

A guide to

Bio-physics & Bio-mathematics

Kasper Peeters

Lecture notes for the modules “Biophysics I & II” at the University of Durham.

“All science is either physics or stamp collecting.”

— Ernest Rutherford

“People do not want to read books anymore. They want an index so they can say, ‘What is the least amount of this book that I have to read?’.”

— Peter Norvig

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Department of Mathematical Sciences
University of Durham
South Road
Durham DH1 3LE
United Kingdom

kasper.peeters@durham.ac.uk

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Intro and overview

Understanding the physics behind biological systems involves many different topics, such as thermodynamics, classical and statistical mechanics, electrodynamics. When you learn these individually and in isolated form, it can be hard to see how to apply the sometimes abstract theory to real-world biological systems. The present text takes a different route, and uses concrete problems as a basis for teaching just enough of the essentials so that you can have a good physical understanding of what is going on.

Typical questions which we would like to know the answer to are

- Why is the world of microbiology so different from the world of macroscopic living things? Why do bacteria not swim like fish?
- How does the seemingly random motion of things inside cells lead to biological structure? Which mechanisms are responsible for creating order inside a cell?
- How do soft materials assemble together to make molecular motors? How do they turn energy into useful, directed work?
- How does information gets transported inside biological systems? Why don't electrical signals disappear over time?

1.1. Tour of the cell

The topics in this book will focus on what happens with biological cells and inside of them. This is a world very different from the one we are used to. In order to get a rough idea of the scales involved, here is one of those “powers of ten” tables adapted for our course:

size in meter	phenomenon
10^{-2}	ultrasound wavelength in tissue
$10^{-3}(mm)$	flea
10^{-4}	amoebas, capillaries
10^{-5}	white blood cell
$10^{-6}(\mu m)$	bacteria
10^{-7}	phage, DNA strands
10^{-8}	globular proteins, cell membrane thickness
$10^{-9}(nm)$	DNA nucleotides
10^{-10}	atoms in DNA

We will mainly focus on scales between 10^{-4} and 10^{-8} meter: the cell, the way it behaves in its environment, and its internals.

Cells, even though there are many types, perform a common set of activities, which include

- They take in chemical or solar energy, of which most gets discarded again as heat, but some gets used to do mechanical work or to synthesise molecules.
- They make their own internal structure, mostly in terms of proteins.
- They reproduce or duplicate.
- They maintain their internal composition and their volume despite the changing exterior conditions.
- Many move about by crawling or swimming.
- They sense and respond to environmental conditions.
- They sense their internal conditions and use this in feedback loops.

1.2. Guide to the literature

While these notes contain the basic material necessary to get you through the “Biophysics” module, you are strongly encouraged to have a look at some additional books, if only to see things from a different perspective.

- P. Nelson, “Biological physics”, W.H. Freeman and Co., 2008.
We will mostly follow this book, though in a different order and with a more mathematical emphasis.
- D. T. Haynie, “Biological thermodynamics”, Cambridge, 2004.
An introductory book on thermodynamics with biological applications throughout; somewhat basic. Useful for the first chapter of these lectures.
- D. S. Goodsell, “The machinery of life”, Springer, 1993.
A very readable book to get an insight into the microscopic world of the cell and its contents.
- We will not do differential equations; see Mathematical Biology and Partial Differential Equations.
- Although we will touch briefly on some statistical aspects of microscopic biology, see e.g. Statistical Methods for more details.

2

Energy balance

2.1. Biological questions

Just as in other areas of physics, many problems in biophysics can be understood by simply ignoring all the details that go on at a small (atomic) scale, and instead focussing on the way in which energy flows at a more macroscopic level. However, *unlike* many standard physics problems, biological physics problems are almost always governed by the fact that they take place at some non-zero temperature. At finite temperature, energy balance can be quite complicated and confusing, and we need a good intuitive grasp of *thermodynamics*.

Naively, you would perhaps expect that at the micro- or nanometer scale, all order would quickly be washed out by the thermal fluctuations. Thermal fluctuations look like they would just lead to some generic repulsive force that tries to mix everything into one big soup (after all, that is what usually happens when you put a mixture of things in a pot and heat it for a long time). But things are more complicated than that. First of all, membranes prevent things from moving in arbitrary ways. This results in an effect known as osmosis pressure. We would like to be able to compute that pressure and see what role it plays in stabilising cells.

Thermal fluctuations often bring a cell from one state to another, as they allow a system to ‘jump’ over energy barriers. The associated reaction rates have to do with the energy ‘cost’ to go from one state to the other, and thermodynamics gives a clear prediction for the rate at which such transitions can occur. Chemical and other reactions of course play an important role in all sorts of cell processes.

Finally, thermodynamical fluctuations lead to an interesting new type of attractive force. This force occurs in situations where the thermally dancing soup surrounding large molecules is prevented from entering between two of them. We never see this kind of force in the macroscopic world, but it can be competing with Coulomb forces, hydrogen bonds or electromagnetic interaction at very small scales.

► *See also:* P. Nelson, “Biological physics”, W.H. Freeman and Co., 2008, chapter 1, 6 and 7, a bit of 8. For more thermodynamics, see D. T. Haynie, “Biological thermodynamics”, Cambridge, 2004.

2.2. Physical theory

2.2.1 Prerequisite: ideal gasses

There is one concept so dominant in thermodynamics that we need to spend a few words on it before we delve into more complicated theory: that of an “ideal gas”.

Ideal gas law.

An ideal gas is a gas in which the molecules do not interact with each other. The energy of the gas is just the kinetic energy of the molecules summed up, and there is no potential energy. From an empirical point of view, what defines an ideal gas is the relation

$$PV = Nk_B T. \quad (2.1)$$

Here P is the pressure, V the volume, N the number of molecules, T the temperature and $k_B = 1.380\,650\,3 \times 10^{-23} \text{ m}^2 \text{ kg s}^{-2} \text{ K}^{-1}$ the so-called Boltzmann constant. If a gas has a sufficiently low density, it can be approximated with the above **ideal gas law**. It can be derived from statistical mechanics but we will not need that derivation here.¹

Average energy of a molecule in an ideal gas.

The second important equation for ideal gasses deals with the energy which is stored in each individual molecule. This is a simple expression,

$$E_{\text{molecule}} = \frac{3}{2} k_B T. \quad (2.2)$$

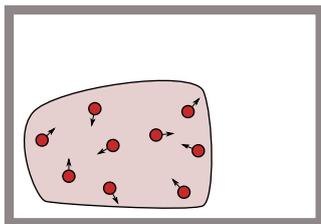
This equation expresses the average kinetic energy of a molecule of an ideal gas in terms of the temperature. You can again derive this relation from first principles, but the upshot is all we will need for our biological applications.

2.2.2 Energy, entropy and temperature

Let us begin by recalling a few basic ideas from thermodynamics. From our experience in everyday life, we know that when we bring two substances at different temperature in contact with each other, a flow of energy will occur. The internal thermal energy of the hotter substance will flow to the cooler substance. Once the combined system has settled into equilibrium, we can again talk about its temperature.

Temperature is thus a property of systems in equilibrium. But interesting things (like the energy flow described above) happen precisely because systems are often not in equilibrium. In order to understand whether a system is in equilibrium, it is not sufficient to simply know its total energy. After all, we can bring a system with a large energy into contact with a system with only little energy, but that does not tell us whether they will be in equilibrium once we allow them to exchange energy.

The reason why the knowing only the total energy is not sufficient is of course that there are *many* microscopic states which can result in a system with the same total energy. Think of a box containing a gas of molecules with some fixed total energy. At the microscopic level, there are many different ways in which the molecules can be moving, and since they constantly bump into each other, their velocities and positions are constantly changing. Whether a system is in equilibrium or not surely depends on how these velocities and positions are distributed over the molecules. If all molecules sit in one corner of the box (as in the figure), there surely is no equilibrium, and the gas will eventually expand to fill the entire box.



If a gas is initially located in a corner, there is no equilibrium. The gas will eventually expand to fill the entire container, thereby maximising the number of available microstates at given fixed total energy.

Let us say the same thing using slightly different wording. Suppose we would do a rapid set of measurements on our sample system in the initial state, with all molecules in one corner. We would see that there is a certain order to the results: the positions of all molecules are always in the corner. In equilibrium, on the other hand, we can find molecules at any possible position inside the fixed container, and there is much less correlation between one measurement and the next. We can thus say that there is a relation between the number of possible microscopic states and the “disorder” of the system. If the number of allowed states is maximal, we have maximal disorder.

¹You may have seen this law in terms of the number of moles of gas molecules, rather than the number of molecules itself. In that case, k_B gets replaced by the gas constant R .

A different way to say that the gas will expand to fill all the available volume is thus:

Statistical postulate: When an isolated system is left alone long enough, it evolves to thermal equilibrium. Equilibrium is not one microstate, but rather that probability distribution of microstates having the greatest possible disorder allowed by the physical constraints on the system.

What we thus need to do is to quantify the concept of “disorder”, given the macroscopic constraints (total fixed energy and total fixed available volume, in our case). The property of the system which does this is the so-called *entropy*.

In terms of the number of microstates Ω , entropy is defined as

$$S := k_B \log \Omega. \quad (2.3)$$

The Boltzmann constant k_B is there by convention and has no physical meaning. However, the logarithm is there for a good reason. Suppose each of N molecules composing the gas can be in one of n_{states} different states (positions and velocities). Then we would in total have $\Omega = (n_{\text{states}})^N$ different states altogether. The logarithm of this quantity depends linearly on N . In effect, the entropy is a measure of the *number of labels* which we have to specify in order to describe the state. If we string N digits between 1 and n_{states} together, we have a number which labels our state.

Note that entropy is *not* conserved: it increases until the system reaches equilibrium. This is actually the statement of the

Second law of thermodynamics: Whenever we release an internal constraint on an isolated macroscopic system in equilibrium, it eventually comes to a new equilibrium whose entropy is at least as great as before.

In spirit it is of course very similar to the statistical postulate, but now formulated purely in terms of the macroscopic concept of entropy.

Now that we know what entropy is, let us come back to ‘temperature’. Consider the system depicted on the right. There are two systems, A and B, initially at different temperatures. The systems can exchange energy (but not particles) because we have just removed a small part of the middle wall, replacing it with a membrane. We would like to define temperature as the quantity that comes to equal values when the two subsystems exchanging energy come to equilibrium. But we have just discussed that equilibrium is the same thing as maximal disorder. So at equilibrium,

$$\left. \frac{dS_{\text{tot}}}{dE_A} \right|_{\text{eq.}} = 0. \quad (2.4)$$

Now since $S_{\text{tot}} = S_A + S_B$ and $E_{\text{tot}} = E_A + E_B = \text{const.}$, this condition translates to

$$\left. \frac{dS_A}{dE_A} \right|_{\text{eq.}} - \left. \frac{dS_B}{dE_B} \right|_{\text{eq.}} = 0. \quad (2.5)$$

Since we want equilibrium to mean that the temperatures of the two systems have become equal, $T_A = T_B$. This is compatible with the equation above if we define temperature as

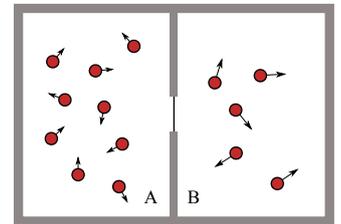
$$T := \left(\frac{dS}{dE} \right)^{-1}, \quad (2.6)$$

where it is understood that we keep the number of particles fixed² This is a some-

²We will come back to changes in numbers of particles in section 2.2.5.

Entropy is a constant times the logarithm of the number of microstates.

Entropy is not conserved (in contrast to energy, which is).



The exchange of thermal energy between the two systems results in thermal equilibrium.

Temperature is the inverse of the derivative of the entropy with respect to the energy, keeping the number of particles fixed.

(end of lecture 2)

what abstract definition, quite far away from how you usually think about temperature. But it has the clear advantage that it is an expression which involves only the two **state functions** of the system: the energy E and the entropy S .

That was a lot of theory. So let us at the end of this section show that it all makes sense if we consider a simple ideal gas. Its kinetic energy is

$$\text{ideal gas : } E_{\text{kin}} = \frac{1}{2}m \sum_{i=1}^N |\vec{v}_i|^2 = \frac{1}{2m} \sum_{i=1}^N |\vec{p}_i|^2. \quad (2.7)$$

For $N = 1$ this just expresses the fact that the momentum three-vector of the particle should lie on a two-sphere with radius $r = \sqrt{2mE_{\text{kin}}}$. For an arbitrary number of particles, the condition is that the allowed values of the $3N$ component vector of momenta are supposed to lie on a sphere of radius $\sqrt{2mE_{\text{kin}}}$ in $3N$ dimensional space. Using the formula for the area of a hypersphere in $3N$ dimensions³ we find that the volume available for the momenta and the coordinates is

$$V_{\text{momenta}} = \frac{2\pi^{3N/2}}{(3N/2 - 1)!} (2mE_{\text{kin}})^{(3N-1)/2}, \quad V_{\text{positions}} = V^N. \quad (2.8)$$

Divide by $N!$ to account for particle exchange, get dimensions right,

$$S_{\text{ideal}} = k_B N \log \left[\frac{V}{N} \left(\frac{E_{\text{kin}}}{N} \right)^{3/2} \times \frac{m}{3\pi\hbar^2} \right] + \frac{5}{2} k_B N. \quad (2.9)$$

This is the so-called **Sakur-Tetrode** formula. At the present stage, most of the details of this formula are actually quite irrelevant, as we are only interested in the dependence on the energy E , not on the dependence on V or N . From (2.9) we get that for an ideal gas the temperature and the energy are related by

$$T = \left(\frac{dS_{\text{ideal}}}{dE_{\text{kin}}} \right)^{-1} = \frac{1}{\frac{3}{2}k_B} E_{\text{kin}}, \quad (2.10)$$

or $E_{\text{ideal}} = \frac{3}{2}k_B T$. This is precisely the right expression.

► *See also:* Nelson's book has a more extensive discussion of entropy in the context of information theory, as well as of ideal gasses.

2.2.3 First law, reversible and irreversible processes

Now that we know that entropy can be used as a quantity to describe systems in and out of equilibrium, we should take a closer look at the way in which energy can be exchanged. We have so far discussed transfer of *heat* (the molecules bouncing on the membrane between the two containers, transferring thermal energy). An alternative way to transfer energy in or out of a system is to make it do *work*. That will happen if the volume of a gas is not constant, and there is some force against which the gas can push. In this context, energy conservation is equivalent to the

First law of thermodynamics: The increase in the internal energy U of a system is equal to the amount of energy added by heating the system, minus the amount lost as a result of the work done by the system on its surroundings.

³The area of a hypersphere in d dimensions is $2\pi^{d/2}r^{d-1}/(d/2 - 1)!$.

In a formula we can write this as

$$dU = \delta Q - \delta W, \quad (2.11)$$

where δQ represents the amount of heat added and δW the amount of work done by the system.

However, neither heat nor work are what we call **state functions** of a system. You cannot, by looking at a system at a particular time, tell what is 'its heat' or 'its work'. The amount of heat absorbed or the amount of work done depend on the particular path which the system has taken through the space of thermodynamic parameters. This is in contrast to the energy E and the entropy S : they can be computed if we know the state of a system at a particular moment in time. We can, however, express the first law (2.11) in terms of changes of state functions alone. For δW this is familiar: the work done by a gas is the same as the pressure times the volume change, $\delta W = PdV$. For the heat absorption, we can make use of the definition of temperature given in (2.6). It states that the increase of energy due to absorption of heat is related to the change of entropy by $\delta Q = TdS$. Together this gives

$$dU = TdS - PdV. \quad (2.12)$$

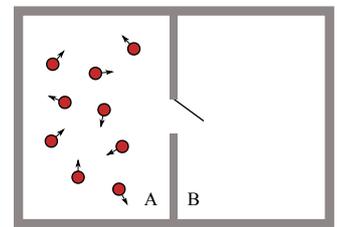
This then gives the first law purely in terms of state functions.

Although this result (2.12) is correct, we have been a bit sloppy in deriving it. To understand what is the problem, consider a situation of the type depicted on the right. Compartment A is filled with gas, while compartment B is empty. At some point, we open the separating door, letting the gas from A expand to fill both compartments. In this case, there clearly is a change in volume, $dV > 0$. However, despite the fact that the pressure of the gas is nonzero, the gas does not push on anything while it expands, so no work is done. So $\delta W \neq PdV$ for this process. Similarly, there is no heat absorbed, since the whole box is isolated. Nevertheless, the entropy changes. So $\delta Q \neq TdS$ for this process either. How can this be compatible with our derivation of the first law?

The key lies in the **irreversibility** of the process we just described. The gas expands to fill the entire container, but this process cannot be reversed. The reason for this irreversibility is that A and B are never anywhere near thermal equilibrium during the expansion. Our derivation of the form (2.12) of the first law assumed that we were dealing with a **reversible** process. Such a process is defined as one which is always close to equilibrium, and can be 'run backwards'.⁴ However, since (2.12) is expressed purely in terms of state functions, which do not depend on the history of the system, it has to be valid irrespective of whether we change the system reversibly or irreversibly. It is only the interpretation of the two terms on the right hand side which is different for the two types of processes ('heat' and 'work' in the reversible case, no such interpretation in the irreversible case).

Since the work done by the irreversible process described above was zero, this type of expansion 'against nothing' is clearly not a good way to extract energy from the system. If we want to extract energy, we have to do things in a controlled way, ideally making the entropy change *vanish* so that the second law of thermodynamics allows us to reverse the process. To illustrate this concept of efficiency in a different setting, let us consider the setup on the right. The idea is that we make energy flow from a hot to a cold body, while extracting some useful part of this flow by making it do work (somehow). Such a setup is called a **heat engine**. The work done by this

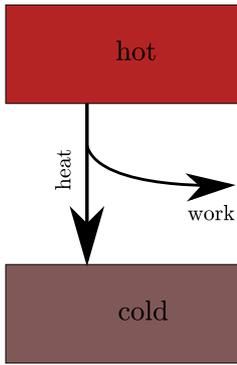
State functions do not depend on the path taken through the space of thermodynamic parameters. The heat Q and work W are not state functions.



Upon opening the separating door between A and B, the gas will expand to fill both halves of the box. However, the pressure in B is zero, so this expansion does no work.

(end of lecture 3)

⁴Note that there is a difference between "quasi-static" and "reversible": you can have two systems at two temperatures equilibrate quasi-statically (by an almost perfectly isolating wall between them, so that the thermal energy exchange goes very slowly). However, this will never be reversible, because the systems are not, at any time, almost in equilibrium.



In a heat engine, heat flows from a hot to a cold body, while some of it is transformed into useful work.

'engine' is, by energy conservation, just

$$\delta W = dQ_h - dQ_c, \quad (2.13)$$

where dQ_h is the energy which flows *out* of the hot body and dQ_c is the energy which flows *into* the cold body. The efficiency (usually called η) is the ratio of the work done versus the energy taken from the hot body,

$$\eta = \frac{\delta W}{dQ_h} = \frac{dQ_h - dQ_c}{dQ_h} = 1 - \frac{dQ_c}{dQ_h} = 1 - \frac{T_c dS_c}{-T_h dS_h}. \quad (2.14)$$

If we have a reversible process, the total entropy of the system does not change. For an irreversible process, the entropy increases. Therefore, $dS_c \geq -dS_h$. This means that the efficiency satisfies

$$\eta \leq 1 - \frac{T_c}{T_h}, \quad (2.15)$$

with maximal efficiency obtained for a reversible process. Note that an efficiency of 'one' can only be obtained if the heat flows to a body at zero temperature. The cold body has to compensate the loss of entropy from the hot body, and at non-zero temperature, it can only do that by absorbing heat, which is then no longer available to useful work.

Biology does, unfortunately for us, not really make any use of these heat engines. However, the general lesson which we learn from it (efficiency is maximal when the entropy change is minimal) holds true in a much more general sense. The important lesson which we should learn from this section is that biological processes will be most efficient if they occur in small, controlled steps. Sudden changes lead to loss of useful energy. For this reason, organisms contain many small molecular-size motors, which take only small steps at a time.

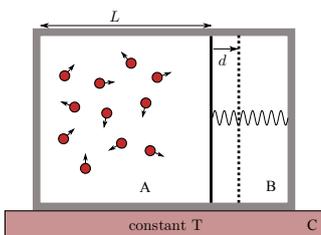
2.2.4 Open systems and free energy

If you have some substance at a non-zero temperature, there is energy stored in the thermal oscillations of the molecules from which the substance is made. However, this energy clearly cannot be extracted if you want to keep the system at the same temperature. We saw something similar in the previous section. There, we noted that if you want to extract heat from a hot body, you need to sacrifice some of the energy to heat up a cold reservoir and make it absorb the entropy which the hot body loses. Not all energy in a hot body is therefore 'free'.

So how much energy can we extract from a hot body and turn into useful work? As expected from the above, this is determined by entropy balance. Consider the situation depicted on the left. It is a container with two compartments, one filled with a gas, the other empty, and a movable piston which is connected to a spring. The whole system sits on a thermal bath which can provide or absorb heat so as to keep the temperature fixed.

The question now is: how much energy will flow in or out of the spring in B? That is to say, how much will the piston move when we let it go? First, let us look at how energy flows. As the gas volume changes, the spring will compress or stretch, and this results in a flow of energy into or out of B. This would change the temperature of the gas, but because of the thermal reservoir, an energy flow from or to C occurs which keeps the energy of A at fixed $E_{\text{gas}} = \frac{3}{2} N k_B T$. There is thus a net flow of energy between the thermal reservoir C and the spring in B.

Now how much energy will flow depends on the entropy balance. From the entropy of an ideal gas (2.9) we can see that the entropy of A changes because of the change of volume. On the other hand, the entropy of C changes because of the



A system connected to a heat bath C which keeps it at constant temperature T . The piston is initially fixed at position L and will move a distance d (to the left or right, depending on the pressure) when it is unfixed. The spring has spring constant f .

energy flow. We can express the latter as

$$\Delta S_C = T^{-1}\Delta E_C = -T^{-1}\Delta E_B. \quad (2.16)$$

It is the sum of these two entropy changes which must be positive according to the second law. So

$$T\Delta S_{\text{tot}} = -\Delta(E_A + E_B) + T\Delta(S_A + S_B) > 0. \quad (2.17)$$

Here we have added two terms (ΔE_A and ΔS_B) which are identically zero, to make the expression look more symmetric.

What does (2.17) mean? If we multiply it by -1 on the left and right, it says that the system does not try to minimise the energy in A+B. Instead, it will try to minimise a different quantity, which involves the entropy. This leads to the definition of the **Helmholtz free energy**,

$$F = E - TS. \quad (2.18)$$

This is the quantity which will come to a minimum when we let the system equilibrate. The Helmholtz free energy F_{A+B} of the open system A+B expresses the amount of useful work obtainable from that system (at a constant temperature and volume). The fact that a minimum in the free energy corresponds to equilibrium is a reformulation of the second law, now for open systems. In the formulation using entropy, it only applies to closed systems.

For open systems, the second law can be reformulated as the statement that equilibrium corresponds to a state of minimal free energy.

Returning to our example above, the entropy change of A is

$$\Delta S_A = \Delta(k_B \ln V^N) = k_B \frac{N\Delta V}{V} = k_B N \frac{d}{L}. \quad (2.19)$$

The energy change is purely due to the change of the length of the spring, and thus given by

$$\Delta E_B = fd. \quad (2.20)$$

Together, these two allow us to calculate ΔF . By setting $\Delta F_A = 0$, we obtain the condition for equilibrium.

In summary, we have thus seen that a system which exchanges heat with its surroundings will go to an equilibrium which is the minimum of the Helmholtz free energy. But there is of course another way to exchange energy with the surroundings: by doing work.⁵ For such a situation, we need an additional term in the free energy, which expresses that some energy will inevitably get lost to the outside world. This brings us to the definition of the **Gibbs free energy**,

$$G = E + pV - TS. \quad (2.21)$$

The Gibbs free energy is the maximum amount of non-expansion work that can be extracted from a closed system; this maximum can be attained only in a completely reversible process. Again, if we have a system at constant pressure and constant temperature, it will eventually settle down in an equilibrium situation which is characterised by the fact that it minimises the Gibbs free energy. One sometimes sees the Gibbs free energy written as

$$G = H - TS \quad (2.22)$$

where H is the so-called **enthalpy**. The enthalpy change of an open system is the heat exchanged by a system at constant pressure.

(end of lecture 4)

⁵Note that we are here talking about doing work which exchanges energy between the open system A+B and the outside world C. In the previous example, the work was done inside the open system A+B, and the energy exchange with the outside world C was only through exchange of heat.

Finally, let us discuss the concept of **entropic forces**. As you know from classical mechanics, the derivative of a potential energy corresponds to a force. This is exactly the same for the Helmholtz free energy which we just discussed.

$$f = -\frac{dF}{dx}. \quad (2.23)$$

In other words, pressure is the derivative of the Helmholtz free energy with respect to a volume.⁶

2.2.5 Boltzmann distribution

So far, we have treated combined systems (like the one in the previous section) in such a way that we essentially ignored the thermal fluctuations in energy in any of the compartments. Provided all compartments are relatively large, that is of course a valid approximation. However, when the open system is very small, it may not be appropriate to only compute quantities like its average energy. Rather, we would like to see what is the probability to find a system in one of its many states. Thus, what we would like to do next is to understand the probability for each of the microscopic states of an open system A , while it is in thermal equilibrium with a much larger system B (which acts as the heat bath, and is thus for all practical purposes ensuring that the temperature of both systems is fixed at some value T).

The key ingredient we will use is the statistical postulate, which says that each and every microstate of the joint system $A + B$ has the same probability, let us call it P_0 . We want to obtain from this the probability to find system A in a particular microstate, if we only know its energy. We can do this by noting that the number of states available for system B is related to its entropy by

$$\Omega_B = e^{S(E_B)/k_B}, \quad (2.24)$$

where we have indicated that the entropy in turn depends on the energy in system B . Because the energy is conserved, we can use $E_B = E_{\text{tot}} - E_A$. Moreover, since system A is small, we can expand the entropy of system B in powers of the small energy E_A . This gives

$$\begin{aligned} S_B(E_B) &= S_B(E_{\text{tot}} - E_A) = S_B(E_{\text{tot}}) - E_A \frac{dS_B}{dE_B} + \dots \\ &= S_B(E_{\text{tot}}) - \frac{E_A}{T} + \dots, \end{aligned} \quad (2.25)$$

where in the last step we have again used the definition of temperature (2.6). The probability of finding system A in a particular state is now

$$P(E_A) = P_0 e^{S_B(E_{\text{tot}})/k_B} \times e^{-E_A/(k_B T)} = \mathcal{N} \times e^{-E_A/(k_B T)}. \quad (2.26)$$

The factor \mathcal{N} is just a given numerical constant, which is often not relevant. The second factor indicates that the probability of finding a particular microstate is suppressed with the exponent of its energy. This is called the **Boltzmann distribution** or **canonical distribution**.

Let us discuss a simple example, in which the system A can only be in two different states. Let these two states have energy E_1 and E_2 respectively, with $\Delta E = E_2 - E_1$. Of course, the probability to be in the first state and the probability to be in

⁶The reason why the Gibbs free energy does not appear in this formula is that the Gibbs free energy subtracts the work done by the pressure. It is precisely that work which we want to measure or balance against an external force.

the second state have to add up to one, $P_1 + P_2 = 1$. Moreover, from the Boltzmann distribution we have

$$\frac{P_1}{P_2} = \frac{e^{-E_1/k_B T}}{e^{-(E_1+\Delta E)/k_B T}} = e^{\Delta E/k_B T}. \quad (2.27)$$

These two equations can be solved to get

$$P_1 = \frac{1}{1 + e^{-\Delta E/k_B T}}, \quad P_2 = \frac{1}{1 + e^{\Delta E/k_B T}}. \quad (2.28)$$

We see that if state 2 is much more energetic than state 1, so that ΔE is large and positive, the system is predominantly in the first state, as expected.

In the discussion above, we have assumed that when the system A changes from one microstate to the other, the total number of particles in A remains conserved. But very often, particles can come from B or disappear into it, making the particle number of A non-conserved in time. Typically, adding a particle to A will imply that the energy of A changes. We can express this quite simply by making use of the first law, $dU = TdS$ for a system at constant temperature and pressure. This leads us to define

$$\mu := -T \left. \frac{dS}{dN_A} \right|_{E \text{ const.}}. \quad (2.29)$$

This quantity is called the **chemical potential** of the particles in system A . You can roughly think about it as the energy change of A which occurs when we add one particle to that subsystem; we will return to the interpretation of the chemical potential in much more detail later.

Now how does our analysis of the distribution of states change if we include the possibility that particles get exchanged between A and B ? This can be computed using a similar procedure. We now have that

$$\begin{aligned} S_B(E_B, N_B) &= S_B(E_{\text{tot}} - E_A, N_{\text{tot}} - N_A) = S_B(E_{\text{tot}}) - E_A \frac{dS_B}{dE_B} - N_A \frac{dS_B}{dN_B} + \dots \\ &= S_B(E_{\text{tot}}) - \frac{E_A}{T} + \frac{N_A \mu}{T} \dots, \end{aligned} \quad (2.30)$$

By the same logic we now find that the probability to find system A in a state with energy E_A and number of particles N_A is given by

$$P(E_A, N_A) = \mathcal{N}' \times e^{(-E_A + \mu N_A)/(k_B T)}. \quad (2.31)$$

This probability distribution is called the **Gibbs distribution** or **grand canonical distribution**. Note that large values of μ imply that A is more likely to contain a large number of particles.

Perhaps the most important outcome of the analysis in this section is that the probability to find the small system in a particular state *only* depends on the energy of that small system. The properties of the large system are practically irrelevant! The only thing we had to know is that $E_B \gg E_A$ and $N_B \gg N_A$. No details about the microstates of B are ever needed.

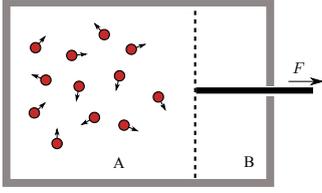
We will make use of the results derived in this section when we discuss reaction rates in section 2.3.2.

(end of lecture 5)

2.3. Application

2.3.1 Osmosis, reverse osmosis and surface tension

Osmosis is a typical example of a force which can easily be computed once you understand the concept of entropy. Consider the system depicted on the right. It has



The osmotic pressure forces water out of region B, through the semipermeable membrane, and into region A, thereby exerting a pressure in the direction indicated.

two compartments, which are separated by a semi-permeable membrane. Compartment A contains a solvent with a particular concentration of solutes, while compartment B contains only the solvent. The membrane allows solvent to pass through, but not the larger solute particles. The question is now what happens to this system if we release the position of the initially fixed membrane.

The easiest way to see what happens is to consider the total entropy. Since the volume available to the solvent is independent of the position of the membrane, its entropy will be a fixed number. The entropy of the solute is given by that of an ideal gas,

$$S_{\text{solute}} = k_B N_{\text{solute}} \log(E_{\text{solute}}^{3/2} V) + \text{const.} \quad (3.1)$$

On the other hand, there is heat flowing from the thermal bath, which gets used to do work against the external force. From these two ingredients we can derive the condition that a small change in volume does not change the entropy, i.e. that the entropy has an extremum. We get

$$dS_{\text{tot}} = k_B N_{\text{solute}} \frac{dV}{V} - \frac{P_{\text{osmotic}} dV}{T}. \quad (3.2)$$

The pressure which is exerted on the membrane is thus given by

$$P_{\text{osmotic}} = c k_B T, \quad \text{with } c := \frac{N_{\text{solute}}}{V}, \quad (3.3)$$

where c is the number density of the solute molecules. This relation is known as the **van 't Hoff relation**. Note that it precisely the same type of relation as the ideal gas law (2.1); the only change is that the pressure has been replaced with the osmotic pressure and the number of particles is not the total number of molecules but instead the number of solute molecules.⁷

What we have discussed here is the system in equilibrium: assuming we exert some pressure on the membrane, we have found the equilibrium position (volume) given that pressure. A different question is what actually happens if you start in a situation in which the exerted pressure is lower or higher than the osmotic pressure for the given volume. In this case, the maximal work that the osmotic pressure can do is obtained by integrating $P_{\text{osmotic}} dV$ over the change in volume. At room temperature $T \approx 300$ K,

$$W = \int_{V_{\min}}^V k_B T \frac{N_{\text{solute}}}{V'} dV' = (k_B T) N_{\text{solute}} \log \frac{V}{V_0} \approx N_{\text{solute}} \gamma \times 4.1 \times 10^{-21} \text{ J}, \quad (3.4)$$

where γ is the logarithm of the maximal and minimal volume of the compartment which contains the solute.

We can also look at osmosis in a somewhat different way. Imagine that we pull on the system with a force which is larger than the osmotic force. This will make the compartment with the solutes more concentrated, as we force the solvent to go to the other compartment. In this process, we perform mechanical work (the membrane pushes on and moves the solute), which gets converted to heat. At the same time, the entropy of the subsystem has decreased (but of course the entropy of the surroundings has increased more). This process is called **reverse osmosis**. If we just look at the subsystem, we see that energy passes through it, and leaves behind increased order (decreased entropy). It is one of the prototypical examples which show that subsystems can increase their order by having energy pass through it.

⁷In experimental literature, you will often see concentrations denoted in 'osmoles per litre'. The osmole number is simply referring to the number of moles of particles that contribute to osmotic pressure, i.e. $N_{\text{solute}} / (6 \times 10^{23})$ in our discussion above.

In biology, osmosis plays a role whenever we have a cell embedded in a solute. A concrete example is a red blood cell, which is embedded in the blood plasma. The concentration of salt in the plasma surrounding the cell has to be carefully tuned, otherwise the osmotic pressure will force water into the cell and make it tear apart (or *lyse*). To make this more quantitative, let us find a formula which relates the tension of a cell membrane to the pressure inside the cell.

Imagine a cell membrane as depicted on the right. There is a surface tension pulling on both sides of the solid line. More precisely, the surface tension is the force per unit length. If we pull on the membrane, such that two closely separated lines get displaced by a distance dx , then the total work that we do equals

$$\delta W_{\text{stretch}} = \Sigma l dx = \Sigma dA. \quad (3.5)$$

This expression, involving the product of the surface tension times the increase in area, holds in general. For a spherical membrane, the increase in area is related to an increase in the radius, as $A = 4\pi R^2$. Thus,

$$dA = dR \frac{dA}{dR} = 8\pi R dR. \quad (3.6)$$

A spherical membrane will expand until the free energy reaches a minimum. Concretely, this means that the free energy reduction from the expansion of the interior has to balance the free energy increase from stretching the membrane. So we have

$$dF = \delta W_{\text{stretch}} - \delta W_{\text{interior}} = \Sigma dA - P dV = (8\pi \Sigma R - 4\pi P R^2) dR = 0. \quad (3.7)$$

where of course we used $V = \frac{4}{3}\pi R^3$. This results a relation between the surface tension and the pressure inside the spherical membrane, the so-called **Laplace formula**,

$$\Sigma = \frac{1}{2} R P. \quad (3.8)$$

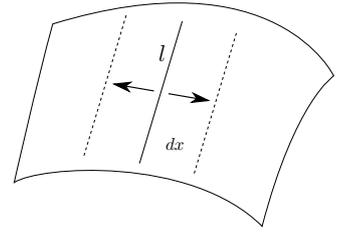
Equipped with Laplace's formula, we can estimate the surface tension which would be needed to support the membrane of a cell when it is put in water. A typical cell has (remember the table in section 1.1) a radius of around $R \approx 10^{-5}$ m. Let us assume that the osmotic pressure comes from the proteins inside the cell, of which there may be quite a lot. Typically, about 30% of the volume of a red blood cell is occupied with globular proteins (the 'volume fraction ϕ equals 0.3'), such as hemoglobin. These proteins have a radius of around 10 nm, which means that their concentration is

$$c = \frac{0.3}{\frac{4\pi}{3} (1 \times 10^{-8} \text{ m})^3} \approx 7 \times 10^{22} \text{ m}^{-3}. \quad (3.9)$$

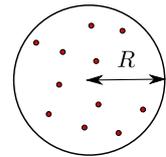
From (3.3) we then find that $P \approx 300$ Pa. Plugging this back into the Laplace formula yields $\Sigma \approx 1.5 \times 10^{-3} \text{ Nm}^{-1}$.

Unfortunately, it turns out that this vastly underestimates the concentration of particles inside the cell which contribute to the pressure. One can measure that blood serum (the fluid in which the red blood cell is sitting) has a concentration of about 0.3 osm L^{-1} , or $c_{\text{serum}} \approx 1.8 \times 10^{26} \text{ m}^{-3}$. This would make the osmotic pressure outside the cell much larger than inside, and result in a collapse of the cell. The conclusion is that there is, apart from globular proteins, substantially more inside the cell that contributes to the pressure on the cell membrane. In fact, we will see later (when we discuss ion transport across membranes) that the cell membrane does a lot of complicated things to maintain a constant volume.

► *See also:* Osmosis is described in some detail in Fermi's book, page 118.



Stretching a membrane by a distance dx in one direction increases its area by $dA = l \times dx$.

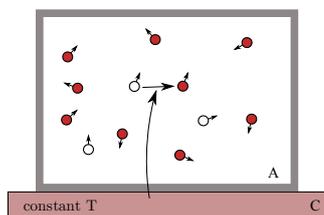


A large cell of radius R in a concentration c of small globular proteins feels an osmotic pressure which tends to tear it apart.

(end of lecture 6)

2.3.2 Reaction rates

Equilibrium does not have to mean that nothing happens. In particular, in chemistry an equilibrium is often **dynamic**. This means that if we have some solution with molecules of two types, there will typically be a reaction that takes type 1 to type 2 and a reaction in the other direction. Dynamic equilibrium then simply means that the two reaction rates are equal, leading to constant concentrations of 1 and 2, even though both molecules are constantly being created and destroyed.



A chemical reaction, turning a particle of type 1 (open circles) to type 2 (filled circles), and using energy in the form of heat from the thermal reservoir.

Relation between chemical potential and concentration for ideal gasses.

In the present section, we want to have a look at such reaction rates. They all follow the pattern as depicted on the left: particles get converted from one type to the other (not necessarily one-to-one though), and in the process, heat is absorbed or released. The number of particles of a given type is therefore *not* the same before and after the reaction step has taken place. The Boltzmann distribution which we discovered in section 2.2.5 lies at the root of our understanding of transition and reaction rates in such generic situations.

The concept of chemical potential will play a very important role in this section. We have seen in section 2.2.5 that it is related to the change of entropy with a change in number of particles. Before we explain how this defines reaction rates, we will first take a closer look at the chemical potential concept, and relate it to the more familiar idea of concentrations. At least for ideal gasses or dilute solutions, these two are closely related. To see this, let us compute (2.29) for an ideal gas. We have derived an expression for the entropy of an ideal gas in (2.9), in terms of E_{kin} , V and N . It is thus simple to find the derivative of the entropy with respect to the number of particles at constant kinetic energy,

$$\left. \frac{dS_{\text{ideal}}}{dN} \right|_{E_{\text{kin}}} = \frac{3}{2} k_B \log \left[\frac{1}{3\pi} \frac{m E_{\text{kin}}}{\hbar^2} \left(\frac{V}{N} \right)^{2/3} \right]. \quad (3.10)$$

However, in order to compute the chemical potential (2.29), we need to keep the *total* energy fixed, not just the kinetic energy. And if we change the number of particles, we will change the total *internal* energy. So what we need to do in order to compute μ is to subtract a term $\epsilon(dS/dN)$ from the change of the entropy, where ϵ is the internal energy of a single particle. Using $E_{\text{kin}} = \frac{3}{2} k_B N T$ this gives

$$\begin{aligned} \mu_{\text{ideal}} &= -T \left(\left. \frac{dS_{\text{ideal}}}{dN} \right|_{E_{\text{kin}}} - \epsilon \left. \frac{dS_{\text{ideal}}}{dE_{\text{kin}}} \right|_N \right) \\ &= \epsilon + k_B T \log c - \frac{3}{2} k_B T \log \left(\frac{4\pi}{3} \frac{m}{(2\pi\hbar)^2} \frac{3}{2} k_B T \right), \end{aligned} \quad (3.11)$$

where $c = N/V$ is again the concentration. Since this involves logarithms of dimensional quantities in the individual terms, it is more natural to write it as

$$\mu_{\text{ideal}} = k_B T \log(c/c_0) + \mu^0(T), \quad \mu^0(T) = \epsilon - \frac{3}{2} k_B T \log \left(\frac{m k_B T}{2\pi\hbar^2 c_0^{2/3}} \right). \quad (3.12)$$

The expression $\mu_0(T)$ is called the **standard chemical potential** for the **reference concentration** c_0 . The important aspect of writing things in this way is that we have isolated the dependence of the chemical potential on the concentration. The bit corresponding to the standard chemical potential only depends on temperature, and is a property of the solution. Even in the presence of interactions between the solvent and solutes, we will get a form like (3.12). So one typically just takes this to be a quantity that simply needs to be looked up in a table.

Let us now see how this all relates to chemical reactions. Let us first consider a simple one, such as depicted in the figure above,

$$P_1 \rightleftharpoons P_2. \quad (3.13)$$

Let us also assume first that this conversion does not cost any energy. In that case, the change of the entropy for one step from the left to the right is

Chemical potentials determine the direction of a chemical reaction

$$\Delta S_{1 \rightarrow 2} = \frac{\mu_1 - \mu_2}{T}, \quad (3.14)$$

by virtue of the very definition of the chemical potential (2.29). The reaction in the opposite direction would instead change the entropy by minus this amount. If you express the chemical potentials in terms of the concentration, we see that the reaction (3.13) will take place whenever the concentration of particles of type 1 is larger than the concentration of particles of type 2. However, since the chemical potentials also contain the internal energies, it is the balance between the two that determines the direction of the reaction.

In general, a conversion of particles in this way will of course not work without some energy exchange with the thermal reservoir. If the internal energies of the two particle types are ϵ_1 and ϵ_2 respectively, you need an energy $\epsilon_2 - \epsilon_1$ from the heat bath in order to make the reaction go from left to right. The reaction in the opposite way will instead release this amount of energy. However, what matters is, as always, the total entropy change. For the combined system of heat bath and reservoir, the entropy change due to heat flow is zero. The total entropy change is thus still $\Delta S_{\text{tot}} = (\mu_1 - \mu_2)/T$.

However, we can view system A as an open system, and write

$$\delta S_{1 \rightarrow 2}^A = \frac{\mu_1 - \mu_2}{T} + \frac{\epsilon_2 - \epsilon_1}{T}. \quad (3.15)$$

We can then use this to compute the change of the free energy in system A . For the process at hand, with fixed volume, we see that one step of the reaction $1 \rightarrow 2$ leads to a change of the Helmholtz free energy given by

Free energy determines the direction of a chemical reaction.

$$\text{constant volume : } \quad \Delta F_A = \mu_2 - \mu_1. \quad (3.16)$$

A different way to say this is that setting $\Delta F = 0$ implies $\Delta S_{\text{tot}} = 0$. If the volume would not be constant, we instead find that

$$\text{constant pressure : } \quad \Delta G_A = \mu_2 - \mu_1. \quad (3.17)$$

Here we see clearly once more the importance of the concept of free energy: it is the free energy which determines in which direction a reaction will go.

(end of lecture 7)

Let us now look at somewhat more complicated reactions, e.g. the conversion of hydrogen and oxygen to water,



The free energy change from left to right will be (we will from now on always write the Gibbs free energy, assuming constant pressure situations),

$$\Delta G_{L \rightarrow R} = 2\mu_{\text{H}_2\text{O}} - 2\mu_{\text{H}_2} - \mu_{\text{O}_2}. \quad (3.19)$$

We can express this in a more useful form by using the expression for the chemical potentials in terms of concentrations. This gives, for equilibrium

$$0 = \frac{\Delta G}{k_B T} = \frac{2\mu_{\text{H}_2\text{O}}^0 - 2\mu_{\text{H}_2}^0 - \mu_{\text{O}_2}^0}{k_B T} + \log \left[\left(\frac{c_{\text{H}_2\text{O}}}{c_0} \right)^2 \left(\frac{c_{\text{H}_2}}{c_0} \right)^{-2} \left(\frac{c_{\text{O}_2}}{c_0} \right)^{-1} \right]. \quad (3.20)$$

For a given fixed c_0 , all the μ^0 coefficients can be looked up in tables, and the formula above then gives us an expression for the ratio of the concentrations *in equilibrium*,

$$\frac{(c_{\text{H}_2\text{O}})^2}{(c_{\text{H}_2})^2 c_{\text{O}_2}} = \frac{K_{\text{eq}}}{c_0}, \quad \text{with} \quad K_{\text{eq}} = e^{-\Delta G/k_B T} = e^{-(2\mu_{\text{H}_2\text{O}}^0 - 2\mu_{\text{H}_2}^0 - \mu_{\text{O}_2}^0)/k_B T}. \quad (3.21)$$

This kind of expression can be generalised to arbitrary reactions, and is called the **mass action rule**. It is often stated in the form of concentrations divided by the reference concentrations,

$$\frac{[\text{H}_2\text{O}]^2}{[\text{H}_2]^2 [\text{O}_2]} = K_{\text{eq}}, \quad \text{with} \quad [X] := \frac{c_X}{c_0}. \quad (3.22)$$

and so on.

Using the computed temperature-dependence of the standard chemical potentials (3.12), one can work out the **equilibrium constant** K_{eq} in terms of the temperature, and see how the equilibrium changes as the temperature is changed.

► *See also:* J. D. Murray, “Mathematical Biology, I: An Introduction”, Springer-Verlag, 2002 chapter 6. P. Nelson, “Biological physics”, W.H. Freeman and Co., 2008 chapter 8.

2.3.3 Depletion forces

We have seen that the free energy can be used to compute a force, just like you can compute a force in classical mechanics by taking the derivative of a potential. Because the free energy contains a term proportional to the entropy, it is possible to have forces which are caused purely by entropic effects. One such is the so-called “depletion force”. The depletion force occurs whenever you have a suspension containing more than one type of particle. An example is depicted on the left. The picture shows two large particles, surrounded by a number of small particles (only one of the small particles is displayed). If the separation between the large particles satisfies $a > D + d$, the volume V' available for the centres of the small ones is simply the total volume minus twice the volume of the large particles with their “exclusion zones”,

$$V' = V - \frac{8\pi}{3} \left(\frac{D+d}{2} \right)^3. \quad (3.23)$$

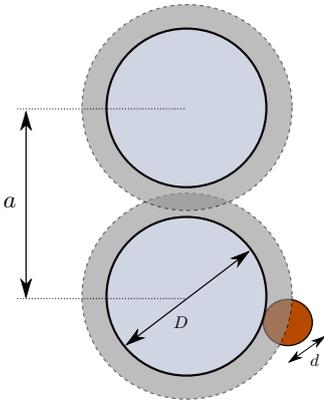
However, when the distance becomes smaller, the exclusion zones start to overlap, and the volume available to the small particles increases.

This increase of available volume will lead to an increase of the entropy of the small particles, and hence a force which attracts the two large particles. This is quite surprising: even though there is no interaction between the particles except when they touch each other, there still is an *attractive force*!

To compute the strength of this force, let us compute the volume V'' available to the small particles when $a < D + d$. This boils down to the geometric problem of computing the volume of the dark shaded almond-shape region in the figure on the left. This is

$$V'' = V' + 2\pi \int_{a/2}^{(D+d)/2} x^2 dy, \quad (3.24)$$

where x and y are the directions in the plane of the figure, with $x^2 = ((D+d)/2)^2 -$



Two large particles of diameter D in the presence of small particles of diameter d . When the separation a becomes smaller than $D + d$, the volume available to the small particles increases, increasing their entropy.

y^2 . This gives

$$\begin{aligned} V'' &= V' + \frac{4\pi}{3} \left(\frac{D+d}{2} \right)^3 - \frac{\pi}{4} \left[(D+d)^2 a - \frac{1}{3} a^3 \right] \\ &= V - \frac{4\pi}{3} \left(\frac{D+d}{2} \right)^3 - \frac{\pi}{4} \left[(D+d)^2 a - \frac{1}{3} a^3 \right]. \end{aligned} \quad (3.25)$$

To compute the force, we first compute the free energy $F = E - TS$ using the fact that $S = k_B N \log(V E^{3/2})$. We then take the derivative with respect to a to find the force. This gives

$$f = -\frac{dF}{da} = -\left(\frac{k_B N T}{V''} \right) \frac{\pi}{4} \left[(D+d)^2 - a^2 \right]. \quad (3.26)$$

If $V \gg (D+d)^3$, we can replace V'' with V in the denominator, and we see that the first factor is simply the osmotic pressure $p_0 = k_B T N / V$.

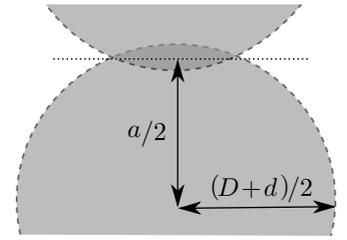
We can convert this force back into a potential energy by integrating with respect to a , obtaining

$$U = -p_0 \frac{\pi}{12} \left[2(D+d)^3 - 3(D+d)^2 a + a^3 \right]. \quad (3.27)$$

The a -independent constant was chosen such that the potential vanishes for $a > D+d$. For $D \gg d$ we can approximate this result by

$$\frac{U}{k_B T} = -\frac{3}{2} \phi \beta \left(\frac{D+d-a}{d} \right)^2, \quad \text{with } \phi = \frac{\pi}{6} d^3 \frac{N}{V}, \beta = \frac{D}{d}. \quad (3.28)$$

Here ϕ is the volume concentration of the small molecules. For a numerical estimate of the strength of this force, let us assume $D/d = 50$ and $\phi = 0.3$ (the ratio we have seen earlier for proteins within a cell), then we find that the minimum of the potential (at $a = D$) takes the value $U = -22.5 k_B T$. This is a substantial energy for biological standards.



The dark shaded region of overlap of the two discs of radius $(D+d)/2$ is the double-counted excluded region.

(end of lecture 8)

► **See also:** S. Asakura and F. Oosawa, "Interaction between particles suspended in solutions of macromolecules", *J. Pol. Sci.* **33** (1958) 183–192, D. Marenduzzo, K. Finnan, and P. R. Cook, "The depletion attraction: an underappreciated force driving cellular organization", *J. Cell Biol.* **175** (2006) 681–686

3

Flowing and swimming

3.1. Biological questions

Biological systems are characterised by a lot of activity at the microscopic scale. Molecules and small organisms move around, fluids like blood flow through capillaries and around cells, and so on. In the present chapter, the goal is to understand these flowing and swimming phenomena from a physics perspective. Just as in the previous chapter, we will see that things at a microscopic scale behave quite differently from those at the macroscopic scale we are used to.

One of the more fundamental questions is to understand the basics of fluid flow in capillaries and around cells and micro-organisms. Inside cells, there are many different localised “factory” sites which produce things which then have to be transported to other sites. For example, mitochondria synthesize ATP, which then gets used throughout the cell. We may speculate that thermal motion, which we have found is a big effect in the nanoworld, somehow causes molecular transport. For transport within the cell, this indeed turns out to be true: diffusion is quick enough to serve as the transport mechanism.¹

Another question in this context is that of bacterial swimming. Bacteria do not actually swim like we humans do, but they instead make use of a mechanism which has more to do with pumping. There is a simple physical principle underlying this phenomenon, and it has all to do with the fact that fluid flow can be smooth (laminar) or turbulent. The small machines that bacteria use to propel themselves are true marvels of engineering, little rotating engines which are only about 45 nm in size!

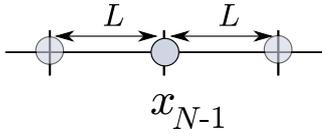
► *See also:* Most of what is discussed in this chapter can be found in Nelson’s book chapter 3, 4 and 5, though not necessarily in the same order.

3.2. Physical theory

3.2.1 Random walks and diffusion

In the previous chapter, we have seen how many properties of multi-particle systems can be described simply in terms of energy and entropy, which give a rough macroscopic description. In the present chapter, we want to look a bit closer at how microscopic systems behave dynamically. The first thing we will analyse is how

¹Diffusion does not do the trick on large distances, e.g. to transport information from your head to your toes; for such transport more advanced mechanisms exist, which we will discuss later.



Setup for a random walk. We consider a particle at position x_{N-1} , with an equal probability to make a step of size L left or right in the given time interval Δt .

individual molecules, embedded in a thermal environment, move about because of thermal fluctuations.

Consider for simplicity a molecule in one dimension, as depicted on the left. It starts out at time $t = 0$ at position $x = 0$. Our main assumption will be that, under the effect of thermal fluctuations of the surrounding particles (which are not displayed here), our molecule will make random steps to the left and right, with an average size L per unit of time Δt . position after $N - 1$ steps as

$$x_N = x_{N-1} + k_N L, \quad (2.1)$$

with k_N being ± 1 with equal probability. On average, over a large number of trials, the chance of arriving to the left of the origin will be the same as the chance of arriving to the right, and the average position will simply be zero, $\langle x_N \rangle = 0$.

However, this of course does not mean that the particle stays put. A better way to measure how far out the particle gets is to compute the average position *squared*. Using (2.1) we can compute this average for the square of the position after N steps, in terms of the position after $N - 1$ steps,

$$\langle (x_N)^2 \rangle = \langle (x_{N-1} + k_N L)^2 \rangle = \langle (x_{N-1})^2 \rangle + 2 \langle x_{N-1} k_N \rangle + L^2 \langle k_N^2 \rangle. \quad (2.2)$$

The second term vanishes: for each partial path that goes through a given point x_{N-1} , there is always a continuation both with $k_N = 1$ and $k_N = -1$, and these contribute with opposite sign to $\langle x_{N-1} k_N \rangle$. For the last term, we use $\langle (k_N)^2 \rangle = 1$ because k_N is either one or minus one, and thus the square is always one. We thus see that the average position squared increases by L^2 for every time step. We can summarise this by writing

$$\langle (x_N)^2 \rangle = N L^2. \quad (2.3)$$

A different way this is sometimes stated is $\sqrt{\langle (x_N)^2 \rangle} = L \sqrt{N}$, which shows that the range travelled grows with the square root of the number of steps.

If our system makes one step for every time interval Δt , then we can also write this expression as

$$\langle (x_N)^2 \rangle = 2Dt, \quad \text{where } D = \frac{L^2}{2\Delta t}, \quad (2.4)$$

The constant D is called the **diffusion constant**. We have here discussed the one-dimensional case, but the generalisation to d dimensions is trivial: motion in each direction is independent, and we thus get

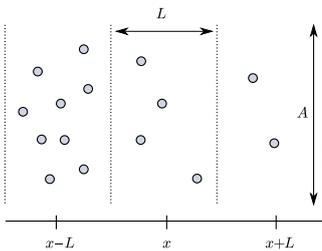
$$\langle (\vec{x}_N)^2 \rangle = 2dDt. \quad (2.5)$$

The mean squared distance thus stays linear in t , with a proportionality constant which depends on the number of dimensions.

The relation (2.5) tells us one particular property of a random walk: if we have a large number of particles, their average squared displacement grows linearly in time. But this is far from the only information about a distribution of particles. We would like to know what happens if we have a large number of particles in some given distribution, and let it evolve for some time. In this case, it is impractical to follow the procedure we used above. Instead, it is much simpler to consider all the particles at once, and see how the distribution itself evolves in time.

Let us consider the situation depicted on the left. It describes a distribution of particles which is non-constant in the x -direction. We have, to make the analysis simpler, artificially divided the volume up into boxes of size L . Remember that we have assumed that in a time interval Δt , a molecule will make a step of size L either to the left or to the right, with equal probability.

We want to compute the number of particles crossing the separation line at $x - L/2$ from left to right. This is determined simply by the fact that half of the



A non-constant density gradient of particles. The system has been divided into imaginary containers of size L centered around x , $x - L$ and $x + L$.

particles in the leftmost box will jump left and half will jump right, and similar for the particles in the middle box. Therefore,

$$\Delta N \Big|_{\text{through } x-L/2} = \frac{1}{2} \left(N(x-L) - N(x) \right) \approx -\frac{L}{2} \frac{dN}{dx}. \quad (2.6)$$

The flux of particles is the number of particles crossing one of these imaginary surfaces, per unit surface area and per unit time. If we also introduce the concentration $c = N/(AL)$, then

$$j(t, x) = -\frac{1}{A\Delta t} \frac{1}{2} L \frac{\partial}{\partial x} \left(LAc(t, x) \right). \quad (2.7)$$

By making use of the definition of the diffusion constant D we can write this as

$$j(t, x) = -D \frac{\partial c(t, x)}{\partial x}. \quad (2.8)$$

This relation, which expresses the flux of particles in terms of the spatial gradient of the concentration, is called **Fick's law**.

It is perhaps worthwhile to emphasise once more that the particles do *not* interact. The change in particle density is simply a consequence of the fact that the concentration is not homogeneous to start with. Here we see, once more, a manifestation of the effect of the second law, which demands entropy increase (even though we have not described things in that way here).

With this knowledge about the flux which passes through every imaginary separator, we can compute the change of particle density in each imaginary box.

$$\frac{\partial N(t, x)}{\partial t} = A \times \left(j\left(x - \frac{L}{2}\right) - j\left(x + \frac{L}{2}\right) \right). \quad (2.9)$$

In the limit in which the imaginary boxes become infinitesimally thin, this becomes

$$\frac{\partial c(t, x)}{\partial t} = -\frac{\partial j(t, x)}{\partial x}. \quad (2.10)$$

where we have divided both sides of the equation by AL . This equation is called the **continuity equation**. Combining this equation with Fick's law gives us

$$\frac{\partial c(t, x)}{\partial t} = D \frac{\partial^2 c(t, x)}{\partial x^2}, \quad (2.11)$$

which is also known as the **diffusion equation**. It is first-order in the time derivative, and second order in the space derivative.

Let us consider a number of simple cases. As expected, if the concentration is uniform, it will not change in time, because the second derivative with respect to x vanishes. The same is actually also true for a concentration which is linear in x . Diffusion will simply maintain this concentration gradient. However, for all other concentration profiles, the evolution in time will be non-trivial.

3.2.2 Viscosity and friction

In the previous section we have seen that diffusion is essentially a consequence of random fluctuations. However, since random fluctuations involve random collisions, we might expect that there is also a connection to *friction*.

To study friction, we will consider a particle which experiences a constant external force. Let us also restrict ourselves to motion in one dimension; again, generalisation to more dimensions is simple. As before, we will assume that the particle

(end of lecture 9)

(lecture 10: homework)

gets a kick every Δt , resetting its velocity to some random value. In between these kicks, the velocity changes according to Newton's law, i.e.

$$\delta x = v_0 \delta t + \frac{1}{2} \frac{f}{m} (\Delta t)^2. \quad (2.12)$$

What is relevant now is the average of this displacement. For the velocity v_0 , the random kicks will make $\langle v_0 \rangle = 0$. The average velocity which the particle acquires is given by $\langle \Delta x \rangle / \Delta t$. This comes out as

$$v_{\text{drift}} = f / \zeta, \quad \text{with} \quad \zeta = 2m / \Delta t. \quad (2.13)$$

The constant ζ is the **viscous friction coefficient**. Note the similarity to the way in which the diffusion constant was obtained.

One very important relation can be derived by noting that the average velocity of one of our randomly walking particles is simply $L / \Delta t$. By multiplying the two constants, we get

$$\zeta D = \frac{L^2 m}{(\Delta t)^2} = mv^2. \quad (2.14)$$

Remember now that for an ideal gas in one dimension, the kinetic energy is $E = 1/2 mv^2$ but it is also given by $E = 1/2 k_B T$. Together, this gives us

$$\zeta D = k_B T. \quad (2.15)$$

This relation between the viscous friction coefficient ζ and the diffusion constant D is called the **Einstein relation**. It is important because it relates to a priori different types of experiments.

Clearly, we expect the coefficient ζ to depend on the shape of the body. There is an empirical relation, the so-called **Stokes formula**, which expresses how it depends on the radius of a spherical body,

$$\zeta = 6\pi\eta R. \quad (2.16)$$

Here η is a parameter which is independent of the body, and determines the viscosity of the fluid. The Stokes formula can be derived from first principles but that requires quite a bit of fluid dynamics, and we will hence not go into that here.

However, it is useful to see η appear in a different context, so as to understand how we can measure it. Consider therefore a setup with two parallel plates, one fixed and the other one moving at some velocity v (a "shearing" motion). In between the plates is a fluid. We now want to know the force which the plates exert on each other. Clearly, if the area of the plates is larger, the force should increase, but if the distance is larger, it should decrease. For small enough v , most fluids follow the simplest possible force satisfying these conditions,

$$\frac{f}{A} = -\eta \frac{v}{d}. \quad (2.17)$$

For non-constant velocity gradient, the right hand side reads $-\eta (dv/dy)$. Since this is shearing motion, the coefficient η is also called the **shear viscosity**. The dimension of viscosity can be obtained directly from (2.17), it is

$$[\eta] = \text{kg m}^{-1} \text{s}^{-1}. \quad (2.18)$$

This will be important later.

It is useful to compare the viscosity force we just discussed with the force which we would get if the material inbetween the plates would be some elastic, rubber type of material. In this case, the force will follow a hook law,

$$f = -k(\Delta z), \quad (2.19)$$

where Δz is the horizontal displacement of the two plates. The constant k often contains the factor A/d (which makes this expression look a bit more similar to the viscosity force). However, what is important here is that this elastic force is proportional to the *strain* $\Delta z/d$. For fluids it is instead proportional to the *strain rate*, v/d .

(end of lecture 11)

3.2.3 Turbulent versus laminar flow

The shear viscosity η is a dimensionful number (dimension $\text{kg m}^{-1} \text{s}^{-1}$), so it does not make any sense to talk about it 'being small': smallness only means something with respect to another number with the same dimensions. There is typically a scale in problems involving viscosity, namely the mass density ρ (dimension kg m^{-3}). But it is impossible to form a single massless number from the two.

What we *can* do, however, is form a number with the dimension of a force (dimension kg m s^{-2}), namely

$$f_{\text{crit}} = \frac{\eta^2}{\rho}. \quad (2.20)$$

We should thus expect that there might be two different types of fluid flow past and around objects, depending on whether we apply forces which are smaller or larger than this **viscous critical force** f_{crit} .

Intuitively, since the viscous critical force is large when the viscosity is large or when the mass density is small, we expect that in such a case, inertial effects of the fluid are most important. If inertial effects are important, we expect that we get **turbulent** flow: if you set things in motion, they will keep going long after you stop pushing. On the other hand, if f_{crit} is small (with respect to an externally applied force), then we expect the viscous forces to be dominant. If you set the fluid in motion and then stop applying a force, the viscous forces will quickly stop the movement. The flow is **laminar**, in the sense that layers of fluid move in a nicely aligned way, without mixing up or swirling.

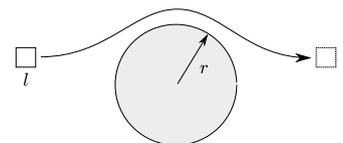
For e.g. corn syrup, the mass density $\rho_{\text{syrup}} \approx 1 \times 10^3 \text{ kg m}^{-3}$ and the viscosity is $\eta_{\text{syrup}} \approx 5 \text{ kg m}^{-1} \text{ s}^{-1}$. As a result, the critical force is $f_{\text{crit}} \approx 2.5 \times 10^{-2} \text{ N}$. If you push a marble through corn syrup with a force less than about 0.01 N, you will see nice laminar flow and no turbulence. However, for water, the mass density is similar but the viscosity $\eta_{\text{water}} \approx 1 \times 10^{-3} \text{ kg m}^{-1} \text{ s}^{-1}$. This leads to a critical force of $f_{\text{crit}}^{\text{water}} \approx 1 \times 10^{-9} \text{ kg m s}^{-2}$, some factor 2.5×10^7 smaller than for corn syrup! But the logic remains the same: if you push a small micro-organism through water with a force of a nanonewton or so, you are well into the laminar regime, and you should not expect turbulence to play a major role. It is very important to realise that the scale at which laminar flow takes over from turbulent flow is set by an *external force*, not by some intrinsic length of the fluid.

Let us now try to get away from this dimensional handwaving, and try to make things a bit more quantitative. Let us focus on a spherical object, which sits in some fluid flow, as depicted on the right. The object has radius r , and we are going to follow a small fluid segment of typical size l (we will drop all factors of 2 and π from now on, so you do not actually need to know the precise shape of this segment). The first thing we need to do is to write down the forces on this fluid segment,

$$f_{\text{ext}} + f_{\text{frict}} = m \times a, \quad (2.21)$$

where $m = \rho l^3$ is the mass of the segment and a its acceleration. We can estimate the acceleration by noting that if the segment would be in orbit around the obstacle, it would undergo a centrifugal acceleration $a = v^2/r$. Together, we thus have

$$f_{\text{ext}} + f_{\text{frict}} \sim \rho l^3 v^2 / r. \quad (2.22)$$



A segment of fluid of typical linear size l flows around a spherical object of radius r .

We now want to compute f_{crit} to see when it is of the same order of the right hand side (in which case friction cannot be neglected and laminar flow will result), or much smaller (in which case turbulence will occur).

The friction force can be estimated directly from the defining relation (2.17), or rather the one in terms of the derivative of v given immediately below that. The net force on our segment of volume l^3 will be given by the force on the top minus the force on the bottom, or $(df/dy) \times l$. Therefore

$$f_{\text{frict}} \sim l^3 \eta \frac{d^2 v}{dy^2}. \quad (2.23)$$

We do not know much about the fluid velocity profile, but to estimate the order of magnitude, we can safely say that the relevant scales here are the velocity itself and the radius of the obstacle. So we will take $d^2 v/dx^2 \sim v/r^2$. Together this gives

$$f_{\text{frict}} \sim \eta l^3 v/r^2. \quad (2.24)$$

Of course, any more accurate estimate would require more knowledge about the fluid flow, but that is not the point here.

We can now define a dimensionless number which determines when friction dominates. This is the **Reynolds number**, defined as the ratio of the inertial force (the right-hand side of (2.22)) and the frictional force,

$$R = vr\rho/\eta. \quad (2.25)$$

When R is small, frictional effects dominate, and laminar flow results. When R is large, inertial effects dominate, and turbulent flow results. Of course, precisely what is 'small' and 'large' in this context cannot be determined from the derivation which we gave, and will have to be observed experimentally.

3.3. Application

3.3.1 Oxygen and blood flow

Bacteria need oxygen, and they will have to absorb that from the environment. We can get a good idea of the rate at which they can absorb oxygen by making use of the diffusion theory we discussed earlier, in particular Fick's law.

Imagine a bacterium as a sphere of radius R . Around it, there is a fluid with a certain non-constant concentration of oxygen. Far away from the bacterium, this concentration will be some fixed number $c(\infty) = c_0$. At the surface of the bacterium, on the other hand, we will set the concentration to zero (all oxygen gets absorbed), i.e. $c(R) = 0$. The question is now what is the rate of flow of oxygen given these boundary conditions.

Since there is no oxygen being produced in the fluid, if you draw concentric spheres around the bacterium, the same amount of oxygen per unit time has to pass through each of them. That is to say, the flux times the area of each sphere has to be a constant, let us call it I ,

$$j \times 4\pi r^2 = -I. \quad (3.1)$$

Inserting this into Fick's law (2.8), we can find the concentration,

$$c(r) = A - \frac{1}{r} \frac{I}{4\pi D}, \quad (3.2)$$

where A is a constant. If we now impose the boundary conditions, we can fix both A and I , and obtain

$$c(r) = c_0 \left(1 - \frac{R}{r}\right). \quad (3.3)$$

because $I = 4\pi DRc_0$. This expression for I is important, because it shows that (as perhaps expected) the amount of oxygen per unit time scales linear with the concentration of oxygen, but it also shows that (perhaps unexpected) the maximum rate at which a bacterium can absorb oxygen scales linear with its radius R . That is not particularly good. The oxygen consumption most likely scales with the volume, i.e. with R^3 . This means that a bacterium cannot get too large, because it will not be able to absorb enough oxygen.

(end of lecture 12)

A better and more efficient way to transport oxygen is of course to use a system of blood vessels. So let us see how oxygen and blood flow through blood vessels. Consider a cylindrical vessel segment of length L . At the vessel wall at $r = R$, the velocity of the fluid has to be zero (the 'no slip condition'). There will thus be a velocity profile $v(r)$, which we want to compute.

In order to do that, let us consider the forces on a cylindrical shell between radius r and $r + dr$, as indicated in the figure. This shell experiences three forces. One is the force due to the pressure drop in the vessel. Along the length L , this drop will be taken to be ΔP , and the resulting force df_1 points (in the figure) upwards,

$$df_1 = 2\pi r \Delta P dr. \quad (3.4)$$

Then there are two frictional forces. One is a force df_2 pulling downwards, exerted by the shell of slower moving fluid at larger radius. The other is a force df_3 pulling upwards, exerted by the shell of faster moving fluid at smaller radius. From the viscosity formula we have

$$df_2 = -\eta 2\pi L (r + dr) \frac{dv(r + dr)}{dr}, \quad df_3 = \eta 2\pi L r \frac{dv(r)}{dr}. \quad (3.5)$$

If we assume that there is no acceleration of the fluid, these three forces have to add up to zero. The velocity derivative in df_2 can be expressed as

$$\frac{dv(r + dr)}{dr} = \frac{dv(r)}{dr} + dr \times \frac{d^2v(r)}{dr^2} + \dots \quad (3.6)$$

The force balance condition then reads

$$\frac{r \Delta P}{L \eta} + \frac{dv}{dr} + r \frac{d^2v}{dr^2} = 0. \quad (3.7)$$

We can solve this differential equation for $v(r)$, and the general solution reads

$$v(r) = A + B \log r - \frac{r^2 \Delta P}{4L \eta}. \quad (3.8)$$

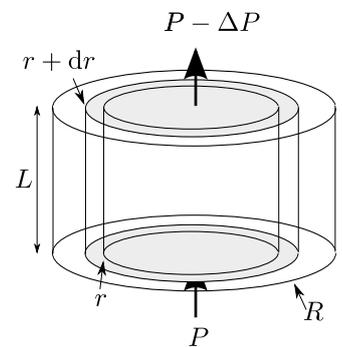
If we want the solution to be regular at $r = 0$, we have to set $B = 0$. Moreover, if we want $v(R) = 0$ then the constant A is fixed. The result is

$$v(r) = \frac{(R^2 - r^2) \Delta P}{4L \eta}. \quad (3.9)$$

The velocity profile for laminar flow inside a cylindrical vessel is thus quadratic in the radius.

From the velocity profile we can compute the total amount of fluid Q that flows through the pipe per unit time. This is obtained by integrating the velocity profile over the cross-section of the vessel,

$$Q = \int_0^R 2\pi r v(r) dr = \frac{\pi R^4}{8L \eta} \Delta P. \quad (3.10)$$



Laminar flow in a cylindrical pipe. The pressure drop along the segment of length L is ΔP .

This is the so-called **Hagen-Poiseuille relation**. It is a bit like Ohm's law, in the sense that the rate of fluid flow ('current') Q is equal to the driving force ('potential drop') divided by a resistance. This resistance Z for fluid flow is

$$Z = \frac{8\eta L}{\pi R^4}. \quad (3.11)$$

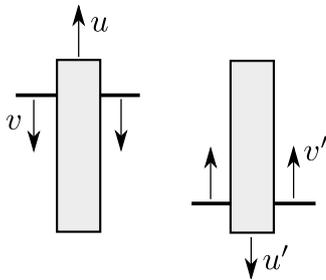
Such Ohm-like relations are, in the case of fluid flow, also known as **Darcy's law**.

For biological purposes, the important consequence of the Hagen-Poiseuille relation is that the rate of fluid flow grows *very* rapidly with the radius R . In terms of the area, the rate is proportional to the square of the cross-sectional area. Therefore, doubling the cross-sectional area of a single vessel is much more efficient than simply having two vessels of the same area. Said in a different way, we need to increase the radius of the vessel by only a little bit in order to get a substantial increase in fluid flow rate.

(end of lecture 13)

3.3.2 Bacterial flagella

When moving around in a low Reynolds-number world, bacteria have to take special measures to ensure that they actually move at all. With laminar flow, swimming is quite different from what it is when there is turbulent flow. In the present section, we will use the formulas for viscosity forces to analyse swimming motion for bacteria.



Schematic picture of the two-stage swimming process for a bacterium with paddles. As computed in the text, this mechanism fails at low Reynolds numbers (laminar flow).

Naively, one might expect that a bacterium can move by using small 'paddles', as indicated in the schematic drawing on the left. During the "power" stroke, the paddles are moved quickly, pushing the bacterium forward. To restore the paddles to their original position, this is then followed by a "recovery" stroke of the paddles at much smaller velocity. In the high Reynolds-number world, this works, but does it work for low Reynolds numbers too?

The important ingredient in this setup is clearly the viscous friction coefficient ζ_0 which determines the force acting on the bacterium, and the viscous friction force ζ_1 acting on the paddles. We can relate the forces on the bacterium or paddle to their velocities by using the defining relation (2.13).

The velocity of the paddles in the first (forward) stroke, relative to the fluid, is $v - u$ downwards, so there is a viscous force $\zeta_1(v - u)$ pointing upwards. Similarly, the velocity of the bacterium itself is u upwards, so there is a force $\zeta_0 u$ pointing downwards. If there is no acceleration, these two forces balance, which means

$$(v - u)\zeta_1 = u\zeta_0 \quad \rightarrow \quad u = \frac{\zeta_1}{\zeta_0 + \zeta_1}. \quad (3.12)$$

If this movement happens for a time Δt , the bacterium moves forward by a distance $\delta X = u\Delta t$. On the second (return) stroke, the paddles move upwards with velocity $v' - u'$, so there is a force $(v' - u')\zeta_1$ downward on the paddle. The bacterium moves downwards with velocity u' so there is an upwards force $u'\zeta_0$. Now the force balance reads

$$(v' - u')\zeta_1 = u'\zeta_0 \quad \rightarrow \quad u' = \frac{\zeta_1}{\zeta_0 + \zeta_1}v'. \quad (3.13)$$

The bacterium now moves a distance $\Delta x' = -\Delta t' u'$. The time intervals have to be chosen such that the paddles return to their original position after the two strokes, which means

$$v'\Delta t' = v\Delta t. \quad (3.14)$$

Combining the lot, we find that

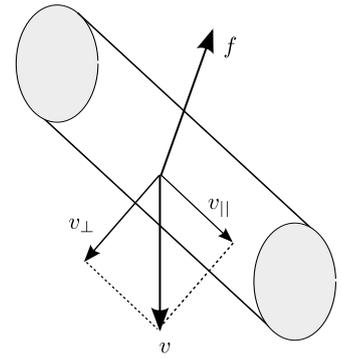
$$\Delta x' = -\frac{v\Delta t}{v'}u' = -\frac{u\Delta t}{u'}u' = -\Delta x. \quad (3.15)$$

This shows that, no matter how you choose v and v' , the return stroke always exactly cancels the effect of the forward stroke. Paddling does not work for a bacterium.

What we need is some motion that is periodic but not *reciprocal* (meaning that there are not two parts of the motion which exactly cancel each other, like in the example above). One way to do that is to have a rotor type of propulsion mechanism. Biology does not often make use of rotary devices (think about how you would get e.g. blood from the fixed to the rotating part of a body to understand why biology does not like rotating motion). However, bacteria do seem to use this mechanism, in the form of **flagella**.

A bacterial flagellum is a helical structure, connected to the main part of the bacterium by a microscopic rotating construction (this 'engine' is only about 45 nm wide). Naively, since all parts of the helix simply move around in circles, i.e. with a velocity which is orthogonal to the helix axis, one would perhaps expect that viscous forces can never push in the direction of the axis. However, that naive reasoning is incorrect. The subtlety lies in the fact that the viscous friction coefficient for a non-spherical object depends on the direction in which the object moves. If we consider the cylindrical segment, the viscous friction coefficient for movement in the orthogonal direction (with velocity v_{\perp} is larger than the coefficient for movement in the parallel direction (with velocity v_{\parallel}). Therefore, there *is* a net force pushing the helix in the direction of the axis.

There are other propulsion mechanisms in use by bacteria, for more information see Nelson's book. They all rely on the fact that the motion is not reciprocal.



A segment of a bacterial flagella; the axis of the helix is horizontal. Even though the velocity of the segment is pointing in the plane of rotation, the viscous force has a component along the axis of the helix.

(end of lecture 14)

3

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