising this free energy with respect to r i.e.

$$\begin{aligned}\frac{\mathrm{d}F}{\mathrm{d}r} =& -\frac{\pi L\kappa_b}{r^2} + 2\pi L\gamma = 0\\ r =& \sqrt{\frac{\kappa_b}{2\gamma}}\end{aligned}$$

To pull a tube we need to exert a force $f > f_c$ such that the free energy $F = L(f_c - f)$ is negative and the tube grows to minimise the free energy. From above we can write this critical force as

$$f_c = \frac{\pi\kappa_b}{r} + 2\pi r\gamma = 2\pi\sqrt{\gamma k_b}.$$

If we measure the force required to pull the tube and the radius of the resulting tube we can then find the surface tension and bending rigidity of the membrane. Typical experimental results give $R \sim 30\,\mathrm{nm}$, $F_c \sim 15\,\mathrm{pN}$, $\kappa_b \sim 20k_BT$ and $\gamma \sim 0.05\,\mathrm{pN/\,nm}$.

7.6 Thermal Fluctuations

Another way of measuring membrane properties is to measure the thermal fluctuations a membrane undergoes. Imagine a locally flat section of membrane with effectively zero spontaneous curvature. Thermal energy will result in small fluctuations u in the height of this membrane. Since these deflections are small we can assume constant topology (so the Gaussian curvature K is constant) and that fluctuations are smooth such that gradients in u are small i.e. $|\nabla u| \ll 1$. The total curvature $C_T = \nabla^2 u$. The Helfrich Hamiltonian is then

$$H = H_0 + \int \mathrm{d}x\mathrm{d}y(\frac{1}{2}\kappa_b(\nabla^2 u)^2 + \frac{1}{2}\gamma(\nabla u)^2)$$

where the Gaussian curvature term is absorbed into the constant H_0. This is conveniently expressed in Fourier space using Fourier modes

$$u_q = \int u e^{-iqr}\mathrm{d}r$$

where q is the inverse wavelength. This gives

$$H = \frac{A}{(2\pi)^2}\int \mathrm{d}q\frac{1}{2}u_q^2(\kappa_b q^4 + \gamma q^2)$$

where there is one mode per area $\frac{(2\pi)^2}{A}$ in q space. Using the equipartition of energy ($\frac{1}{2}k_BT$ per mode) we can find the correlations from the average energy per mode:

$$\langle\frac{1}{2}(\kappa_b q^4 + \gamma q^2)u_q^2\rangle = \frac{1}{2}k_BT$$

giving

$$\begin{aligned}\langle u_q u_{q'}\rangle =& \frac{k_B T}{(\kappa_b q^4 + \gamma q^2)} && \text{for } q = q' \\ =& 0 && \text{for } q \neq q'\end{aligned}$$

i.e. each oscillation mode is independent. To convert back to amplitude fluctuations:

$$\langle u^2\rangle = \int \mathrm{d}\frac{q}{(2\pi)^2} \int \mathrm{d}\frac{q'}{(2\pi)^2} \langle u_q u_{q'}\rangle$$

The fluctuations can be imaged directly for low q up until the resolution limit.

Topic 8

Fluctuation-dissipation theorem & violations

8.1 Einstein relation

You may have come across the Einstein relation before (see section 1.7.2). The Einstein relation is a special case of the fluctuation-dissipation theorem. It states that for a system in thermal equilibrium

$$D = \frac{k_B T}{\xi}$$

where D is the diffusion constant and ξ is the friction coefficient. Diffusion provides the fluctuations and the friction is the dissipation. Hence Einstein's relation says that diffusion and friction are related which is a special case of saying that fluctuations and dissipation are related.

The details of the mathematics in the rest of this topic are provided as optional extra. The important thing for this course is the concept of the fluctuation dissipation theorem and that it is only true in equilibrium. It is violated in systems out of equilibrium such as molecular motors.

8.2 Correlation functions

Consider the statistical physics of an equilibrium fluid. For a fluid with N particles there are $6N$ degrees of freedom. $\boldsymbol{r}_i$ is the position of particle i and $\boldsymbol{p}_i$ is its momentum. The Hamiltonian is the function $H(\boldsymbol{r}_i, \boldsymbol{p}_i)$. As

discussed in topic A, the partition function is given by

$$Z = \int \prod_i \mathrm{d}\boldsymbol{r}_i \mathrm{d}\boldsymbol{p}_i e^{-H(\boldsymbol{r}_i,\boldsymbol{p}_i)/(k_B T)}$$

and the free energy is $F = -k_B T \ln Z$.

The average value of an operator (an observable) $A(\boldsymbol{r}_i, \boldsymbol{p}_i)$ is given by

$$\langle A \rangle = \frac{1}{Z} \int \mathrm{d}\boldsymbol{r}_i \mathrm{d}\boldsymbol{p}_i e^{-H/(k_B T)} A(\boldsymbol{r}_i, \boldsymbol{p}_i) \tag{8.1}$$

e.g. if A is the density $\rho(\boldsymbol{r}) = \sum_i \delta(\boldsymbol{r} - \boldsymbol{r}_i)$ then $\langle \rho(\boldsymbol{r}) \rangle = N/V$ If the operator A is independent of time then at time t it is $A(\boldsymbol{r}_i(t), \boldsymbol{p}_i(t))$ where the positions and momenta can be obtained by solving the equations of motion as a function of time t and the initial conditions $\boldsymbol{r}_i^0, \boldsymbol{p}_i^0$. The average $\langle A(t) \rangle$ can be calculated by averaging over the initial positions and momentums i.e.

$$\langle A(t) \rangle = \frac{1}{Z} \int \mathrm{d}\boldsymbol{r}_i^0 \mathrm{d}\boldsymbol{p}_i^0 e^{-H(\boldsymbol{r}_i^0,\boldsymbol{p}_i^0)/(k_B T)} A(\boldsymbol{r}_i^0, \boldsymbol{p}_i^0, t) \tag{8.2}$$

This is independent of t. If equation (8.1) is equal to equation (8.2) then the system is ergodic (Liouville theorem).

We can calculate the 2 point correlation function $G(t, t') = \langle A(t) A(t') \rangle$ (the correlation in A at 2 different points) as:

$$\langle A(t) A(t') \rangle = \frac{1}{Z} \int \mathrm{d}\boldsymbol{r}_i^0 \mathrm{d}\boldsymbol{p}_i^0 e^{-H(\boldsymbol{r}_i^0,\boldsymbol{p}_i^0)/(k_B T)} A(\boldsymbol{r}_i^0, \boldsymbol{p}_i^0, t) A(\boldsymbol{r}_i^0, \boldsymbol{p}_i^0, t')$$

The system has time translation invariance i.e. $G(t + \tau, t' + \tau) = G(t, t')$. If we choose $\tau = -t$ then we have $G(0, t' - t) = G(t, t')$ i.e. the correlation function is only dependent on $(t - t')$. It is invariant under time reversal $t \to -t$ i.e.

$$G(t, t') = \langle A(t) A(t') \rangle = G(t - t') = G(|t - t'|).$$

We now consider the correlation of fluctuations. Consider a fluctuation $\delta A(t) = A(t) - \langle A \rangle$. The fluctuation correlation function is then $C(t - t') = \langle \delta A(t) \delta(A') \rangle$. Time reversal invariance gives $C(t) = C(-t)$ and $C(t) = G(t) - \langle A \rangle^2$ i.e.

$$C(t - t') = \langle A(t) A(t') \rangle - \langle A \rangle^2$$

which is the second cumulant of A. For example let A be the density $\rho = N/V$ and $\delta\rho = \rho - \langle \rho \rangle$. The correlation function for density can be measured by x-ray or neutron scattering.

8.3 Relaxation towards equilibrium

Imagine perturbing a fluid with an external force f so the Hamiltonian $\mathcal{H}(\boldsymbol{r}_i, \boldsymbol{p}_i) \rightarrow \mathcal{H} + \Delta\mathcal{H}$ where $\Delta\mathcal{H} = -f(t)A(\boldsymbol{r}_i, \boldsymbol{p}_i)$. Imagine that at time $t = 0$ we remove the force $f \rightarrow 0$. We then ask how the system relaxes once the force is removed. i.e. $f(t)$ is a step function. The system is prepared with Hamiltonian $\mathcal{H} + \Delta\mathcal{H}$ under force f for time $t < 0$ and then evolves with Hamiltonian $\mathcal{H}$ with zero applied force for time $t \geq 0$. The force f is some generalised thermodynamic force and is a small perturbation. For $t < 0$ we measure $\langle A\rangle_{\mathcal{H}+\Delta\mathcal{H}} = \langle A\rangle$. For $t \geq 0$ we measure $\langle A\rangle_{\mathcal{H}} = \langle A\rangle_0$ where $\langle\rangle_0$ denotes the average in the absence of the perturbation. We want to calculate $\Delta A(t) = \langle A\rangle - \langle A\rangle_0$ as it decays over time. The average $\langle A\rangle$ is given by;

$$\langle A(t)\rangle = \frac{\int \mathrm{d}\boldsymbol{r}_i^0 \mathrm{d}\boldsymbol{p}_i^0 A(\boldsymbol{r}_i^0, \boldsymbol{p}_i^0, t) e^{-\mathcal{H}(\boldsymbol{r}_i^0, \boldsymbol{p}_i^0) + \Delta\mathcal{H}(\boldsymbol{r}_i^0, \boldsymbol{p}_i^0)/(k_B T)}}{\int \mathrm{d}\boldsymbol{r}_i^0 \mathrm{d}\boldsymbol{p}_i^0 e^{-(\mathcal{H}+\Delta\mathcal{H})/(k_B T)}} \tag{8.3}$$

We now perform a first order expansion in $\Delta\mathcal{H}$. The denominator is Z and becomes

$$Z = \int \mathrm{d}\boldsymbol{r}_i^0 \mathrm{d}\boldsymbol{p}_i^0 \left(1 - \frac{\Delta\mathcal{H}}{k_B T}\right) e^{-\mathcal{H}/(k_B T)} = Z_0 \left(1 - \frac{\langle\Delta\mathcal{H}\rangle_0}{k_B T}\right)$$

and the numerator becomes

$$\int \mathrm{d}\boldsymbol{r}_i^0 \mathrm{d}\boldsymbol{p}_i^0 A(\boldsymbol{r}_i^0, \boldsymbol{p}_i^0, t) \left(1 - \frac{\Delta\mathcal{H}}{k_B T}\right) e^{-\mathcal{H}/(k_B T)} = Z_0 \left(\langle A\rangle_0 - \frac{\langle\Delta\mathcal{H} A(t)\rangle_0}{k_B T}\right)$$

and therefore equation (8.3) becomes:

$$\langle A(t)\rangle = \frac{\langle A\rangle_0 - \langle\Delta\mathcal{H}A(t)\rangle_0/(k_B T)}{1 - \langle\Delta\mathcal{H}\rangle_0/(k_B T)} = \langle A\rangle_0 - \frac{\langle\Delta\mathcal{H}A(t)\rangle}{k_B T} + \frac{\langle A\rangle_0\langle\Delta\mathcal{H}\rangle_0}{k_B T} \tag{8.4}$$

We now put in the Hamiltonian for perturbation we have been considering i.e. $\Delta\mathcal{H} = -f(t)A$ leading to;

$$\begin{aligned}
\langle A(t)\rangle =& \langle A\rangle_0 - \frac{f}{k_B T}\langle A(0)A(t)\rangle_0 + -\frac{f}{k_B T}\langle A\rangle_0^2 \\
\Delta A(t) =& \langle A(t)\rangle - \langle A\rangle_0 = \frac{f}{k_B T}(\langle A(0)A(t)\rangle_0 - \langle A\rangle_0^2) \\
\Delta A(t) =& \frac{f}{k_B T} C(t)
\end{aligned} \tag{8.5}$$

i.e. the relaxation of the perturbation ΔA is directly proportional to the relaxation of the thermal fluctuations $C(t)$. This is the Onsager regression hypothesis.

8.4 Response function

A more general form of perturbation $\Delta\mathcal{H} = -f(t)A$ is linear response:

$$\Delta A(t) = \langle A(t)\rangle - \langle A\rangle_0 = \int \mathrm{d}t'\chi(t,t')f(t')$$

which is the most general expression that is linear in $f(t)$. $\chi(t,t')$ is the response function. It obeys time invariance i.e. $\chi(t,t') = \chi(t-t')$. $\chi(t,t') = 0$ if $t < t'$ because of causality i.e. it only depends on a force in the past, $\chi(t) = 0$ if $t < 0$. Therefore

$$\Delta A(t) = \int_{-\infty}^{t} \chi(t-t')f(t')\mathrm{d}t'$$

For example for a step function $f(t<0) = f$ and $f(t \geq 0) = 0$ then

$$\Delta A(t) = \int_{-\infty}^{0} \chi(t-t')f\mathrm{d}t'$$

If we let $u = t-t'$ then $\Delta A(t) = \int_t^\infty \chi(u)f\mathrm{d}u$. Using the Onsager hypothesis equation (8.5) we obtain

$$\frac{fC(t)}{k_BT} = f\int_t^\infty \chi(u)\mathrm{d}u$$

which when differentiated gives the fluctuation dissipation theorem:

$$\boxed{\frac{\partial C}{\partial t} = -k_BT\chi(t)} \qquad \text{for } t > 0 \tag{8.6}$$

where $C(t)$ is the fluctuation in the non perturbed system and $\chi(t)$ is the response function to a perturbation with force $f(t)$. These 2 functions $C(t)$ and $\chi(t)$ can be measured by different experiments, the results of which can be related by the fluctuation dissipation theorem equation (8.6). The fluctuation dissipation theorem is very general: it applies to any system at thermodynamic equilibrium for small perturbations f, $\Delta\mathcal{H}$ (so linear response valid).

8.5 Frequency space form

The Fourier transform of the thermal fluctuation $c(t)$ is called the power spectrum $\tilde{c}(\omega)$ and is given by

$$\begin{aligned}\tilde{c}(\omega) =& \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} c(t) e^{i\omega t} \mathrm{d}t \\ c(t) =& \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} \tilde{c}(\omega) e^{-i\omega t} \mathrm{d}\omega\end{aligned}$$

(NB the convention of $+i\omega t$ for variable time and $-ikx$ if the variable was x ensures waves propagate in the forward direction.) Since $c(t) = c(-t)$ (even) we can write

$$\begin{aligned}\tilde{c}(\omega) =& \frac{2}{\sqrt{2\pi}} \int_{0}^{\infty} c(t) \cos \omega t \ \mathrm{d}t \\ -i\omega\tilde{c}(\omega) =& \frac{2}{\sqrt{2\pi}} \int_{0}^{\infty} \frac{\partial c}{\partial t} \sin \omega t \ \mathrm{d}t\end{aligned} \tag{8.7}$$

The Fourier transform of the response function is given by

$$\tilde{\chi}(\omega) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} \chi(t) e^{i\omega t} \mathrm{d}t = \frac{1}{\sqrt{2\pi}} \int_{0}^{\infty} \chi(t) e^{i\omega t} \mathrm{d}t$$

because $\chi = 0$ for $t < 0$. We define:

$$\tilde{\chi}(\omega) = \chi'(\omega) + i\chi''(\omega)$$

where $\chi'(\omega) = \frac{1}{\sqrt{2\pi}} \int_0^{\infty} \chi(t) \cos(\omega t) \mathrm{d}t$ is the real part and $\chi''(\omega) = \frac{1}{\sqrt{2\pi}} \int_0^{\infty} \chi(t) \sin(\omega t) \mathrm{d}t$ is the imaginary part. Using the fluctuation dissipation theorem equation (8.6) we can relate this to equation (8.7) as follows

$$\begin{aligned}i\omega\tilde{c}(\omega) =& -\frac{2}{\sqrt{2\pi}} \int_{0}^{\infty} \frac{\partial c}{\partial t} \sin \omega t \ \mathrm{d}t \\ =& \frac{2k_B T}{\sqrt{2\pi}} \int_{0}^{\infty} \chi(t) \sin \omega t \ \mathrm{d}t \\ =& 2ik_B T \chi''(\omega)\end{aligned}$$

$$\text{therefore} \quad \boxed{\tilde{c}(\omega) = \frac{2k_B T}{\omega} \chi''(\omega)} \tag{8.8}$$

Equation (8.8) relates the power spectrum $\tilde{c}(\omega)$ to the imaginary part of the response function (associated with dissipation). This is another form of he fluctuation dissipation theorem (in frequency space).

8.6 Examples

Electric circuit

Consider a simple electric circuit consisting of a resistor of resistance R, a capacitor of capacitance C and a battery applying a voltage V for time $t < 0$ and $V = 0$ for time $t > 0$. The charge Q on the capacitor then decays with time as $Q = CVe^{-t/(RC)}$. The response function is

$$\begin{aligned} Q(t) &= \int_{-\infty}^{0} V\chi(t-t')\mathrm{d}t' \\ Q(t) &= V\int_{0}^{\infty} \chi(u)\mathrm{d}u \\ \frac{\mathrm{d}Q}{\mathrm{d}t} &= -V\chi(t) \\ \chi(t) &= \frac{1}{R}e^{-t/(RC)} \end{aligned}$$

The Fourier transform is $\tilde{\chi}(\omega) = \frac{1}{R}\frac{1}{\frac{1}{RC}-i\omega}$ and the imaginary part:

$$\tilde{\chi}''(\omega) = \frac{\omega RC^2}{1+\omega^2(RC)^2}$$

The correlation function of the fluctuations in charge is $C_Q(t) = \langle Q(0)Q(t)\rangle$ and its Fourier transform is

$$\tilde{C}_Q(\omega) = \frac{2k_BTR^2C^2}{1+\omega^2(RC)^2}$$

The current intensity is given by $I = \frac{Q}{RC}$ and the intensity spectrum is:

$$\tilde{C}_I(\omega) = \int_{-\infty}^{\infty}\langle I(0)I(t)\rangle e^{i\omega t} = \frac{2k_BT}{R}\frac{1}{1+\omega^2(RC)^2}$$

Hair cell bundles

Hair cells (found e.g. in the ear) have bundles of tiny hairs. If the fluctuation dissipation theorem works in this system then the temperature T is equal to $T_{\text{eff}}(\omega) = \frac{\omega\tilde{C}(\omega)}{2k\chi''}$. However if $T_{\text{eff}} \neq T$ the fluctuation dissipation theorem is violated and this means that either the perturbation applied is not small enough for linear response theory to be valid or the system is not in thermal equilibrium. Experiments can measure both the power spectrum $\tilde{C}(\omega)$ and

the response function χ''. Experiments on hair bundles of dead cells show $T_{\text{eff}} = T$ however for living cells $T_{\text{eff}} \neq T$ (only equal for very low or very high ω). This shows that the living hair cells are out of equilibrium i.e. they consume energy and do work to detect sound. It is now thought that this work is done by molecular motors.

Topic 9

Molecular motors

9.1 Structure and function

Diffusion is too slow. It takes about 2 minutes for a protein to diffuse across a cell and this is slower than the $\sim$ s timescale of typical biological processes. To solve this problem molecular motors are used by cells to transport cargos such as proteins. Molecular motors move with ballistic motion (faster than diffusion). They are molecules that consume chemical energy to produce mechanical forces. The energy comes from chemical reactions e.g. the hydrolysis of ATP i.e. ATP $\rightarrow$ ADP + P_i which has a chemical potential $\Delta\mu = 25k_BT$. This is greater than zero because in a cell this reaction is not in chemical equilibrium because ATPsynthase continuously makes ATP so that there is always an excess of ATP in a cell keeping the system out of equilibrium.

Experiments have shown that motors typically move with velocity $\sim 1\mu\mathrm{m\,s}^{-1}$ and a stall force (the load force at which they stop moving) of $\sim 6\,\mathrm{pN}$.

Motors that "walk" along filaments are classified as processive or non-processive. A processive motor stays bound to its filament and makes several steps before falling off. A non-processive motor only makes one step. The duty ratio is defined as $r = \frac{t_{\mathrm{on}}}{t_{\mathrm{on}}+t_{\mathrm{off}}} = \frac{k_{\mathrm{on}}}{k_{\mathrm{on}}+k_{\mathrm{off}}}$ where t_{on} is the time spent on the filament and $k_{\mathrm{on}} = t_{\mathrm{on}}^{-1}$ is the rate of binding on. e.g. kinesin $r \geq 0.5$ has 2 heads so one head is always on. Muscle myosin has $r \sim 0.02$ so must work in groups of N motors so $Nr > 1$ to ensure there's always a motor bound i.e. for muscle myosin $N > 50$. In muscles $N \sim 300$.

9.1.1 Examples

- Intracellular transport e.g. kinesin on microtubules (e.g. along axons in neurons)
- Muscles: myosin II and actin $\rightarrow$ muscle contraction (Huxley)
- cilia and axonemes (flagella) - dynein on microtubules e.g. sperm
- mitosis (cell division) - lots of motors involved
- inner ear hair cells - myosin 1c
- rotary motors e.g. ATPsynthase (300rotations/s), bacterial flagella
- DNA motors e.g. RNApolymerase, DNApolymerase

9.2 Thermodynamics

For a molecular motor "walking" on a filament the chemical "force" $\Delta\mu$ has conjugated flux n = number of ATP molecules consumed per unit time. The mechanical force f has conjugated flux v (velocity). The energy dissipated is $fv + n\Delta\mu > 0$. A molecule is a motor if $n\Delta\mu > 0$ (receives energy from ATP) and $fv < 0$ (produces mechanical work). The yield efficiency$\eta = \frac{-fv}{n\Delta\mu}$.

9.3 Brownian Ratchet

This is based on Feynman's ideas.

We consider a 2 state model of a 1-headed molecular motor: a ground state 1 in which the motor is strongly bound to the filament and an excited state 2 in which it is weakly bound to the filament. The potential in the strongly bound state $V_1(x)$ is a periodic polar potential set by the period and polarity of the filament. It has a ratchet shape such that it goes up by u over a short distance a and then down by u over a longer distance b, periodically. The potential in the weakly bound state V_2 is constant. The motor can transition between states with a rate k_{12} up from V_1 to V_2 and with a rate k_{21} down from V_2 to V_1. The rate k_{12} depends on ATP hydrolysis for the energy to jump to the excited weakly bound state. ATP induces a conformational change in the motor which causes it to detach from the strongly bound state. When in the weakly bound state the motor diffuses

a distance $x = \sqrt{2Dt} = \sqrt{\frac{2D}{k_{21}}}$ where $t = 1/k_{21}$ is the time spent in the weakly bound state. If the motor diffuses backwards and $x < b$ it will fall back down to the potential minimum it stated in. If it diffuses forwards and $x > a$ it will end up in the next potential minimum a distance $a + b$ further on. The optimal rate k_{21} is then such that $a^2 < \frac{2D}{k_{21}} < b^2$.

9.3.1 Motor velocity

Here we calculate the average velocity of the motor. Let the probability the motor, when in the weakly bound state, goes forwards be p and the probability it goes backwards be $(1-p)$. If the motor diffuses in the weakly bound state then $p = 1/2$. The average distance is then given by:

$$\langle x \rangle = (1-p)0 + p(a+b) = p(a+b) = \frac{1}{2}(a+b)$$

the average velocity is $v = \langle x \rangle / t$ where the time $t = \frac{1}{k_{21}} + \frac{1}{k_{12}} + t_s$ where t_s is the time taken to slide down to the potential minimum. This can be calculated by considering the force due to the potential $\frac{u}{b}$ where u is the depth of the potential minimum. The force balance on the motor in the strongly bound state can then be written as

$$\frac{u}{b} - \xi v_1 = 0$$

where ξ is the friction coefficient. From this we can find the velocity $v_s = \frac{u}{\xi b}$ with which the motor moves down to the potential minimum. Therefore $t_s = \frac{b}{v_s} = \frac{\xi b^2}{u}$ and the average motor velocity is

$$v = \frac{p(a+b)}{\frac{1}{k_{21}} + \frac{1}{k_{12}} + \frac{\xi b^2}{u}}$$

9.3.2 Stall force

If we apply an external load force f the motor will slow down. In the weakly bound state the probability of diffusing forward will become force dependent i.e. $p(f)$. In the strongly bound state the velocity of moving down the potential will become $v_s = \frac{\frac{u}{b} - f}{\xi}$ therefore the average velocity will become

$$v = \frac{p(f)(a+b)}{\frac{1}{k_{21}} + \frac{1}{k_{12}} + \frac{\xi b^2}{u - fb}}$$

The stall force is defined as the force at which the motor stops moving i.e. when $v = 0$. This occurs under two conditions. Firstly $v = 0$ when $f = u/b$, which is when the external force tilts the potential upwards so that it becomes horizontal. Secondly $v = 0$ when $p(f) \to 0$ which occurs when the force balances thermal energy such that the motor is under a biased diffusion backwards resulting in no overall forward motion. This happens when $k_B T \sim fa$ therefore the stall force f_s is given by

$$f_s = \frac{k_B T}{a}$$

9.3.3 Full Fokker Planck treatment *(Optional extra)*

Note that Fokker Planck equations are a special case of master equations.

Let $P_1(x,t)$ be the probability that a motor is at position x at time t in the ground strongly bound state. Similarly let $P_2(x,t)$ be the probability that a motor is at position x at time t in the excited weakly bound state. The Fokker Planck equations are given by:

$$\begin{aligned} \frac{\partial P_1}{\partial t} + \frac{\partial j_1}{\partial x} &= k_{21}P_2 - k_{12}P_1 \\ \frac{\partial P_2}{\partial t} + \frac{\partial j_2}{\partial x} &= k_{12}P_1 - k_{21}P_2 \end{aligned} \tag{9.1}$$

The fluxes are given by:

$$\begin{aligned} j_1 &= -D\frac{\partial P_1}{\partial x} - \frac{P_1}{\xi}\frac{\partial V_1}{\partial x} + \frac{1}{\xi}P_1 f \\ j_2 &= -D\frac{\partial P_2}{\partial x} - \frac{P_2}{\xi}\frac{\partial V_2}{\partial x} + \frac{1}{\xi}P_2 f \end{aligned}$$

where the first terms on the right hand side are diffusion with diffusion constant D, the second terms are convection due to the potential and the final terms are due to the external force f. Note that the convection term in the j_2 equation is zero since the potential V_2 is constant.

At thermal equilibrium the probability distributions P_1 and P_2 are given by the Boltzmann distribution i.e. $P_1(x) = \frac{1}{Z}e^{-V_1(x)/(k_B T)}$ and $P_2 = \frac{1}{Z}e^{-V_2/(k_B T)}$. In steady state $\frac{\partial P_1}{\partial t} = \frac{\partial P_2}{\partial t} = 0$ and in the absence of external force, from the Fokker Planck equations (9.1) above the fluxes (currents) vanish $j_1 = j_2 = 0$ if:

$$k_{12}P_1 = k_{21}P_2 \tag{9.2}$$

This equation (9.2) is called the *detailed balance* condition. It is always obeyed in equilibrium. Therefore the rates are given by $k_{12} = Zk(x)e^{V_1/(k_B T)}$

and $k_{21} = Zk(x)e^{V_2/(k_BT)}$. In other words at thermal equilibrium the motor velocity is zero and therefore doesn't work. This implies it has to be out of equilibrium to work.

In the presence of ATP we get 2 types of motor transitions: equilibrium transitions and non equilibrium transitions involving ATP. e.g.

$$\begin{aligned} k_{12}(x) =& Zk(x)e^{V_1(x)/(k_BT)} + \alpha(x)e^{(V_1(x)+\mu_{ATP})/(k_BT)} \\ k_{21}(x) =& Zk(x)e^{V_2(x)/(k_BT)} + \alpha(x)e^{(V_2(x)+\mu_{ADP}+\mu_{P_i})/(k_BT)} \end{aligned}$$

Let

$$k_{12}(x) = k_{21}(x)e^{(V_1(x)-V_2)/(k_BT)} + \Omega(x)$$

where $\Omega(x)$ is the out of equilibrium bit given by

$$\Omega(x) = \alpha'(x)e^{(V_1(x)+\mu_{ADP}+\mu_{P_i})/(k_BT)}\left(e^{\Delta\mu/(k_BT)} - 1\right)$$

Clearly if $\Delta\mu = 0$ then the detailed balance condition (equation 9.2) is satisfied and $v = 0$. The system is out of equilibrium if $\Omega(x) \neq 0$ i.e. if $\Delta\mu \neq 0$.

9.3.4 Long time behaviour

At long times the motion is approximately that of a biased random walk. At long times $l_D \gg l$ where $l = a + b$ the period of the ratchet and $l_D = \sqrt{2Dt}$ is the diffusion length. Then the probabilities are given by

$$P_{1,2} = \frac{g_{1,2}(x/l)}{\sqrt{4\pi D_{\text{eff}}t}}e^{-(x-vt)^2/(4D_{\text{eff}}t)}$$

which is biased diffusion of a particle of velocity v with diffusion constant D_{eff}. $g_{1,2}(x/l)$ are periodic functions of how the motor feels the local periodicity. The average motor force is balanced by the average friction force $-\xi v$ and the velocity is then

$$v = \frac{1}{\xi}\int_0^l \mathrm{d}x \left(g_1(-\frac{\partial V_1}{\partial x}) + g_2(-\frac{\partial V_2}{\partial x})\right)$$

The effective diffusion constant is not equal to the diffusion constant $D_{\text{eff}} \neq D$ i.e. $D_{\text{eff}} \neq \frac{k_BT}{\xi}$ so the Einstein relation is broken. D_{eff} = thermal noise + stochasticity of the transition i.e. $D_{\text{eff}} > D$ i.e. $D_{\text{eff}} > \frac{k_BT}{\xi}$ NB if the filament is symmetric g_i is even and $\frac{\partial V_i}{\partial x}$ is odd and therefore the integral over a period vanishes and $v = 0$ i.e. there is no motion if the filament is not polar.

9.4 What is needed for a motor to work?

- filament polar (asymmetric)
- thermal fluctuations
- out of equilibrium (detailed balance broken)

NB Intermediate filaments are non polar so motors cannot walk along them. Thermal fluctuations are not essential if V_2 is not constant e.g. if it is also a ratchet shape out of phase with V_1 and transitions occur at the minima of the potentials the system can work without thermal fluctuations. This is a good model for a 2 headed motor (e.g. kinesin) that's always bound.

Topic 10

Photosynthesis

10.1 Biological free energy

Where does the energy come from to drive biological systems out of equilibrium such that they can perform their various functions? Ultimately the energy required for life comes from the sun and photosynthesis is the biological process converting energy from the sun into a form that living matter can use. The overall energy conversion process is that photons from the sun fuel biochemical reactions, which in turn produce work and heat. The photosynthetic chemical reaction can be summarized by:

$$CO_2 + H_2O \xrightarrow{\gamma} O_2 + \text{sugars}$$

Animals don't get their energy directly from the sun by photosynthesis but by eating sugars made in plants. The process of getting energy from sugars is called respiration and can be summarized chemically by:

$$O_2 + \text{sugars} \longrightarrow CO_2 + H_2O$$

These chemical reactions are *redox* reactions (reduction-oxidation reactions) whereby electrons are transfered between chemical species. Oxidation is loosing electrons and reduction is gaining electrons (see section 10.3 for more details).

The process of getting energy from the sun to a form used in living systems can be broken down into different stages. The first stage is known as *light harvesting* whereby energy from photons from the sun is used to form a molecule called NADH (nicotinamide adenine dinucleotide plus hydrogen) or to pump H^+ ions (protons) across a membrane to generate what is called the *protomotive force* or *pmf* due to the charge separation across

the membrane. This protomotive force drives the synthesis of ATP (adenosine triphosphate) from ADP (adenosine diphosphate) plus P_i (inorganic phosphate). The free energy provided by the pmf is given by

$$\Delta G = q\Delta V + k_B T \ln \frac{c_{\text{in}}}{c_{\text{out}}}$$

where q is the charge, ΔV is the electrical potential dirfference across the membrane and $c_{\text{in,out}}$ are the concentrations for protons inside and outside. This synthesis of ATP is done by the membrane protein rotary molecular motor *ATP synthase*. The chemical energy stored in the molecules NADH and ATP is used to reduce carbon dioxide (CO_2) producing sugars/carbohydrates for long term energy storage and food. Hydrolysis of ATP,

$$\text{ATP} \longrightarrow \text{ADP} + \text{P}_i$$

provides energy directly for e.g. molecular motors. This hydrolysis reaction gives $\Delta G \sim 20 k_B T$ (depending on the concentrations of ATP, ADP etc). Humans have $\sim 250\,\text{g}$ of ATP but synthesis and hydrolyse about their own body weight of ATP each day.

10.2 Overview of photosynthesis

Photosynthesis occurs in plants, algae and some bacteria. More precisely, in green plants & algae it occurs in the chloroplasts, which are organelles in leaf cells. Evolutionarily chloroplasts probably originated from photosynthetic bacteria (cyanobacteria) that were engulfed by the eukaryotic cells. Chlorophyll (green pigment) molecules in the chloroplasts absorb light. They absorb mostly blue and red light, reflecting green giving leaves their colour. Chlorophyll is the most common but other photosynthetic pigments also exist such as carotene, xanthophyll and phycobiliproteins, each absorbing light at different wavelengths. The photosynthetic reactions involving light occur in the thylakoid membranes in chloroplasts. Using water and photons, these reactions produce oxygen, ATP (adenosine triphosphate) and NADPH (nicotinamide adenine dinucleotide plus hydrogen). These molecules fuel carbon based reactions in the stroma of the chloroplasts. These redox reactions, collectively known as the *Calvin cycle* or *carbon fixation*, use carbon dioxide (CO_2) and water to produce sugars/carbohydrates with oxygen as a byproduct. The carbohydrate base unit produced is CH_2O (glucose being 6 of these base units).

10.3 Photon capture

The sunlight reaching the Earth's surface is $\sim 4\%$ ultraviolet, $\sim 43\%$ visible, and the rest infared. One photon provides insufficient energy to break the chemical bonds in water. This is fortunate since we don't want to disintegrate in the sunshine! The chemical reaction producing the sugar glucose is:

$$6\mathrm{CO_2} + 6\mathrm{H_2O} \xrightarrow{\gamma} \mathrm{C_6H_{12}O_6} + 6\mathrm{O_2}$$

This occurs in 2 half reactions:

$$\begin{aligned} \text{oxidation of water:} \quad & 2\mathrm{H_2O} \longrightarrow \mathrm{O_2} + 4\mathrm{H^+} + 4\mathrm{e^-} \\ \text{reduction of carbon dioxide:} \quad & \mathrm{CO_2} + 4\mathrm{H^+} + 4\mathrm{e^-} \longrightarrow \mathrm{CH_2O} + \mathrm{H_2O} \end{aligned}$$

Each electron transfer event required one photon. The above half reactions show that to produce one carbohydrate unit 4 electons must be removed from water and 4 electrons added to carbon dioxide. This makes 8 electron transfer events per carbohydrate unit. One molecule of glucose ($\mathrm{C_6H_{12}O_6}$) has 6 carbohydrate units and therefore requires 48 photons.

The probability of more than one photon arriving at the same time in the same place is negligible. Tthe average number of photos arriving at one water molecule is $\langle n \rangle = IV_m/(N_A hc\nu)$ where $I = 1.4\,\mathrm{kW\,m^{-2}}$ is the intensity, ν is the frequency of light, V_m is the molar volume of water, N_A is Avagadro's number, c is the speed of light and h is Planck's constant. This leads to the probability of 2 photons in one water molecule being about one in 10^6 litres of water. Since the probability of more than one photon arriving at the same time in the right place is negligible, energy from photons need to be collected at different times and places. Therefore photons need to be absorbed by chlorophyll (or another photosynthetic pigment) and delivered to the *reaction centre*. This is achieved in *photosystems* consisting of a reaction centre surrounded by many *light harvesting complexes* or *antenna complexes* containing proteins and chlorophyll molecules. Photons arrive at a rate of about 1 photon per chlorophyll molecule per second. Different chromophores within the complexes absorb at different angles and different wavelengths. A single chlorophyll molecule absorbs a single photon, exciting a single electron into the first excited state. This electron could decay giving off light (fluorescence) or heat. More usefully electron (charge) transfer from donor to acceptor or resonance energy transfer. These processes transfer energy to the reaction centre. These processes are discussed further in the following sections.

10.4 Electron transfer

Energy from photons must be temporarily stored and delivered to the reaction centre. This is achieved by electron transfer. The aim is to separate positive and negavie charges as far away as possible from each other (across the membrane to generate the protomotive force) and to avoid charge recombination. This is like a capacitor. Light excites an electron in the donor. The donor gives this excited electron to the acceptor i.e.

$$\mathrm{D} + \mathrm{A} \xrightarrow{\gamma} \mathrm{D}^* + \mathrm{A} \longrightarrow \mathrm{D}^+ + \mathrm{A}^-$$

The underlying physics of this can be considered by writing down a Hamiltonian for the donor-bridge-acceptor system, $H = H_n + H_e$ made up of the nuclear and electronic contributions. Using the Born-Oppenheimer approximation (separation of nuclear and electonic variables) the wavefunction can be written as $\psi(R, r) \approx \chi_n(R)\phi_e(r)$. A further approximation is to assume a 2 state model for the electron. This is valid when the energies of the donor and acceptor orbitals are close compared to that of the bridge states (i.e. we assume the latter is unoccupied). We can then write the electronic part of the Hamiltonian as

$$H_e = \sum_m E_m |\phi_m\rangle\langle\phi_m| + \sum_{m,n} V_{mn} |\phi_m\rangle\langle\phi_n|$$

The diagonal terms are the energies of the chromophore states and the off diagonal terms are the electronic couplings (how strong the states couple to each other). The rate of electron transfer is then given by

$$k_e \propto |\langle\phi_m|H|\phi_n\rangle|^2 = |V_{mn}|^2.$$

where $V_{mn} = \Delta E/2$ where ΔE is the energy gap between the donor and acceptor energy levels.

10.5 Energy transfer

Energy can be transfered from donor to acceptor, without transfering an electron. This is called *resonance energy transfer* or Förster Resonance Energy Transfer (FRET). Initially the donor has an electron in the excited state. This excited state energy is transfered to the acceptor, exciting an acceptor electron whilst the donor electron returns to the ground state, i.e.

$D^* + A \rightarrow D + A^*$. The energy is transfered by dipole-dipole coupling. The potential energy of 2 interacting dipoles is given by:

$$V_{mn} = \frac{\kappa \mu_m \mu_n}{4\pi\epsilon_0 r^3}$$

where μ_m is the dipole moment of molecule m, κ is the orientation factor and r is the distance between the donor and acceptor. The rate of energy transfer is given by

$$k_{\text{RET}} \propto |V_{mn}|^2 \propto \left(\frac{R_0}{r}\right)^6$$

where R_0 is the Förster distance which is the separation at which the ernergy transfer efficiency is 50% and depends on the overlap between the donor emission spectrum and the acceptor absorption spectum (the spectral lines are broadened by thermal flucuations). The Förster distance is the separation at which the probability of spontaneous decay is the same as that of energy transfer to the acceptor. The sensitive $1/r^6$ distance dependence means that energy is transfered more efficiently in lots of short hops than long leaps. The FRET efficiency or *quantum yield* is given by

$$\eta_{\text{FRET}} = \frac{k_{\text{RET}}}{k_{\text{RET}} + k_f} = \frac{1}{1 + \left(\frac{r}{R_0}\right)^6}$$

where k_f is the spontaneous decay rate.

Quantum electrodynamics (QED) is the more advanced theory underpinning this, but this is beyond the scope of this course.

Appendix A

Revision: Thermodynamics & Statistical Physics

Here I provide a brief overview of thermodynamics and statistical physics for those who don't know or have forgotten.

Thermodynamics is about macroscopic properties of matter in equilibrium, which we can measure, e.g. temperature. Statistical physics is about relating these macroscopic properties of matter to the underlying microscopic quantities, e.g. the velocities of air molecules.

A.1 Laws of thermodynamics

0th law

Definition of temperature: if 2 systems are in thermal equilibrium with a 3rd system then they are in thermal equilibrium with each other. i.e. if $A \equiv C$ and $B \equiv C$ then $A \equiv B$.

1st law

Conservation of energy: the internal energy of an isolated system is constant

$$\mathrm{d}U = \delta Q + \delta W$$

where δQ is the heat transferred to the system and δW is the work done on the system. NB some text books define the work done by the system as positive so have the opposite sign for the work term.

For an ideal gas, $pV = nRT$ where p is pressure, V is volume, T is temperature, n is the number of moles ($1\,\mathrm{mole} = 6 \times 10^{23}$ molecules) and R is the molar gas constant. This is the equation chemists use. Physicists prefer $pV = Nk_BT$ where N is the number of molecules and k_B is Boltzmann's constant. For an ideal gas the work done on the system is $\delta W = -p\mathrm{d}V$ therefore

$$\mathrm{d}U = \delta Q - p\mathrm{d}V$$

$\mathrm{d}U$ is an exact differential but δQ and δW depend on the path taken. Different systems will have different expressions for the work done. e.g. for an elastic band $\delta W = \boldsymbol{f} \cdot \mathrm{d}\boldsymbol{l}$.

An *adiabatic* system is one in which $\delta Q = 0$ and therefore $\mathrm{d}U = \delta W$.

2nd law

Heat can not spontaneously flow from colder to hotter. Entropy, S, never decreases in an isolated system. Entropy, S, always increases in an isolated system. Entropy is a measure of disorder.

If we exchange heat δQ at temperature T then $\mathrm{d}S \geq \frac{\delta Q}{T}$. If the system is reversible (we can add heat and take it away again without loosing any heat) then $\delta Q = T\mathrm{d}S$ and

$$\mathrm{d}U = T\mathrm{d}S - p\mathrm{d}V$$

This gives definitions of temperature, $\frac{1}{T} = (\frac{\partial S}{\partial U})_V$, and pressure, $p = (\frac{\partial U}{\partial V})_S$.

3rd law

As temperature is cooled towards absolute zero $T = 0\,\mathrm{K} = -273^\circ\mathrm{C}$ entropy S goes to a minimum and all processes stop. It is impossible to reach absolute zero temperature.

Statistical Physics

A macroscopic measurement of a quantity G is actually the time average of fluctuating values of G, i.e. $\langle G \rangle_t$. The microscopic configuration of a system is defined by all the microscopic variables e.g. a gas has $6N$ variables (3 position and 3 momentum/velocity variables for each particle). The set (or ensemble) of all possible configurations is called the *phase space*.

A system is *ergodic* if during the time taken for a measurement the system explores $\approx$ all microscopic configurations. The ergodic hypothesis is that over long enough time all accessible microstates are equally probable. For an ergodic system the time average measurement is equal to the ensemble average measurement over many identical macroscopic systems with different microstates:

$$\langle G \rangle_t = \langle G \rangle_{\text{phase space}}$$

Most systems (e.g. air, water) are ergodic. Examples of non ergodic systems are sand and glass. In these systems the particles get stuck or blocked or jammed in subspaces of possible configurations and they cannot explore all microstates. This means on short time scales they behave like solids but on very long time scales they behave like liquids.

The number of configurations is the microstates with a given macrostate. This is called the statistical weight, Ω. The entropy is given by:

$$S = k_B \ln \Omega$$

This is Boltzmann's equation. At equilibrium a system will be in the macrostate with maximum entropy. For 2 independent systems $\Omega = \Omega_1 \Omega_2$ so the entropy, $S = S_1 + S_2$, is additive and extensive (scales linearly with number of particles N).

A.2 Statistical ensembles

Microcanonical ensemble

The microcanonical ensemble is used for a system that is completely isolated, with no energy exchange with its environment. The total number of particles, N, volume, V, and total internal energy E are fixed. If all microstates are equally likely then $p_i = 1/\Omega$ and $S_i = -k_B \ln p_i$. Normalisation means $\sum_i p_i = 1$. Therefore entropy of microstate i is $S_i = -k_B \ln p_i$. This gives the statistical definition of entropy:

$$S = -k_B \sum_i p_i \ln p_i$$

where the weighting p_i allows for the p_is to be different. The partition function is given by

$$Z_\mu = \sum_i \delta(E - \epsilon_i)$$

where ϵ_i is the energy of microstate i.

Canonical ensemble

The canonical ensemble is used for a system in thermal equilibrium with a reservoir (heat bath) that is much larger than the system. Energy (heat) can be exchanged between the system and the reservoir but the number of particles, N, volume, V, and temperature, T are fixed.

The probability that the system is in a particular microstate with energy ϵ_i is proportional to the number of possible microstates of the reservoir that have energy $E_R = E - \epsilon_i$ where E is the total internal energy of the system plus the reservoir. i.e. $p_i = p(\epsilon_i) \propto \Omega(E - \epsilon_i)$. Since the reservoir is much larger than the system we can assume that $E \gg \epsilon_i$ and expand $\ln \Omega(E - \epsilon_i)$ using the Taylor series expansion:

$$\ln \Omega(E - \epsilon_i) = \ln \Omega(E) - \epsilon_i \frac{\mathrm{d} \ln \Omega(E)}{\mathrm{d}E}$$

from the definition of entropy $S = k_B \ln \Omega$ we obtain $\frac{\mathrm{d} \ln \Omega(E)}{\mathrm{d}E} = \frac{\mathrm{d}}{\mathrm{d}E}(\frac{S}{k_B}) = \frac{1}{k_B}\frac{\mathrm{d}S}{\mathrm{d}U} = \frac{1}{k_B T}$ where we have used the definition of temperature $\frac{1}{T} = (\frac{\partial S}{\partial U})_V$. This gives:

$$p(E_s)_i = e^{-\frac{\epsilon_i}{k_B T}}$$

which is the Boltzmann distribution where $\frac{1}{Z}$ is the normalisation constant:

$$Z = \sum_i e^{-\frac{\epsilon_i}{k_B T}}$$

which is called the *partition function*. The continuous version is

$$Z = \frac{1}{N!} \int \mathrm{d}\boldsymbol{p}^N \mathrm{d}\boldsymbol{x}^N e^{\frac{-H}{k_B T}}$$

where $H(\boldsymbol{p}, \boldsymbol{x})$ is the Hamiltonian ($H = T + V$ where T is the kinetic energy and V is the potential energy), $\boldsymbol{p}$ is the momentum and $\boldsymbol{x}$ is the velocity.

The *Helmholtz free energy* F is minimised for a system that can exchange energy with the environment at constant number of particles, N, volume, V, and temperature T.

$$F = U - TS$$

Minimising F is an alternative way of expressing the 2nd law of thermodynamics (maximising S). $\mathrm{d}F = \mathrm{d}U - T\mathrm{d}S - S\mathrm{d}T = -S\mathrm{d}T - p\mathrm{d}V$.

For a system at constant N, pressure p and T (but allowing the volume to vary) the *Gibbs free energy* G is minimised.

$$G = F + pV = U - TS + pV$$

$\mathrm{d}G = -S\mathrm{d}T + V\mathrm{d}p$. This is the relevant thermodynamic function for most chemical and biological systems.

NB if volume is independent of pressure then $G = F$. This is the case for incompressible systems, true for most liquids.

From the statistical definition of entropy $S = -k_B \sum_i p_i \ln p_i$ and the Boltzmann distribution $p_i = \frac{1}{Z} e^{-\frac{\epsilon_i}{k_B T}}$ we obtain

$$\begin{aligned}
S =& -k_B \sum_i \frac{1}{Z} e^{-\frac{\epsilon_i}{k_B T}} \ln\left(\frac{1}{Z} e^{-\frac{\epsilon_i}{k_B T}}\right) \\
S =& -k_B \sum_i \frac{1}{Z} e^{-\frac{\epsilon_i}{k_B T}} \ln\left(-\frac{\epsilon_i}{k_B T} - \ln Z\right) \\
S =& \frac{1}{Z}\langle E\rangle + k_B \ln Z = \frac{U}{T} + k_B \ln Z \\
F =& U - TS = U - U - k_B T \ln Z \\
F =& -k_B T \ln Z
\end{aligned}$$

This is the statistical definition of the free energy. If we know the partition function Z we can calculate the free energy F and from it all other thermodynamic quantities.

Grand canonical ensemble

The grand canonical ensemble is used for a system in thermodynamic (thermal and chemical) equilibrium with a reservoir. Energy and particles can be exchanged between the system and the reservoir. The *chemical potential* μ, the volume V and the temperature T are fixed. Allowing the number of particles N is to vary (particles can be exchanged) means $\mathrm{d}U = T\mathrm{d}S - p\mathrm{d}V + \mu\mathrm{d}N$ and similarly the term $\mu\mathrm{d}N$ is added to $\mathrm{d}F$ and $\mathrm{d}G$. The chemical potential is defined as:

$$\mu = \left(\frac{\partial U}{\partial N}\right)_{S,V} = \left(\frac{\partial F}{\partial N}\right)_{T,V} = \left(\frac{\partial G}{\partial N}\right)_{T,P}$$

The partition function for the grand canonical ensemble is give by:

$$Z_G = \sum_N \sim_i e^{\beta(\mu N = \epsilon_i)}$$

where $\beta = \frac{1}{k_B T}$ and the sum over all microstates with N particles must be performed first followed by the sum over all N.

Appendix B

Solving the Diffusion equation

The diffusion equation,

$$\frac{\partial c}{\partial t} = D\frac{\partial^2 c}{\partial x^2}$$

can be solved using Green's functions as follows. Decompose the concentration, c, into the family of solutions $G(x - x_0, t)$ where G is the Green's function and describes the evolution of an initial state. Consider the case where all the particles start at the origin $x = x_0 = 0$ then $G(x, 0) = \delta(x)$. G obeys the diffusion equation: $\frac{\partial G}{\partial t} = D\frac{\partial^2 G}{\partial x^2}$. The Fourier transform of G at $t = 0$ is

$$\tilde{G}_k(0) = \int G(x, 0)e^{-ikx}\mathrm{d}x = \int \delta(x)e^{-ikx}\mathrm{d}x = 1$$

The time evolution of the Fourier transform is $\tilde{G}_k(0) = e^{-Dk^2t}$ and therefore

$$G(x, t) = \frac{1}{2\pi}\int \tilde{G}_k(0)e^{ikx}e^{-Dk^2t}\mathrm{d}k = \frac{1}{2\pi}\int e^{ikx}e^{-Dk^2t}\mathrm{d}k$$

since the inverse Fourier transform of a Gaussian gives a Gaussian. Therefore

$$G(x, t) = \frac{1}{\sqrt{4\pi Dt}}e^{-\frac{x^2}{4Dt}}$$

This is the Green's function for the diffusion equation. It tell us the distribution of end points of a random walk centred at the origin $x = 0$. For a random walk centred at $x = x_0$ the initial condition is $\delta(x - x_0)$. Any initial condition $c(x, 0)$ can be written as a superposition of delta functions (point sources of concentration):

$$c(x, 0) = \int c(x_0, 0)\delta(x - x_0)\mathrm{d}x_0 = \int c(x_0, 0)G(x - x_0, 0)\mathrm{d}x_0$$

therefore the *general* solution to the diffusion equation is:

$$\begin{aligned} c(x,t) &= \int c(x_0,0)G(x-x_0,t)\mathrm{d}x_0 \\ &= \int c(x_0,0)\frac{e^{-\frac{(x-x_0)^2}{4Dt}}}{\sqrt{4\pi Dt}}\mathrm{d}x_0 \end{aligned}$$

i.e. the concentration at time t is given by the initial concentration convoluted with the Greens function G.