3.3 Brownian Motion

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

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

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

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

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

where η is the specific viscosity of the fluid.

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

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

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

[*Am. J. Phys.* **45**(1), 1977] by Purcell contains many interesting observations about this limit.

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

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

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

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

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

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

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

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

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

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

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

It is then easy to check that

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

while the mean-squared dispersion is given by

$$\left\langle [x(t) - x(0)]^2 \right\rangle = \int_0^t dt'_1 dt'_2 \, \langle \eta(t'_1)\eta(t'_2) \rangle = 2Dt. \tag{3.43}$$

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

The stocastic Eq. (3.38) is the *Langevin equation* for the coordinate x. Different realizations of the force $\eta(t)$ lead to different values of $x(t)$; we can also construct a corresponding *Fokker-Planck* equation governing the evolution of the probability $p(x, t)$. In the absence

of a potential (as discussed above), this is simply the diffusion equation, with a diffusive *probability current* $J_D = -D\partial p/\partial x$. More generally, we can write the continuity equation

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

where J now includes an additional drift term such that

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

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

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

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

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

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

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

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

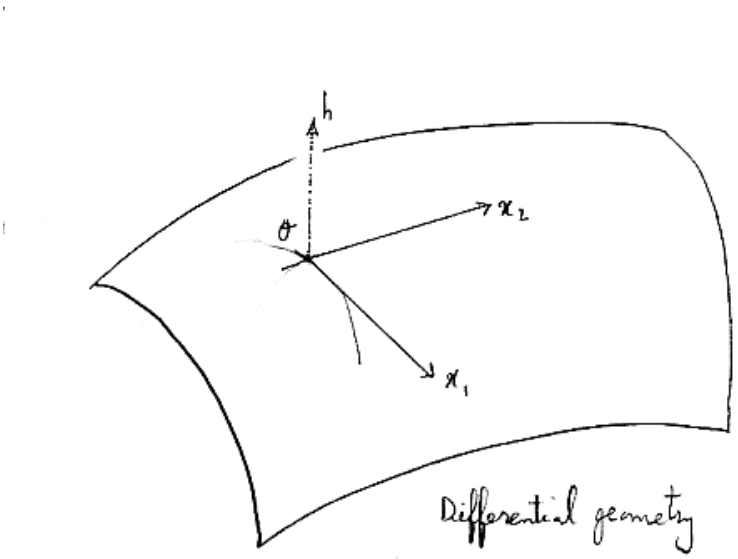
$$\boxed{D = \mu k_B T.} \tag{3.49}$$

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

3.4 Cell Membranes

Biological cells are enclosed by a membrane, separating various internal molecules and organelles from the outside world. However, the outside world provides the necessary nutritional elements and survival signals that must be transported to the inside. The chief component of the cell membrane is a bilayer of lipid molecules. These phospholipid molecules have a long fatty tail that is hydrophobic, and polar heads that are hydrophobic. In water, such amphiphilic molecules spontaneous self-assemble to form bilayer surfaces, as well as enclosed vesicles. Biological membranes contain many more components, including various proteins involved in transport and signaling. However, we shall initially focus on describing shapes and fluctuations of simple lipid bilayers. The thickness of a bilayer is around 5nm, considerably less than the dimension of the cell. To discuss the shapes and fluctuations of the membrane at large scales, we can regard it as a continuous surface. This is akin to describing DNA as a worm-like chain.

The first topic we need to address is how we describe a curved membrane. Once we have an energy function (or functional), we can use it to address several intriguing topics, including the reason red blood cells have their characteristic double-dimpled shape. This level of description is equally applicable to any surface, such as a soap bubble, and is best achieved using tools of *differential geometry.*



Within this framework, configurations of a surface are characterized as follows: Pick a point O on the film, and draw the plane tangent to the surface at O. Choose a pair of coordinates (x_1, x_2) on the tangent plane. In the close vicinity of O, the tangent plane and the surface coincide. How do the surface and the tangent plane separate as we move away

from O? We measure the "height" $h(x_1, x_2)$ between the tangent plane and the surface along the normal vector at point O. Expanding $h(x_1, x_2)$, the first terms that can appear are quadratic, i.e.

$$h(x_1, x_2) = \frac{1}{2} \sum_{i,j=1}^{2} c_{ij} x_i x_j + \mathcal{O}(x^3) \,, \tag{3.50}$$

where the matrix c_{ij}, given by

$$c_{ij} = \left. \frac{\partial^2 h}{\partial x_i \partial x_j} \right|_{x=0} \,, \tag{3.51}$$

is the 2×2 *curvature tensor.*

This is not the most ideal description of the curvature, because it depends the choice of coordinate axes. We are thus encouraged to look for properties of c_{ij} which are invariant under changes of coordinates. One such property is the trace of the tensor, i.e. the sum over its diagonal elements,

$$\text{tr } C = c_{11} + c_{22} = \frac{1}{R_1} + \frac{1}{R_2} \equiv 2H. \tag{3.52}$$

Note that each element of the matrix has dimensions of inverse length. We have denoted the eigenvalues of the tensor as $1/R_1$ and $1/R_2$, known as the *principal radii of curvature.* Their average, indicated above by H, is known as the *mean curvature.* Another invariant of the matrix is its determinant

$$\det C = c_{11} c_{22} - c_{12} c_{21} = \frac{1}{R_1} \cdot \frac{1}{R_2} \equiv K, \tag{3.53}$$

which is known as the *Gaussian curvature.*

Physically we expect that deformations of the surface are accompanied by an *energy* cost. The energy cost should certainly not depend on the coordinate system chosen to parametrize the surface, and must thus be a function of shape invariants such as the curvatures identified above. In the spirit of Hooke's law for elasticity of a spring, we expand the energy cost up to quadratic order in deformations. The Gaussian curvature K is already quadratic; H is linear, and we would include an H^2 term. There is also a leading term, akin to the natural length of the spring, which measure the area of the surface. Including a corresponding surface tension cost, the energy function up to quadratic terms is

$$E = \int dA \left[\gamma + \frac{\kappa}{2} (H - H_0)^2 + \bar{\kappa} K \right] . \tag{3.54}$$

In Eq. (3.54), γ parameterizes the surface tension, κ is the "bending rigidity," and H_0 is the "spontaneous curvature." (Such a spontaneous curvature requires an asymmetry between the two sides of the membrane, and could be an effect of different concentrations of various molecules in the two leafs of the bilayer.) The parameter $\bar{\kappa}$ is called the "Gaussian rigidity."

Note that while the energy functional in Eq. (3.54) provides an excellent description of a soap bubble, and to some extent for lipid bilayers, it is not applicable to a piece of paper, or to a rubber balloon. The reason is that the soap film, and most membranes can be

regarded as two dimensional fluids: their constituent molecules move freely relative to each other relaxing any external shear stress. By contrast the molecules in a sheet of paper, or in a balloon are permanently linked opposing shear stresses. Thus there is a additional shear energy cost which must be included for rubber, which is practically infinite for a piece of a paper.

We usually do need need all the parameters in Eq. (3.54) in a physical situation. For example, the *Gauss-Bonnet theorem* states that for all shapes topologically equivalent to a sphere,

$$\int dA\, K = 4\pi, .$$

Thus as a sphere wiggles, expands and contracts, there is no contribution to energy cost coming from $\bar{\kappa}$. More generally, for any closed surface

$$\int dA\, K = 4\pi\chi_E\,, \tag{3.55}$$

where the Euler characteristic χ_E is a topological invariant related to the number of holes (e.g. for a donut $\chi_E = 0$). Furthermore, in many cases involving lipid bilayers, $\gamma \approx 0$. The reason is that the phospholipid layers are typically immersed in a solution containing phospholipid molecules, allowing exchanges to take place. (The exact mechanism here is subject to debate; the observation that $\gamma \approx 0$ can be taken as an experimental fact.)

For small deformations around a flat surface, we use the so-called "Monge" representation. Over a reasonably-sized patch, we can describe the surface by a function $h(x_1, x_2)$, and Eq. (3.54) (for $H_0 = 0$) then leads to

$$\begin{aligned} E &= \int dx_1 dx_2 \sqrt{1 + \left(\frac{\partial h}{\partial x_1}\right)^2 + \left(\frac{\partial h}{\partial x_2}\right)^2}\left[\gamma + \frac{\kappa}{2}(\nabla^2 h)^2\right] \\ &\approx A + \frac{\gamma}{2}\int dx_1 dx_2 (\nabla h)^2 + \frac{\kappa}{2}\int dx_1 dx_2 (\nabla^2 h)^2\,. \end{aligned} \tag{3.56}$$

We shall assume that $\gamma \approx 0$, in which case the leading term comes from ∇^h, which is in fact related to the mean curvature since

$$\begin{aligned} \nabla^2\left(\frac{1}{2}\sum_{i,j} c_{ij} x_i x_j\right) &= c_{11} + c_{22} \\ &= 2H. \end{aligned}$$

Deformations of the surface are best described as superposition of normal modes (undulations) obtained through the Fourier transform

$$h(\vec{x}) = \sum_{\vec{q}} e^{i\vec{q}\cdot\vec{x}}\tilde{h}_q\,, \tag{3.57}$$

and correspondingly

$$\nabla^2 h = \sum_{\vec{q}} (-q^2) e^{i\vec{q}\cdot\vec{x}} \tilde{h}_q. \tag{3.58}$$

The energy is then a sum of contributions from normal modes as

$$E = \sum_{\vec{q}} \frac{\kappa}{2} q^4 |\tilde{h}_q|^2 \,. \tag{3.59}$$

Employing the Boltzmann weight, we conclude that each mode is independently distributed as a Gaussian of zero mean, and variance

$$\left\langle |\tilde{h}_q|^2 \right\rangle = \frac{k_B T}{\kappa q^4}. \tag{3.60}$$

Since the energy cost of an undulation decreases with wavenumber $q = 2\pi/\lambda$, it is easy quite easy to excite long wavelength modes, whose typical amplitude diverges as $1/q^2$.

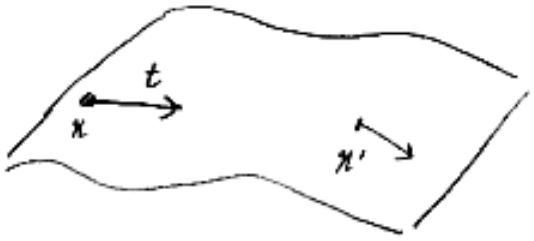
The overall height fluctuations of the surface at any point are obtained by summing the contributions of all Fourier modes, resulting in

$$\begin{aligned} w^2 &= \sum_q \left\langle |\tilde{h}_q|^2 \right\rangle \\ &= \frac{k_B T}{\kappa} \int \frac{d^3\vec{q}}{(2\pi)^2} \frac{1}{q^4} \\ &= \frac{k_B T}{2\pi\kappa} \int_{\pi/L}^{\pi/a} \frac{dq}{q^3} \,. \end{aligned}$$

The upper and lower limits of the integral are reflect respectively L, the linear size of the membrane patch, and a, its thickness. the integral is clearly dominated by its lower cutoff, leading to a width that grows with the size of the patch as

$$w^2 = \frac{k_B T}{4\pi\kappa} \cdot \frac{L^2}{\pi^2} \,. \tag{3.61}$$

For typical membranes κ ranges between 2 to 20 $k_B T$, leading to $w \approx L/20$; i.e. for a patch of size $L = 2$ μm, we expect height fluctuations of around $w \approx 0.1$ μm.



We earlier asked the question of "how straight is a polymer?" We can similarly inquire about if we can define a *persistence length* over which a membrane remains flat despite thermal fluctuations. As in the case of polymers we can examine the decay of orientation fluctuations (e.g. by looking at $\hat{n}(\mathbf{x}) \cdot \hat{n}(\mathbf{x}')$ where $\hat{n}(\mathbf{x})$ is the unit surface normal at point $\mathbf{x}$. Alternatively, we can look at tangent correlations, $\langle \nabla h(\mathbf{x}) \cdot \nabla h(\mathbf{x}') \rangle$. Using Eq. (3.60) it is possible to show that these correlations decay exponentially with separation $|\mathbf{x} - \mathbf{x}'|$, with a correlation length given by

$$\xi_P \approx a \exp\left(\frac{c\kappa}{k_B T}\right) . \tag{3.62}$$

3.4.1 Transport Across Membranes

Hydrophobic molecules such as O_2, CO_2, N_2 and benzene can pass through a lipid bilayer, but smaller ions such as H^+, Na^+ and K^+ cannot. This is due to an *electrostatic barrier.* In water, an ion "feels" a dielectric constant around 80, but within the lipid bilayer, the dielectric constant is of order 1. This creates an energy barrier of almost two orders of magnitude, making it unfavorable for ions to enter (and thereby pass through) the cell membrane. In cases where it is biologically necessary for ions to be transported across the membrane, nature must provide special arrangements to do so.

One such device is a passive ion channel, essentially protein with a channel decorated by polar elements creating a low energy environment for ions to pass through. However, passive motion cannot be the only means for ions to go in and out of a cell, as the concentrations of many common ions are radically out of balance between the inside and the outside of the cell. To achieve transport against the chemical potential that encourages uniformity of concentrations, there must be agents that consume energy to actively maintain a chemical gradient.

The concentration differences of these charged ions lead to membrane potentials, described by the *Nernst equation*

$$\phi = \frac{k_B T}{ez} \log\left(\frac{n_1}{n_2}\right) . \tag{3.63}$$

The order of magnitude is set by $k_B T/e$, which is around 25 mV.