BERTRAND FOURCADE

PHYSICS OF THE COLLOIDAL DOMAIN - LECTURE NOTES

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Forword

These lectures notes are available at : https://www-liphy.univ-grenoble-alpes.fr/Lecture-Notes-and-Material-M1. They will be upgraded during the lectures at regular intervals. Therefore, there is no need to print them ! Students will be evaluated through homeworks (2) and final exam (50 %).

2
Introduction : Why ?

What is soft matter/colloidal domain ? Polymers, surfactants, liquid crystals, colloidal suspensions, gels (gelatine !), food etc.

What is the characteristic property of "soft order": Minute changes in the chemistry makes big changes, i.e. has macroscopic (mesoscopic) effects.

This is where Biology, physics and chemistry meet. Structures of biological molecules depend on the interactions between atomes and molecules, and the interplay between energy and entropy, which results in the remarquable ability of biological systems to self-assemble and control their own replication. It is interesting to emphasize the concepts which bridge biology and the colloidal domain.

Why colloids/soft-matter/bio-nanotech etc. are important ? Numerous industrial applications (cosmetics, food industry, drug delivery with multifonctional nanoparticles ...)

We assume:

1. Basic knowledge with essential principles for chemical structures, reactivity and bonding;
2. Basic Concepts of molecular biology;
3. Basic maths.

Remember: Soft matter is different from biology because self-assembly is not synonymous of self-organization. However the organization of cellular structures (functional and structural) depends on a delicate interplay between energy and entropy. These concepts are common to the three fields.

What are the characteristic properties of the colloidal domain ?

1. Mesoscale (1 - 100 μm) with marked consequences: We observe huge thermal fluctuations !
2. Disordered: Polymers look like spaghetti; Liquid crystals (oblong molecules) are a state of matter which has properties between those of conventional liquids and those of solid crystals. For instance, a liquid crystal may flow like a liquid, but its molecules may be oriented in a crystal-like way. : see positional order and orientational order, Fig. **??** , huge fluctuations

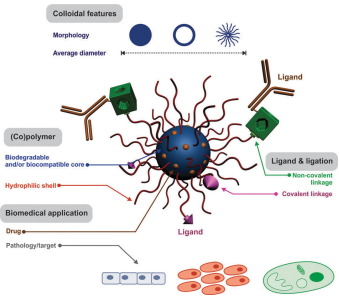


Figure 2.1: Design for drug-loaded nanocarriers, such as liposomes, nanoparticles, micelles etc. [**?**]

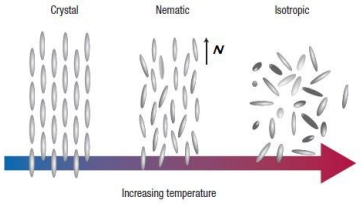


Figure 2.2: Positional order gives regular distances between molecules. Orientational order means that groups of molecules lie in the same direction.

(thermal fluctuations, small number of molecules), (thermal and non-thermal noise) noise.

3. Living systems are out-equilibrium systems. In equilibrium, there is only one steady state. When systems are out of equilibrium, there can have more than in steady states.

4. Systems where connectivity plays an important role (see gels and percolation)

5. Systems where geometry is not trivial (see self-similarity and fractals)

6. Systems where the interactions between the (macro)molecules are weak (very different from solid state physics). In particular:

   (a) Van de Waals interactions: They are attractive and due to dipole-dipole interaction which oriente each other so net attraction results. For two spherical objects (geometry is important, distance d, radii R)) at small distance

   $$U = -\frac{A}{12}\frac{R}{d} \tag{2.1}$$

   which means $U > kT$: Thermal energy is not strong enough to overcome the Van der Waals interaction which dominates.

   (b) Electrostatic interactions: They are generally screened because of counter ions in the solvent. Competition between attractive van der Waals and repulsive electrical double-layer forces determines the stability or instability of colloidal systems.

   (c) Steric forces: are long range and important. Example are stealth liposomes with a polymeric corona to prevent recognition by the immune system.

   (d) Entropic forces (rubber elasticity which contact upon heating)

   (e) Mechanics (ex: adhesion, biopolymers): bending, stretching.

Energy scales:

1. For ionic or covalent bond: Typically, 1 ev = 1.610^{-19}J;

2. Soft order in physics and biology, thermal energy $\approx 1/40$ ev is the relevant scale.

We have for the thermal energy

$$kT(300K) = \frac{1}{40}\,\text{ev} = 410^{-12} \times 10^{-9} J \tag{2.2}$$

Thus the convenient unit for the force is pN and the relevant scale for the distance is nM.

General references for these lectures are:

1. For the point of view of physics: Physical Biology of the Cell, by Rob Phillips and al, Garland. Biological Physics, Energy, information, life, by P. Nelson, Freeman.

2. For the point of chemistry: Physical Chemistry; P. Atkins and Julio de Paula, Oxford

3. For the point of view of Biology: The molecules of Life, Physical and chemical principles, by J. Kuriyan et al, Garland.

3
Self-assembly of amphiphiles: Thermodynamics of interface

3.1 *Introduction: A brief note on history*

The colloidal domain is where chemistry, biology and physics meet. Membranes have a long history which started in 1890 with Ch. E. Overton who discovered that cells are envolopped in a selectively permeable layer. The story continued for more than a century. In 1972, Singer and Nicholson published a paper where they proposed the so-called fluid mosaic model for cell membranes. This model describes the membrane as a fluid, lipidic bilayer (lipid + cholesterol) in which macromolecules and proteins are incorporated.

We will see that lipidic bilayers form spontaneously above a well determined critical concentration. This is one of the most elementary form of spontaneous self-assembly where phospholipidic molecules aggregate themselves into a thin bilayer (60 Å thick) and form a vesicle (small bag, $\approx 20\mu m$). Self-assembly is a hot subject in chemistry and in Nano-sciences in general. But it should not be confused with self-organization. The latter is a much broader and deeper subject. It is characteristic of active, i.e. out of equilibrium, phenomena seen in living cells.

We start with simple amphiphilic molecules.

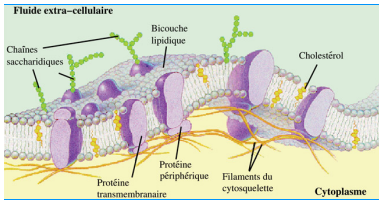


Figure 3.1: The fluid mosaic membrane mode according to Singer and Nicholson.

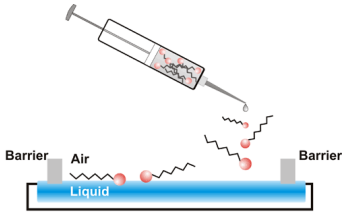


Figure 3.2: The Langmuir and Langmuir-Blodgett techniques allow preparing molecular monolayers and their transfer onto solid substrates

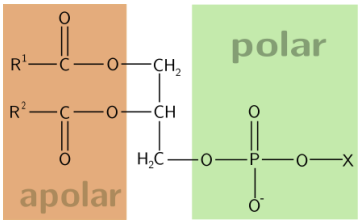


Figure 3.3: An amphiphile is a chemical compound possessing both hydrophilic (water-loving, polar) and lipophilic (fat-loving) properties. Such a compound is called amphiphilic or amphipathic. This forms the basis for a number of areas of research in chemistry and biochemistry, notably that of lipid polymorphism. Organic compounds containing hydrophilic groups at both ends of a prolate (in the aggregate) molecule are called bolaamphiphilic. Common amphiphilic substances are soaps, detergents and lipoproteins.

3.2 *Amphiphilic molecules form aggregates with well-defined properties: Aggregation at low concentration*

Each lipid or surfactant has two well-defined parts: A hydrophobic and a hydrophilic part. The hydrophobic effect is mainly due to entropy : the non-polar part of the amphiphile modifies the structure of the surrounding water. In contrast, polar molecules or polar parts of amphiphilic molecules strongly repeal each other because of electrostatic interactions. If we put amphiphilic molecules into water, they will locate at the air-water interface with their polar head pouring into water and their tail will try to stand out. The same is also true for surfactant molecules (SDS, sodium dodecyl sulfate).

Assume that we have control on the concentration of surfactant molecules. For concentration below 10^{-3} M, SDS molecules will concentrate at the air-water interface. The surface tension decreases with increasing the concentration of SDS. Above 10^{-3} M, the surface tension is, however, almost constant. What happens ? Aggregate form spontaneously with well-defined properties. This critical concentration is called the CMC (for critical micellar concentration).

The schizophrenic character of the molecule leads to the formation of aggregates called micelles. The hydrophobic tails protect themselves from water by forming a core while the polar heads stay outside (see Fig. **??** below for a textbook picture). However, beside this textbook picture, on should note that

1. There is no denser core;
2. The heads are not perfectly arranged;
3. The micelles are not shape-persistent.

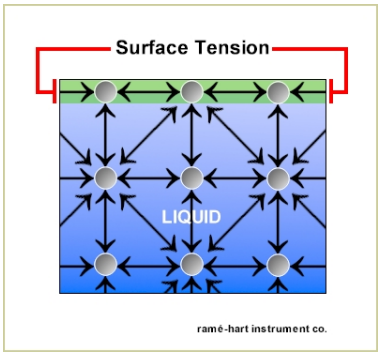


Figure 3.4: At small concentration, SDS molecules concentrate at the surface. The surface tension (resistance to stretch or to compress the film) can be measured.

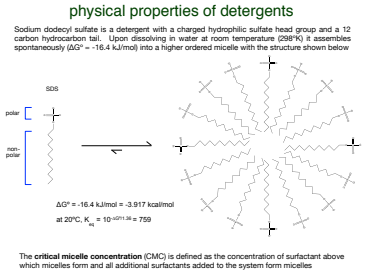


Figure 3.5: SDS.

3.3 *Surface tension*

Molecules in a fluid feel a mutual attraction. When this attractive force is overcome by thermal agitation, the molecules pass into a gaseous phase. Let us first consider a free surface, for example that between air and water, i.e. a liquid-gas interface. A water molecule in the fluid bulk is surrounded by attractive neighbors, while a molecule at the surface has a reduced number of such neighbors and so in an energetically unfavorable state. The creation of new surface is thus energetically costly, and a fluid system will act to minimize surface areas.

To understand that surface tension can affect the shape of an object, it is useful to recall the following theorem. Consider a given volume V of incompressible material. What is the shape of an object composed of this material that minimizes the area ? The answer (in any dimension), is simple. The shape is a sphere. Therefore, the sphere is the shape which minimizes surface tension at a given volume.

Nomenclature: σ denotes the surface tension (at a fluid-gas interface). A related concept is the interfacial tension (depending on the context, this surface tension is noted either γ or σ) at a fluid-fluid or fluid-solid interface.

If we use the **c.g.s.** system :

1. The unit of force is 1 dyne = 1 g cm s^{-2} = 10^{-5} N (roughly the weight of a mosquito).
2. For the pressure 1 atm $\approx$ 100 kPa = 10^5 N/m^2= 10^6 dynes/cm^2.
3. The unit of σ (or γ) is dyne/cm = mN/m.

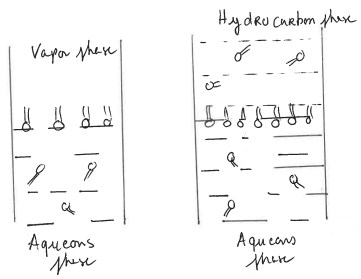


Figure 3.6: Adsorption of surface-active molecules as an orientational monolayer at air-water or oil-water interfaces.

3.4 *Surface activity*

Materials such as short chain fatty acids and alcohols are soluble in both water and oil solvents. The hydrocarbon part of the molecule for its solubility in oil, while the polar part −COOH or OH group has sufficient affinity to water to water to drag a short-length non-polar hydrocarbon chain into aqueous solution with it. If these molecules become located at an air-water or an oil-water interface, they are able to locate their hydrophilic headgroup in the aqueous phase and allow the lipophilic hydrocarbon chain to escape into the vapor or oil phase. The strong adsorption of such materials at surfaces or interfaces in the form of oriented MONOMOLECULAR LAYER (monolayer) is termed surface activity. Surface active materials, i.e. surfactants, consist of molecules containing both polar and non-polar parts. By sitting at the interface, amphiphilic molecules lower the surface tension of the interface.

3.5 *How do we measure surface tension ?*

There are many methods. The capillary rise method is the most accurate one, since it dos not involve a disturbance of the interface. The formula for capillary rise can be derived by balancing forces on the liquid column. The weight of the liquid with density ρ is balanced by the upward force due to surface tension. This formula can also be derived using pressure balance.

$$\sigma = \frac{rh\Delta\rho g}{2\cos\theta} \tag{3.1}$$

which, for zero contact angle, reduces to

$$\sigma = \frac{1}{2}rh\Delta\rho g \tag{3.2}$$

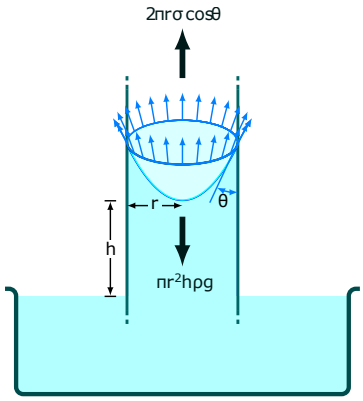


Figure 3.7: Capillary rise.

Liquid	γ or σ
Water	72.8
Benzene	28.9
Acetone	23.7

Table 3.1: Surface tension against water for liquids at 20°C (in mN.m^{-1}).

Exercice 3.1 *As usual, it is useful to define dimensionless numbers. Check that the Bond number*

$$Bo = \frac{\rho g a^2}{\sigma} \frac{\text{Gravity}}{Curvature} \tag{3.3}$$

is a dimensionless ratio. The Bond number indicates the relative importance of forces induced by gravity and surface tension. Note that these two forces are comparable when $Bo = 1$, which arises at a length scale corresponding to the capillary length

$$l_c = \sqrt{\frac{\sigma}{\rho g}} \tag{3.4}$$

For water-air $\sigma = 70$ dynes/cm, $l_c = 2$ mn.

For an example where gravity plays a role, see Fig. **??** where we use the Evolver program to simulate a drop sitting on a substrate with and without gravity.

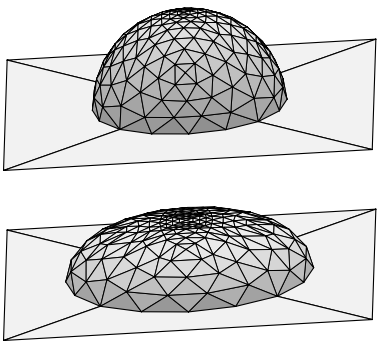


Figure 3.8: Effect of gravity on the shape of a drop sitting on a substrate. Two drops sitting on a substrate with the same contact angle and the same volume. For the top one, the gravity is set to zero and the shape is a spherical cap. For the bottom one, gravity is such that its capillary length is smaller than its radial dimension. In this case, gravity influences the shape of the drop and its shape is no more spherical.

3.6 *Contact angle and wetting*

In spreading wetting, a liquid already in contact with the solid spreads so as to increase the solid-liquid and liquid-gas interfacial areas and decreases the solid-gas area. Let us define the difference between the surface energy (per unit area) of the substrate when dry and wet:

$$S = E_{\text{substrate}}(\text{dry}) - E_{\text{substrate}}(\text{wet}) = \gamma_{SG} - (\gamma_{SL} + \gamma_{LG}) \qquad (3.5)$$

To remember this formula, it suffices to remind ourselves that in the dry state, there is only one solid-gas interface. We have the following cases:

1. $S > 0$: Total wetting. If the parameter S is positive, the liquid spreads completely in order to lower its surface energy. Condition favorable for this condition is a high value of γ_{SG} (high energy surfaces like glass, clean silicon) and a lower value of γ_{SL} (ethanol, toluene).

2. $S < 0$: The drop does not spread but, instead, forms at equilibrium a spherical cap resting on the substrate with a contact angle θ . A liquid is said to be "mostly wetting" when $\theta < 90^\circ$, and "mostly non-wetting" when $\theta > 90^\circ$.

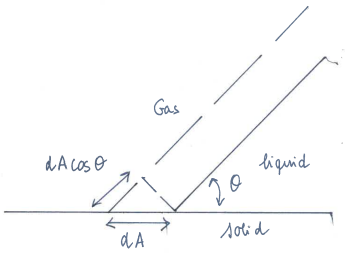


Figure 3.9: Contact angle at the gas-liquid-solid interface. The boundary of the drop sitting on a solid surface can be assimilated as a straight line with contact angle θ.

To revover Young's equation, recall that the equilibrium is such that the total surface free energy of the system is minimum, i.e.

$$\gamma_{SG} A_{SG} + \gamma_{SL} A_{SL} + \gamma_{LG} A_{LG} \qquad (3.6)$$

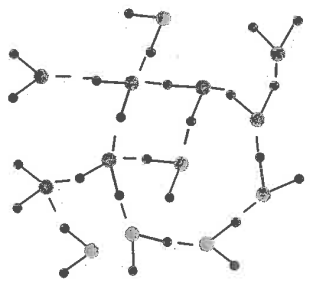
is a minimum (note that we consider the total energy, since the $\gamma's$ are multiplied by the area of the interfaces). Consider a liquid making an equilibrium contact angle, θ, to spread an infinitesimal amount further, so as to cover an extra area, dA, of the solid surface. The increase of liquid-gas interfacial area is, therefore, $dA\cos\theta$ and the increase of free energy is given by (see Fig. **??**)

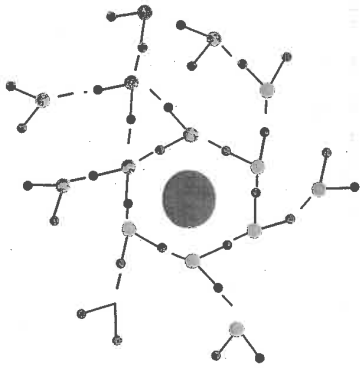
$$dG = \gamma_{SL} dA + \gamma_{LG} dA\cos\theta - \gamma_{SG} dA \qquad (3.7)$$

If the system is at equilibrium, $dG = 0$ (the first derivative is zero), and

$$\gamma_{SL} + +\gamma_{LG}\cos\theta - \gamma_{SG} = 0 \qquad (3.8)$$

known as the Young's equation.





Remark 1 *The wetting of a hydrophobic solid surface by an aqueous medium is considerably helped by the addition of surface-active agents.*

3.7 What is the hydrophobic effect ?

Hydrocarbons are only slightly soluble in water: they are hydrophobic. The accommodation of a hydrocarbon molecule in water is accompanied by an increase in an associated free energy. The unfavorable free energy change accompanying the dissolution of the hydrocarbon results from structural changes in the solvent around each solute molecule. This is the phenomenon of hydrophobic hydration. The total volume of solvent so affected by a pair of solute molecules is less when the two are close together than when they are far apart, as illustrated schematically in Fig. **??**. The result is an effective, solvent-mediated attraction between the two. This is the hydrophobic attraction.

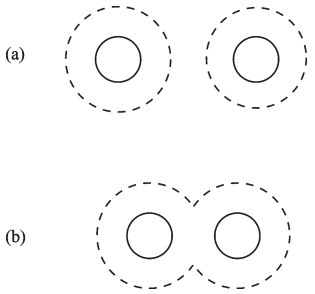


Figure 3.11: Two hydrophobic molecules, (a) far apart, and (b) close together. The regions within the dashed curves represent schematically the volumes of solvent that are significantly affected by the presence of the solutes. The total volume so affected by the pair is smaller in (b) than in (a).

3.8 Critical micellar concentration

Micelles (Example : Mayonnaise) We observe the following properties:

(i) Aggregate form spontaneously at a well-defined micelle concentration.

(ii) Aggregation is a start-stop process. Adding more surfactant results in the formation of more micelles of the same size.

(iii) Aggregate have well-defined properties: The maximum radius of a spherical micelle is set by the length of the hydrocarbon chain.

(iv) The critical micelle concentration decreases with the chain length.

Number of carbon atoms	8	10	12	14	16	18
cmc/10^{-3} mol dm^{-3}	140	33	8.6	2.2	0.58	0.23

Table 3.2: Critical micelle concentration for a homogous series of sodium alkyl sulfates in water at 40°C.

We may think of the abrupt change between the freely dissolved surfactant system and the micellar system as a phenomenon akin to a phase transition. It is NOT, however, a phase transition, since thermodynamic quantities do not experience any singularities as one passes from one regime to the other one.

As we will see shortly, it, however, a cooperative phenomena. We may first think aggregation as an accretion phenomena where one adds one surfactant molecule at a time to build a micelle. This is the stepwise way of thinking

$$S + (N-1)\,S \rightleftharpoons S_2 + (N-2)\,S \rightleftharpoons S_3 + (N-3)\,S \rightleftharpoons \dots \qquad (3.9)$$

We will not go this way: It does not give an abrupt change and gives a broad distribution of micelle size. In contrast, we will assume that N surfactant molecules decide to form 1 micelle at once. [S] being the concentration of free surfactant,

$$NS \rightleftharpoons S_N \qquad (3.10)$$

with equilibrium constant

$$K_N = \frac{[S_N]}{S^N} \tag{3.11}$$

The total surfactant concentration expressed in moles of monomers is

$$[S]_T = N[S_N] + [S] = N\,K_N[S]^N + [S] \tag{3.12}$$

And we can rewrite the first equation as:

$$N\,[S_N] = NK_N\,S^N \tag{3.13}$$

so that Eqs (**??** + **??**) gives the variations of the number of surfactants in micelles, $N\,[S]_N$, versus the total number of moles of surfactants (free + in micelles), $[S]_T$.

When [S] is small, $[S_N]$ is small and does not vary with S_T. We have in this regime

$$\frac{d\,N[S_N]}{d[S]_T} \to 0 \text{ when } N \to \infty \text{ and } [S] \to 0 \tag{3.14}$$

In the other limit where all surfactant molecules have gone into the micelles, $N\,K_N\,S^N \gg S$, we have $[S_T] \approx N\,[S_N]$

$$\frac{dN[S_N]}{d[S]_T} \to 1 \text{ when } [S]_T \to \infty \tag{3.15}$$

Therefore, the slope between the two regime goes to infinity at some magic concentration S. We call this concentration the CRITICAL MICELLE CONCENTRATION, i.e. the CMC.

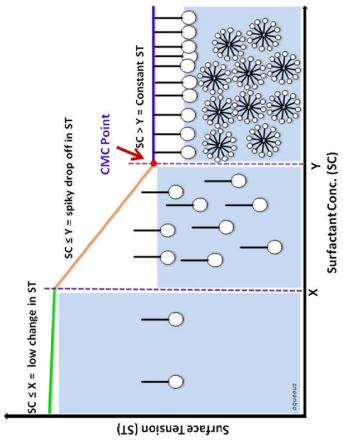


Figure 3.12: Relation between surfactant concentrations (SC) and surface tension (ST) and CMC of surfactant.

3.9 *How surfactant molecules decrease the surface tension*

Complexes systems are often composed of interfaces between different phases. The simplest example of such a system is an interface between different phases (a liquid phase, a vapor phase and a solid phase phases for a fluid layer atop a solid surface). Surfactant molecules tend to aggregate at air water interfaces in such a way that their polar head reside in water with their hydrocarbon in air. For microemulsions (dispersion of droplets of oil in water), the surfactant molecules sit at the oil-water interface. Such interfaces are generally refereed as "surfaces" with an energy proportional to the area of contact between the two phases

The surface tension is given by the change in the free energy as the amount of interfacial area is varied

$$\gamma = \frac{\partial F}{\partial A} \tag{3.16}$$

and a surface tension is always positive or zero. It cannot be negative. If this the case, the system would be unstable with respect to the creation of an infinite area of contact between the two phases and the concept of an interfacial area would be meaningless (the concept of interface assumes tacitly that the width of the interface

is much smaller than the other length scales characterizing the bulk properties of the two phases in contact. An an example, take the size of the droplet. If these two length scales are comparable, this description does not make sense).

What does a surfactant molecule (soluble and insoluble) is to decrease the surface tension. To see this, consider first the case of a surfactant which is not soluble in the solution. This surfactant behave as an ideal gas on the fluid with area A. For and ideal gas, we will see that the entropy is

$$S = A\sigma(\ln \sigma a_0 - 1) \tag{3.17}$$

where σ is the area density of surfactant molecules:

$$\sigma = \frac{N_s}{A} \tag{3.18}$$

where N_s is the fixed number of surfactant molecules (remember that the surfactant molecules are not soluble, so that they sit at the interface). The notation σ for the surface density is standard and has the same meaning as the volume density ρ. In this formula we shall derive later on, a_0 is a constant with the dimension of a molecular area. S ins (**??**) is nothing more that the entropy of a perfect gas in two dimensions. Going back to the free energy $F_S = U - TS$ of the interface, we must add to the bare surface tension $A\gamma_0$ (i.e. the surface tension in the absence of surfactants), the contribution due to the surfactant molecules. This gives

$$F_S = \gamma_0 A + AT\sigma(\ln \sigma a_0 - 1) + A\sigma u_0 \tag{3.19}$$

where u_0 is the difference in energy for a surfactant molecule on the surface compared with the energy in the bulk. Remember (**??**), so that σ depends on A (N_S is fixed), so that $A\sigma u_0 = N_S u_0$. Taking the derivative including the variation of σ gives

$$\gamma = \gamma_0 - T\sigma \tag{3.20}$$

so that the surface tension is decreased. This is so because when the area in increased, the translational entropy of the surfactant molecules is increased.

Remark 2 *All this does NOT apply to bilayer where the only way to change the area is to stretch tangentially to the bilayer. This mechanical stretching has the form*

$$f_{stretch} = \frac{1}{2}\gamma\left(\frac{a}{a_0} - 1\right)^2 \tag{3.21}$$

where γ is called a surface tension constant. In this formula, a is the area per polar head and a_0 is a reference state.

3.10 The packing parameter, Israelachvili (1976)

This a very useful concept. We introduce the following parameters:

1. The surfactant tail volume v_0.
2. The equilibrium area a_0 per molecule at the aggregate interface.
3. The tail length l_0.

For common surfactant with SINGLE tail

$$\frac{v_0}{l_0} = 0.21\, nm^2 \tag{3.22}$$

The packing parameter P is dimensionless

$$P = \frac{v_0}{a_0 l_0} \tag{3.23}$$

and is a geometrical parameter. As an example, consider a spherical micelle with aggregation number g. We have

$$V_{core} = gV_0 = 4/3\pi R^3 \tag{3.24}$$

$$A = ga_0 \tag{3.25}$$

so that $R = 3V/a_0$. For a spherical micelle with positive curvature $R \leqslant l_0$, so that the the packing parameter P is less than $1/3$.

Changes in the critical packing parameter P of surfactant molecules give rise to different aggregation structures, see Fig. **??**.

Typically, we have:

1. $P < 1/3$ for a single chain surfactant. Micelles are spherical.
2. $1/3 < P < 0.5$ for single-chain surfactant with small head group (or in conditions where the electrostatic interaction between the headgroups are screaned). The micelles are cylindrical.
3. $0.5 < P < 1$: Double-chain surfactants with large head group. The aggregate structures are vesicles made up of bilayers.

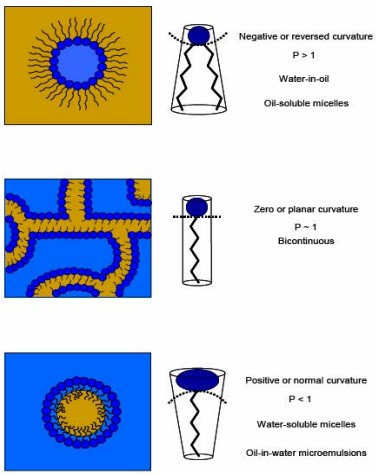


Figure 3.13:

3.11 *The free energy model for micelles (according to Tanford, 1976)*

This model explains the basic feature of micellization. Everything is in the headgroup area. We formulate the standard free energy difference between a surfactant molecule present in the aggregate and one in the singly dispersed state in water. In general, the temperature T and the pressure P are control parameter. Thus the appropriate thermodynamics potential is the Gibbs free energy $G(T, P)$: this is an important point. You must use the thermodynamic potential (free energy, Gibbs free energy ... which depends on the parameters that are under our control. Having control on the pressure P is not the same as having control on the volume V.)

Surfactant molecules pass from the solution to the agrgegate because they experience a smaller energy in the micelle. To compute the difference, we must concentrate on the free energy per molecule. In other words, we will focus on the chemical potential

$$\mu(T, P) = \left.\frac{\partial G}{\partial N}\right|_{T,P} \tag{3.26}$$

which is the energy one has to spend to add one molecule of surfactant to a system in the presence of the others.

Assuming aggregates with g molecules, this free energy difference PER SURFACTANT is the sum of free contributions

$$\left(\frac{\Delta\mu_g}{kT}\right) = \underbrace{\left(\frac{\Delta\mu_g}{kT}\right)\Big|_{\text{Transfer}}}_{-} + \underbrace{\left(\frac{\Delta\mu_g}{kT}\right)\Big|_{\text{Interface}}}_{+} + \underbrace{\left(\frac{\Delta\mu_g}{kT}\right)\Big|_{\text{Head}}}_{+} \tag{3.27}$$

1. The first contribution is negative. By forming a micelle, surfactant avoids the contact between hydrocarbon tails and water. This free energy is independent of the size of the aggregate and of its shape.

2. The second is positive and corrects the first one. There is a residual contact between water and hydrocarbon tails. This term is proportional to the headgroup area: σa, where a typical value for $\sigma = 50 dynes/cm = 0.1 kT/\text{Å}^2$.

3. There is a headgroup electrostatic repulsion. This term is proportional to $1/a$ (with some power depending on the model). For interfaces composed of ionic headgroups, we take : α/a, where $\alpha > 0$ is some phenomenological constant. This term can be considered as the first term in the expansion of the interaction free energy as per molecules in powers of the surface density of headgroups $\rho \propto 1/a$.

We now assume that micelles are in thermodynamics equilibrium. The headgroup area is therefore the one which minimizes the free energy. The first being independent of the headgroups, it drops out. The system adjusts a at a_e

$$\sigma - \frac{\alpha}{a^2} = 0 \text{ at } a = a_e \tag{3.28}$$

or

$$a_e = \left(\frac{\alpha}{\sigma}\right)^{1/2} \tag{3.29}$$

with

$$g = 1/a_e \tag{3.30}$$

in appropriate units, since we compare micelles of the same area made of different surfactants.

In conclusion :

1. The tail transfer is responsible for aggregation, it has no influence nor on size or shape.

2. The size and the shape result from a trade-off between the residual contact and the headgroup repulsion.

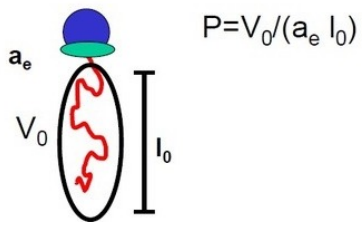


Figure 3.14: Packing parameter

Exercice 3.2 *1. Consider a spherical micelle with aggregation number g (the aggregation number is the number of lipids forming the micelle). Recall that the packing parameter is defined as*

$$P = \frac{V_0}{a_e l_0} \tag{3.31}$$

where V_0 is the surfactant tail volume, a_e is the equilibrium area per molecule of the aggregate, and l_0 is the fully extended tail length.

2. *Give V_{core} and A. Deduce R ($V_{core} = gV_0 = 4\pi R^3/3$, $A = ga_e = 4\pi R^2$. $R = 3V_0/a_e$.)*

3. *From the condition $R < l_0$, give the range for P where spherical micelles can exist (the micelle core is packed with surfactant tails without any empty space).* $P < 1/3$

4. *Repeat the same calculation for a cylindrical micelle (assume an infinite cylinder and do the calculation per unit length).* $P < 1/2$

5. *Assume a bilayer of half-bilayer thickness R of the spherical vesicle. Do the same calculation per unit area of the spherical vesicle.* $P < 1$.

6. *Therefore, if we know the molecular packing parameter, the shape and size of the equilibrium aggregate can be readily identified. What is your prediction for lipid with "small headgroup" and "large headgroup" ? (micelles versus lamellae)*

7. *Assume that a single tail surfactant forms a micelle. What is your prediction for the shape of the aggregate for a surfactant with the same headgroup but with two tails ? (bilayers instead of micelles)*

8. *As we have seen, the influence of solvent is to decrease the surface tension of an interface. What happens if we had a surfactant to a micellar solution ? (interfacial tension decreases, a_e increases and P decreases. Bilayers to micelles).*

4
Gels and percolation

4.1 Introduction: What is a gel ?

Gelatin or gelatine (from Latin: gelatus meaning "stiff" or "frozen") is a translucent, colorless, flavorless food ingredient, derived from collagen taken from animal body parts. To make a gel, one must start with at least two different constituents. The initial state is a fluid (water) in which one dissolves a molecular compound (a polymer or a protein). This state is the "sol". Under some circonstances (PH, temperature, concentration), there is a phase transition. The sol becomes a gel [1]. The gel has the mechanical properties of a solid under the action of macroscopic forces (elasticity). Gel are important for the food industry ... or the tire industry (vulcanisation)

Fig. **??** gives us a qualitative idea of what a polymer gel is (see [**?**]):

1. It is a reticular structure: the different component chains are connected by means of bridges.

2. A gel is an open structure: in many cases, the gap between constituent chains is filled with a large fraction of solvent. Local physical measurements (spectroscopies, electronic or nuclear resonance, etc.) then indicate liquid-type behavior. But mechanical measurements on a large scale indicate the presence of a solid-type elasticity. This duality is one of the features the most interesting gels.

Bridges can be achieved by covalent bonds. But they can also be obtained by physical mechanisms:

1. association of three chains to form a helix like gelatin, from a collagen solution;

2. association by hydrogen bonding and Van der Waals forces as for some polysaccharides;

3. association through micelles.

[1] In french: solution-glification

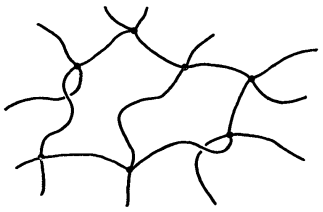


Figure 4.1: Qualitative image of a polymeric gel: We have assumed here that each node is connected with four branches.

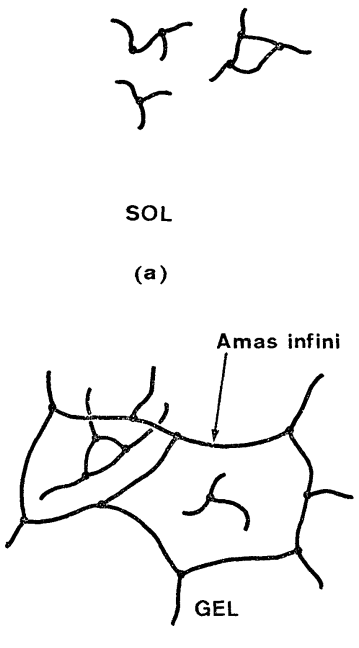


Figure 4.2: Stage of gel formation a) in the sol phase, there are a wide variety

4.2 Sol-Gel transition

Let's take as an example a polymerization reaction that produces larger and larger branched molecules. At the beginning of the reaction, the products are still relatively light: they form a fluid (or "sol") whose viscosity increases over time. Then, at a certain point, the situation changes dramatically: a giant molecule with a spatial extension comparable to the dimensions of the container appears. From that moment on, the system resists macroscopic mechanical traction: it has become a gel.

One way to study this transition is to place a small magnetic bead in a field gradient: it then undergoes a weak force a) in the sol phase, this tends to give it a constant speed (proportional to a viscosity η) b) in the gel phase, the displacement of the ball is constant and inversely proportional to a certain elastic modulus, say E. One finds that both the viscosity and the the elastic modulus have critical behavior (i.e. the viscosity η becomes infinites at the transition and the rigidity modulus E becomes zero)

1. $\eta = cte\,(p_c - p)^{-s}$, for $p < p_c$ $(s > 0)$;
2. $E = cte\,(p - p_c)^{t}$, for $p > p_c$ $(t > 0)$.

where s and t are critical exponents (independent on the way briges are formed). This behavior is reminiscent of critical phase transitions (second order near a critical point) and we are going to see that the sol-gel transition can be connected to a general geometrical phenomena called percolation, see Fig.**??**.

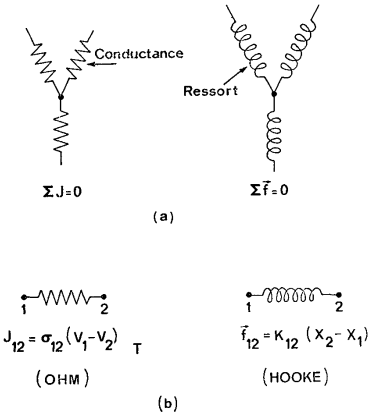


Figure 4.3: Analogies between mechanical properties of gels and electrical properties of percolation networks. (a) Kirchoff's law expresses that the algebraic sum J of currents arriving at a node is zero. The law of equilibrium of forces on a node has the same structure. The analogue of Ohm's law is Hooke's law.

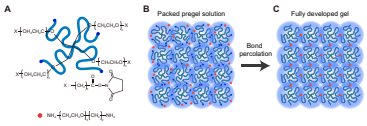


Figure 4.4: Star polymer: tetrafunctional poly(ethylene glycol) (PEG) with active ester end groups; bifunctional cross-linker: 1,14-diamino-3,6,9,12-tetraoxatetradecane (amino-PEG4-amine). (B) Stoichiometric mixture of the star polymer and the cross-linker in a good solvent. The system is uniformly prepacked with the star polymers. (C) Polymer gel formed by end-linking of the star polymers with the small cross-linkers via bond percolation. 2D schematics are shown instead of the real 3D polymer network for the sake of legibility (see [**?**]).

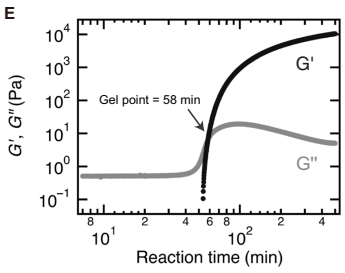


Figure 4.5: E) Gelation of the star polymers is confirmed by dynamic viscoelastic measurements. G' and G'' represent the storage and loss shear moduli, respectively (see [**?**]).

4.3 Percolation

As a brief introduction to percolation, consider a simple square lattice (see Fig.**??**). Each bond in the lattice is occupied with probability p. A cluster of bonds is defined as the set of neighboring occupied bonds. For simplicity, we only consider bond percolation here because site percolation is similar in many respects. When $p = 0$, all bonds are empty. For small p, there is a sparse population of bonds resulting in only small clusters (top left). As p increases, the mean size of the clusters grows (top right, bottom left) and when $p = 1$, all bonds are occupied. Hence, as p increases from 0 to 1, there appears a specific value of p at which a large cluster, the incipient percolation cluster, emerges providing full connectivity of the network from one side to the other for the first time. The shortest contiguous path on the percolating cluster is traced with red (bottom left). If the size of the lattice approaches infinity, the transition from an unconnected to a connected lattice occurs sharply when p crosses a critical threshold called the percolation threshold, p_c . Whatever property a bond represents, this property percolates through the network and the emergence of the percolating cluster represents a phase transition.

Let us now consider the probability P that a bond belongs to the percolating cluster. It is easy to see that P itself also has singular behavior, since $P = 0$ for $p < p_c$ (no connectivity across the lattice), while P increases continuously for $p > pc$, eventually approaching 1. Close to the transition, just above p_c, P follows a power law

$$P \propto (p - p_c)^{\beta} \tag{4.1}$$

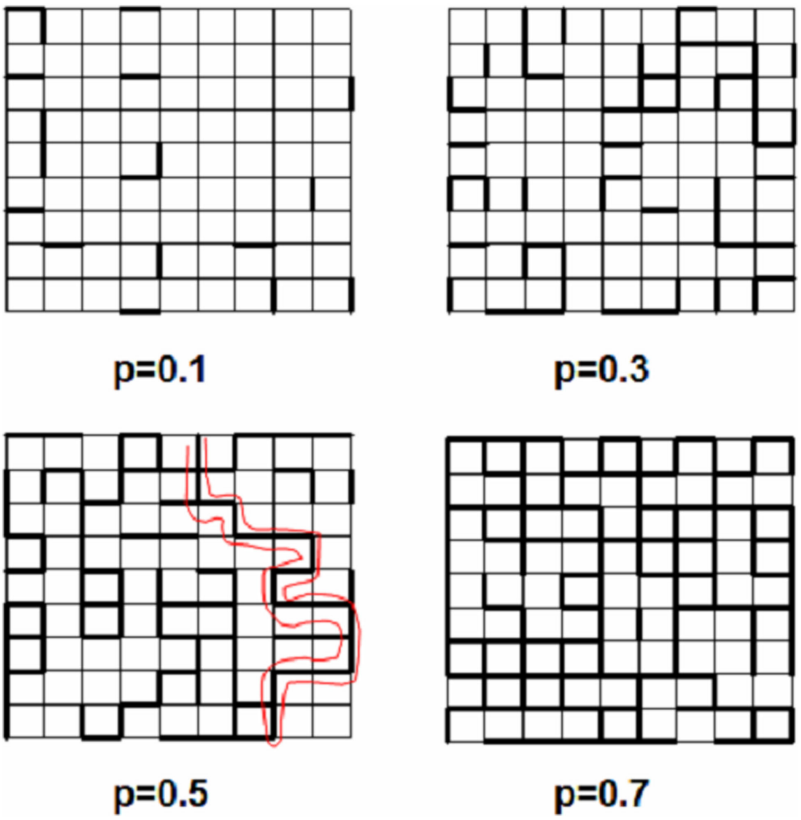


Figure 4.6: Bond percolation on a square lattice (thin lines) for different values of the probability p. Thick line segments are occupied with probability p. The red curve marks the shortest percolating pathway at $p = p_c = 0.5$.

This transition is known as the percolation transition and it conveniently models, for example, fluid flow through a porous medium in which bonds present/absent in the lattice represent open/blocked channels. While the numerical value of p_c depends on the type of lattice, the critical exponents such as β are independent of the microscopic details of the lattice and only depend on the dimension of the space. The percolation transition is similar to other continuous phase transitions with P playing the role of the ORDER PARAMETER and β the critical exponent of the order parameter. On average (i.e. averaging over many realizations of the network, which is not self-averaging at $p = p_c$), the infinite cluster is self-similar or fractal.

4.4 *Self-similarity, fractals and all that*

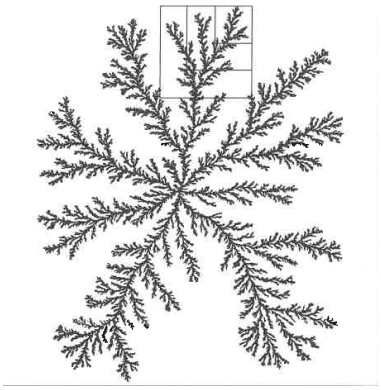


Figure 4.7: A typical (stochastic) fractal generated using a diffusion-limited aggregation model.

"How long is the coast of Britain ? " is the title of paper published by Benoit Mandelbrot in 1967 where he shows that the degree of complication of non-rectifiable curves (similar to the curve of Fig. **??**) can be characterized by a quantity D that has many properties of a "dimension", through it is fractional.

Consider the object of Fig. **??**. This object illustrates diffusion-limited growth (the simulation can be done more along the lines of a standard molecular dynamics simulation where a particle is allowed to freely random walk until it gets within a certain critical range whereupon it is pulled onto the cluster). Imagine concentric radii R centered at the middel of the cluster. The number particles in a circle of radious R scales as

$$N(R) \propto R^D \tag{4.2}$$

Figure 4.8: The Sierpinski gasket.

where $D < d$ is a non-integer value (d is the dimension of the embedding space). For a regular object embedded in a a d-dimensional Euclidean space, this law would have the form $N(R) \propto R^d$. Cluster with non-trivial D are typically self-similar. This property means that a larger part of the cluster after being reduced "looks the same" as a smaller of the cluster before being reduced. This feature can be visualized in Fig. **??** where parts of different sizes (included into rectangular boxes) can be compared.

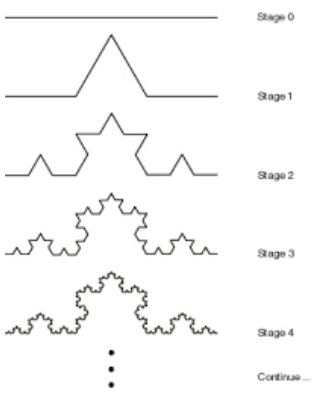


Figure 4.9: The von Koch curve.

The volume of an object can be measured by covering it with $d-$*dimensional* balls of radius l. Then the expression

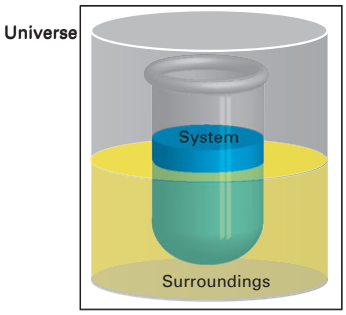
$$V(l) = N(l) l^d \tag{4.3}$$

gives an estimate of the volume, where $N(l)$ is the number of balls needed to cover completely the object. D is defined through the scaling of $N(l)$ as a function of decreasing l. For an euclidean structure in embedding dimension d, if we divide the scale l by a factor x, the number of balls needed to cover the object will increase by a factor x^d. For a non-trivial fractal structure, this is not the case, as seen in the following exercice.

Exercice 4.1 *Consider Figs* **??** *and* **??**. *Show that the fractal dimensions are* $D = \ln 3/\ln 2$ *and* $\ln 4/\ln 2$

5
Energy and entropy

5.1 Quick reminder: Intensive and extensive parameters, internal energy and entropy



Thermodynamics focuses on macroscopic systems, i.e. systems with a very large number of molecules. Thermodynamics ignores fluctuations and should be applied with care to small systems, i.e. single molecules. Thermodynamics seeks to describe static equilibrium, which are states which system usually evolve.

What do we call a sample ? A sample is the system of interest. The rest of the world is the surrounding where observations are made. We can distinguish:

1. Open systems which can exchange both energy and matter with the surrounding.

2. Closed systems which can exchange energy but no matter with the surrounding.

3. Isolated systems with no exchange at all. Boring stuff !

To describe equilibrium and non-equilibrium we first introduce the concept of internal energy U. U is the sum of the kinetic energy of the components, of their potential energy and of their mutual interaction energy.

Second, we distinguish between two types of variables:

1. Extensive variables such as internal energy, volume, number N_i of the component indexed by i. These variables scale with the number of components (i.e. they double if we multiply the number of components by two). In all cases, we can divide them by the volume V and define the appropriate density. Walls separate the system of interest from its surrounding and provide boundary conditions. It is by manipulation of walls that extensive parameters are altered.

2. Intensive variables are variables such as the pressure P, the temperature T or external fields such as an electrical field E where it makes no sense to define a density. Manipulating intensive variables is a way to apply work on the system.

Thermodynamics assumes that there exists equilibrium states which are completely characterized by their internal energy, their volume V and the number N_1, $N_2, \ldots N_r$ of components. Consider two equilibrium states A and B differing in their internal energy. We can measure the difference between them, $U_B - U_A$, and we will often work with differentials assuming that the two states differ sightly. So, $U_B - U_A$ becomes dU.

The basic problem of thermodynamics is to determine the values of the extensive parameters which gives a complete description of the equilibrium states. Obviously, these parameters are "special". As now usual in sciences, we seek for an optimum principle which, in a more mathematical language, is equivalent to an extremum principle. We POSTULATE that there exists a function, called the entropy, of the extensive parameters

$$S = S(U, V, N_1, \ldots, N_r) \tag{5.1}$$

such that the values of the extensive parameters are such those that maximise this function over the manifold of unconstrainted states. From definition (**??**), the entropy S is also an extensive variable. Under general assumptions, this equation can be inverted, so that (**??**) is equivalent to

$$U = U(S, V, N_1, \ldots, N_r) \tag{5.2}$$

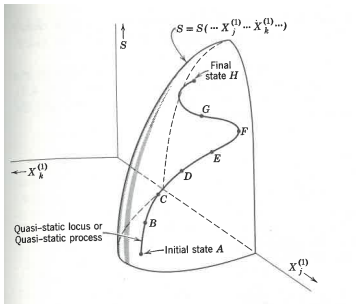


Figure 5.1: The representation of the hypersurface $S = S(U, V, N)$ in the thermodynamic configuration space. This figure represents also a path for a quasi-static process.

We compute the the first differential

$$dU = \left(\frac{\partial U}{\partial S}\right)_{V,N_i} dS + \left(\frac{\partial U}{\partial V}\right)_{S,N_i} dV + \sum_i \left(\frac{\partial U}{\partial N_i}\right)_{S,V} dN_i \tag{5.3}$$

and we remark that the partial derivatives are INTENSIVE parameters. We define

$$\begin{aligned}
&\left(\frac{\partial U}{\partial S}\right)_{V,N_i} = T \text{ , the temperature} \\
&\left(\frac{\partial U}{\partial V}\right)_{S,N_i} = -P \text{ , the pressure} \\
&\left(\frac{\partial U}{\partial N_i}\right)_{S,V} = -\mu_i \text{, the electrochemical potential of the ith component}
\end{aligned} \tag{5.4}$$

and use this notation to write

$$dU = TdS - pdV + \sum_i \mu_i dN_i \tag{5.5}$$

We will recognize in the next sections that TdS is the heat flux. This equation summarizes the three possible ways for a system to change its internal energy : heat flux, mechanical work, and exchange of molecules. All that with the surroundings.

By definition an equation of state is a relationship which expresses intensive parameters in terms of extensive parameters. For example,

$$\begin{aligned}
T &= T(S, V, \ldots, N_i, \ldots) \\
P &= P(S, V, \ldots, N_i, \ldots) \\
\mu_i &= \mu_i(S, V, \ldots, N_i, \ldots)
\end{aligned} \tag{5.6}$$

5.2 *Interpretation of the extremum principle: entropy is mixing*

Consider Fig. **??**. We assume that the membrane is permeable to sucrose molecules. Sucrose will diffuse through the membrane until the concentrations inside and outside the bag are equal. The final equilibrium state is the state which maximizes the MIXING of sucrose with water.

What is that determines the irreversible process that leads to it ?

Clearly, this is not a mechanical process. A mechanical system reaches it equilibrium states by going down the scale of its mechanical, i.e. potential, energy. Here, sucrose solutions are almost ideal, meaning that their energy is almost independent of their concentration. The main difference between the initial and final state lies in the number of ways sucrose oleules are distributed over the total volume. There are more ways to distribute sucrose molecules in a large volume than in a small one. What the system does is that it maximizes the mixing entropy.

What shows also the figure is tat work (and heat) exchanged with the surroundings depends on the path taken from the initial to the final state. We can do the experiment in a quasi-static way by moving a permeable piston so that we reach reversibly the same final state (uniform mixing).

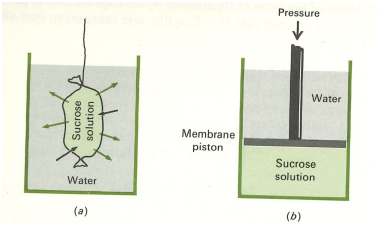


Figure 5.2: A dialysis experiment in which sucrose will diffuse our if a bag and water in until equilibrium is attained. This process is irreversible and no work is done. A way of doing the same experiment reversibly. The membrane of the piston is impermeable to sucrose and permeable to water. If the pressure on the piston is gradually reduced, the same final state of uniform mixing is attained, see [**?**].

5.3 *The first law of thermodynamics*

In the process of going from A to B, The work DONE on the system is measured by the methods of mechanics and is associated with a change in volume dV. We write for quasi-statics processes (the meaning of $đ$ is explained below)

$$đW = -PdV \tag{5.7}$$

where P is the pressure controlled from the surrounding. It is sometimes noted P_{ext}.

We define the heat flux TO the system as the difference in internal energy between the final and the initial state diminished by the work done on the system.

$$đQ = dU - đW \quad \text{at constant mole number} \tag{5.8}$$

Note that this equation gives the definition of what we call heat and that heat corresponds to an energy transfert. This equation is also equivalent to

$$dU = đQ + đW \quad \text{at constant mole number} \tag{5.9}$$

We now explain the meaning of the symbol $đ$. In the process of going from A to B, the work done on the system depend a priori on the process and different ways for going from A to B may give a priori different works. Therefore, $đW$ and $đQ$ are the work and heat

in a particular process. However, the energy difference dU between two equilibrium states cannot depend on a particular path joining them and we employ the usual differential symbol dU.

Since work and heat refer to particular modes of energy transfer, each is measured in energy units. The practical units is the calorie, or 4.18 J. Eq. (**??**) is the statement of the first law in thermodynamics which can be formulated as follows.

Changes in energy occur as a consequence of adding and subtracting heat, $đQ$, and work, $đW$ to the system. Before going on, it is important to make the sign convention clear. If we add energy to the system by performing work, $đW$ is always positive. If the system does some kind of work, then $đW < 0$. If the system receive heat, $đQ$ is positive. If the system loses heat during the process, then $đQ$ is negative.

5.4 *The definition of the Boltzmann's entropy*

In classical text books in thermodynamics, the entropy (from the greek, evolution) is defined via the ratio

$$S = \frac{Q}{T} \tag{5.10}$$

where Q is the heat and T the temperature. This leads to the formulation of the second principle (a machine cannot perform work without heat flux between two sources and these sources cannot be at the same temperature)

In these lectures, it is more appropriate to use the definition of Bolzmann. For a given macroscopic state, there exists a huge number of microscopic configurations (states of the particules). For example, we can divide a container into a grid of M compartments. We decide that the size of the compartment is such that we can put at most one molecule in one compartment. If there are N molecules, we will assume $N \ll M$, i.e. diluted solutions. Here the number the configurations W corresponds to the number of ways we can distribute the N particules among the M compartments. In the same way and for a gaz of particles, there are a large number of different configurations (speed, position) for the particles which gives the same macroscopic pressure.

We have the definition

$$S = k_B \ln W \tag{5.11}$$

Note 1 *If we combine two systems, let say A and B molecules, then*

$$W_{A+B} = W_A \times W_B \tag{5.12}$$

which means that entropy is additive (extensive)

$$S_{A+B} = S_A + S_B \tag{5.13}$$

as it should be.

5.5 A mathematical interlude

The multiplicity, W, for N molecules distributed among M grid points is (the size of the grid point is the size of a molecule, so there is at most one molecule per compartment)

$$W = \frac{M!}{N!(M-N)!} \tag{5.14}$$

and is easy to demonstrate:

- M choices for the first molecule. There is, therefore, $M-1$ choices for the second one (one molecule per box) and so on. We have:
$$\frac{M!}{(M-N)!} = M(M-1)\dots(M-N+1) \tag{5.15}$$
- There are N choices for the first molecules, $(N-1)$ ones for the second one etc. The way we draw the molecules does not matter, since all all them leads to the same configuration. Therefore, we divide by $N!$

We shall use the following formula (Stirling) which works very well when n is large ($n > 2$ in practice)

$$n! = (n/e)^n \tag{5.16}$$

This means:

$$\begin{aligned}\ln W &= \ln \frac{M!}{N!(M-N)!} \\ &= -M\left[\frac{N}{M}\ln\frac{N}{M} + (1-\frac{N}{M})\ln\left(1-\frac{N}{M}\right)\right] \\ &\simeq -N\ln\frac{N}{M} \quad \text{if (small concentration, or small mole fraction)} \frac{N}{M} \ll 1\end{aligned} \tag{5.17}$$

so that the entropy per unit volume is

$$S = -k_B \ln c \tag{5.18}$$

Exercice 5.1 *The exact approximation (Stirling formula) for n! is*

$$n! = \left(\frac{n}{e}\right)^n \sqrt{2\pi n}\left(1 + O(\frac{1}{n})\right) \tag{5.19}$$

Compare the left-and-right hand side for n= 3,4, and 10. Show that the use of the simple Stirling formula **??** *gives a reasonable approximation (it will be useful to compute* $\ln n!$ *instead of* $n!$*).*

The MULTIPLICITY of a system increases as the volume increases. We consider a gas in a container. This container is divided into grid boxes with at most one gas molecule per box. The multiplicity of a molecular system is defined as the number of different configurations or conformations of the component atoms or molecules that are equivalent. For what follows, it will be useful to use the following definition:

Definition 5.5.1 *A* STATE *of system is characterized by the global properties of the system, such as the temprature, pressure, or number of molecules. A* MICROSTATE *is a specific configuration of molecules that is consistent with the state. Each state corresponds to many different microstates, see Fig.* **??**.

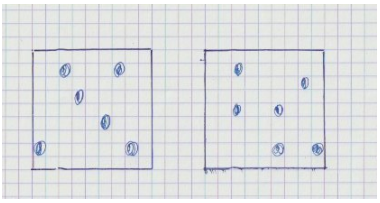


Figure 5.3: The container is divided into into boxes. The grid boxes need to be small enough to accomodate only one molecule. When comparing to systems, it is crucial to have the same size for the grid boxes. Two microstates (configurations) are shown for the same state.

Exercice 5.2 *Compute the change in entropy for a a system of n molecules in a system with N boxes. Using Stirling formula, show that the entropy increases as on increase the volume of the system forom N to $2N$.*

5.5.1 The binomial distribution

This is the probability to get k successes in n trials for an event occuring with probability p. The probability distribution is given by

$$P(x = k) = C_N^k p^k (1-p)^{N-k} \tag{5.20}$$

From the binomial expansion

$$1 = 1^N = (1 - p + p)^N = ((1-p) + p)^N = \sum_{k=0,N} C_N^k p^k (1-p)^{N-k} \tag{5.21}$$

we see that $p(k)$ is normalized

$$\sum_{k=0,N} p(k) = 1 \tag{5.22}$$

The case $p = 1/2$ corresponds to flipping a coin.

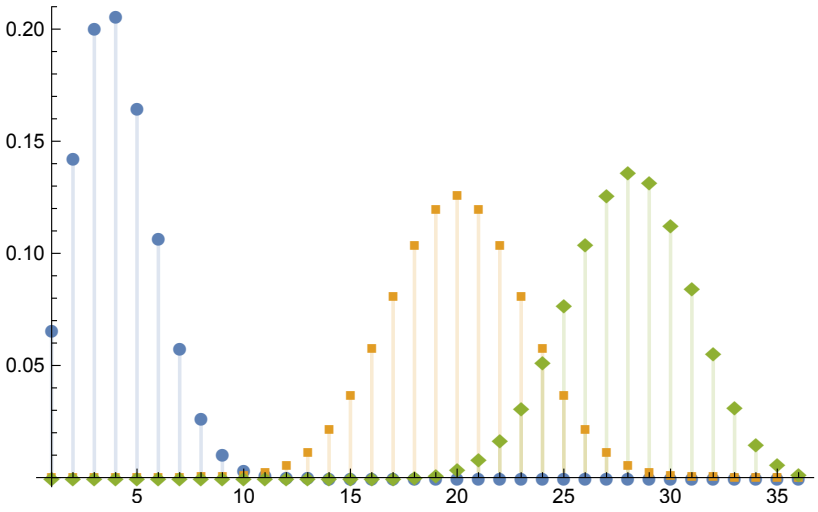


Figure 5.4: Binomial distribution for $p = 0.1, 0.5, 0.7$.

Exercice 5.3 *Analogies between mismatches in DNA and coin flips. During the replication process, errors (mismatches between the base pair) are introduced are being introduced in the newly synthesized strand.*

1. *We denote the probability of a mismatch being introduced as p. What is the mean value of mistakes ? (hints: remember $k!/k = (k-1)!$)*

5.5.2 *The normal distribution*

When the number of events is very large, the probability distribution of the normal distribution is well approximated by the Gaussian (or normal) distribution. The normal random variable has probability distribution

$$f(x) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left\{\left[-\frac{(x-\mu)^2}{2\sigma^2}\right]\right\} \tag{5.23}$$

The mean is μ and the variance is σ^2. As $\sigma \to 0$, the random variable is almost sure. With these definitions, (**??**) is normalised to 1, so that the $\sigma \to 0$ limit gives the δ-Dirac function.

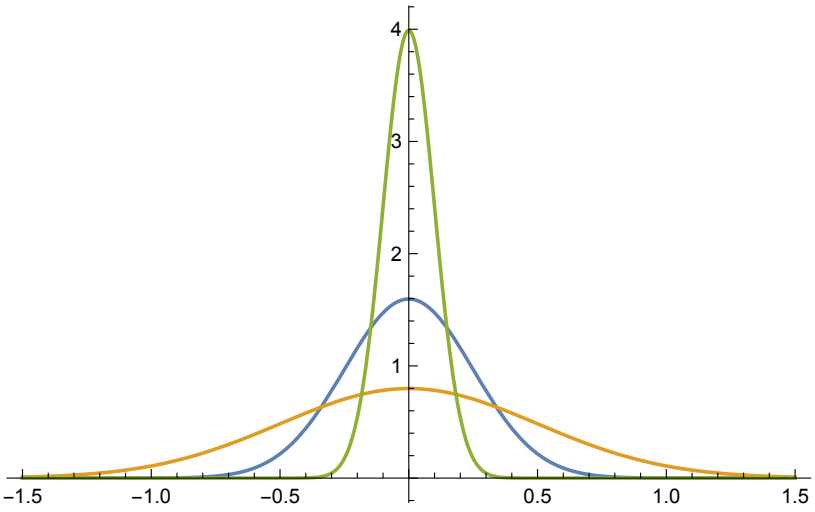


Figure 5.5: The normal distribution tends to a Dirac distribution as $\sigma \to 0$.

Exercice 5.4 *If you have not done before, the following trick is useful. To calculate*

$$\int_{-\infty}^{+\infty} dx \exp\left\{\left[-\alpha x^2\right]\right\}$$

, evaluate first

$$\left[\int_{-\infty}^{+\infty} dx \exp\left\{\left[-\alpha x^2\right]\right\}\right]^2 = \int_{-\infty}^{+\infty} dx \exp\left\{\left[-\alpha x^2\right]\right\} \int_{-\infty}^{+\infty} dy \exp\left\{\left[-\alpha y^2\right]\right\} \tag{5.24}$$

and use polar coordinates. While you are at it, take the derivative with respect to α to calculate $< x^2 >$.

5.6 *The second law of thermodynamics*

One statement of the second law of thermodynamics if that the combined entropy of the system and the surroundings always increases for a spontaneous process. This is equivalent to saying that the entropy of a system and its surroundings has a maximum value at equilibrium.

To illustrate the application of maximum entropy principle, we consider a simplified model for osmosis.

The system is divided into two halves by a semipermeable barrier. The barrier allows type A molecules to pass freely, but blocks the passage of the B molecules. For simplicity, we assume the same number N of A and B molecules.

We divide each half of the chamber into M grid boxes with $M \gg N$. The value of entropy on the left side of chamber can be calculated as follows

$$\frac{S_l}{k_B} = \frac{S_r}{k_B} = N \ln \frac{M}{N} \tag{5.25}$$

We start from a situation where all the A molecules are on the right with the B in the left half. Assume now that a fraction x of A molecules have crossed the barrier. This means that xN A molecules are in the compartment occupied by the B molecules (which cannot cross the barrier). Since the two kinds of molecules act independently of each other, the total entropy for the left compartment is the sum

$$\frac{S_l}{k_B} = N \ln \frac{M}{N} + Nx \ln \frac{M}{Nx} \tag{5.26}$$

The right compartment has now $(1-x)N$ molecules and its entropy is

$$\frac{S_r}{k_B} = N(1-x) \ln \frac{M}{N(1-x)} \tag{5.27}$$

So the total entropy is therefore given by

$$\frac{S}{k_B} = \frac{S_l}{k_B} + \frac{S_r}{k_B} = 2N \ln \frac{M}{N} - N\left[x \ln x + (1-x)\ln(1-x)\right] \tag{5.28}$$

and the change in entropy per A molecule (divide par N)

$$\frac{\Delta S}{k_B} = -\left[x \ln x + (1-x)\ln(1-x)\right] \tag{5.29}$$

From the figure, see Fig **??**, S is maximum when $x = 1/2$, meaning that half of A molecules have diffused on the left half.

In this situation the B molecules in the left chamber contribute a constant value to the total entropy and the volume of each compartment is held constant. As the A molecules move to the left, the density in the left hand-side increases and the osmotic pressure increases. This phenomenon is known as the osmotic pressure (if living cells are transferred to low solute concentration, cells burst).

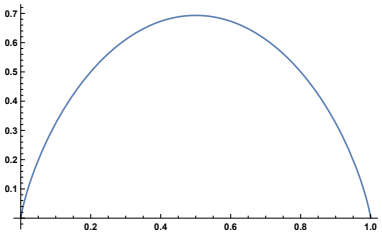


Figure 5.6:

5.7 *Consequences of the extremum principle*

Recall that the entropy is an extensive function. Therefore,

$$S = S(U, V, N) \tag{5.30}$$

From this, we have for the internal energy U

$$dU = TdS - pdV + \mu dN \tag{5.31}$$

where $-pdV$ is the work done on the system (the work provided by the external force), and dN is the change in the number of molecules (we consider one type of molecules). From this, one finds,

$$dS = \frac{1}{T}dU + \frac{p}{T}dV - \frac{\mu}{T}dN \tag{5.32}$$

where μ is the chemical potential. We show that the statement that the entropy is maximal implies that temperature, pressure and chemical potentials for systems in contact are equal.

5.7.1 *Thermal equilibrium*

We consider the system and the surrounding and assume the composite system is isolated. This means:

$$U_{sys} + U_{sur} = \text{ constant} \tag{5.33}$$

as imposed by the closure of the composite system as a whole. We also assume that (a) there is no exchange of matter between the system and its surrounding and (b) that the volume is kept constant (i.e. there is a test tube plug). According the extremum principle, the values os U_{sys} and U_{sur} will be such as to maximize the entropy

$$dS = 0 \tag{5.34}$$

The additivity of the entropy gives the relation:

$$S = S_{sys}(U_{sys}, V_{sys}, \ldots) + S_{sur}(U_{sur}, V_{sur}, \ldots) \tag{5.35}$$

As U_{sys} and U_{sur} are changed by energy transfert, the entropy change is:

$$dS = \left(\frac{\partial S_{sys}}{\partial U_{sys}}\right)_{V_{sys}} dU_{sys} + \left(\frac{\partial S_{sur}}{\partial U_{sur}}\right)_{V_{sur}} dU_{sur} \tag{5.36}$$

From the definition of temperature

$$\left(\frac{\partial S}{\partial U}\right)_{sur} = \frac{1}{T} \tag{5.37}$$

we have

$$dS = \frac{1}{T_{sys}}dU_{sys} + \frac{1}{T_{sur}}dU_{sur} \tag{5.38}$$

By the conservation equation $dU_{sys} + dU_{sur} = 0$

$$dS = \left(\frac{1}{T_{sys}} - \frac{1}{T_{sur}}\right) dU_{sys} \tag{5.39}$$

Since the condition for extremum demands that dS vanishes, we have as a condition for equilibrium

$$\frac{1}{T_{sys}} = \frac{1}{T_{sur}} \tag{5.40}$$

5.7.2 *Mechanical equilibrium*

The same argument gives

$$P_1 = P_2 \tag{5.41}$$

Exercice 5.5 *Assume no energy transfer and no transfer of molecules. So*

$$dS = \left(\frac{\partial S_{sys}}{\partial V_{sys}}\right)_{U_{sys}, N_{sys}} dV_{sys} + \left(\frac{\partial S_{sur}}{\partial V_{sur}}\right)_{U_{sur}, N_{sur}} dV_{sur} \tag{5.42}$$

*Derive (**??**) using $V_{sys} + V_{sur} = constant$.*

5.7.3 *Chemical equilibrium*

Consider

$$2\,H_2 + O_2 \rightleftharpoons 2\,H_2O \tag{5.43}$$

We can write in general

$$0 \rightleftharpoons \sum_j \nu_j A_j \tag{5.44}$$

where ν_j are stoichiometric coefficients, $(-2, -1, 2)$ for the reaction above. The fundamental equation of the system is

$$S = S(U, V, N_1, \ldots, N_r) \tag{5.45}$$

In the course of the chemical reaction, the total energy U and the volume V remain fixed. The change in entropy is then

$$dS = -\sum_{j=1}^{j=r} \frac{\mu_j}{T} dN_j \tag{5.46}$$

Since the change in mole number are proportional to the stoichiometric coefficients

$$dS \propto -\frac{\mu_j}{T} \nu_j \tag{5.47}$$

Then the extremum principles dictates

$$\sum_j \mu_j \nu_j = 0 \tag{5.48}$$

Example 5.1 *If*

$$A_1 \rightleftharpoons A_2 \tag{5.49}$$

Then

$$\mu_1 = \mu_2 \tag{5.50}$$

In summary, the principle of maximum entropy for system $1 + 2$ leads to the conditions

1. Equilibrium for the chemical work $\mu_1 = \mu_2$.
2. Equilibrium for the mechanical work $p_1 = p_2$.
3. No net heat transfert between $T_1 = T_2$.

5.8 Thermodynamic potentials

Consider gaz in a compartment of volume V. If we move the wall (the piston), the volume changes and there is also a change in pressure on the piston will follows the change in volume. Conversely, if we change the pressure on the wall, the volume will follow the change in pressure and will adapt to the new situation. We need, therefore, a bookkeeping mechanism to manage this adaption mechanism between an intensive variable and its extensive conjugate partner.

The whole thing is to focus on independent versus dependent variables. The independent variable is the ONE that is changed by the person who is doing the experiment. The dependent variable is the ONE which depends on the outcome of the experiment. In the preceding example:

1. Process of type 1: When we move the wall by a mechanical system, the independent variable is the volume. The dependent variable is the pressure on the piston.

2. Process of type 2: When we change the pressure on the piston, the independent variable is the pressure, and the dependent one is the volume.

Observe that an intensive dependent or independent variable is always conjugated to an extensive independent or dependent variable.

Consider again the energy differential

$$dU = TdS - PdV + \mu dN \tag{5.51}$$

This equation means that the increase dU of U follows the ones of (S, V, N) chosen as independent variables. This equation implies also that the pressure P adapts to a change in V, since

$$P = -\left(\frac{\partial U}{\partial V}\right)_{S,N} \tag{5.52}$$

Experiments of type 1 controlling the volume are not of great interest to the biochemist. Reactions usually take place in a test tube at a constant pressure of 1 atm. The temperature is also constant. To deal with type 2 experiments, see Fig. **??**, write

$$G = U - TS + PV \tag{5.53}$$

which defines the Gibbs free energy. Now differentiate

$$dG = dU - TdS - SdT + pdV + VdP = SdT + VdP + \mu dN \tag{5.54}$$

which means that, from the point of view of G, the variables T, P, N are the independent variables. So, we write

$$G = G(T, P, N) \tag{5.55}$$

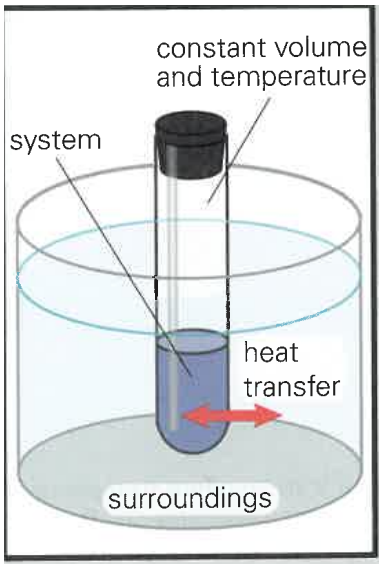


Figure 5.7: (a) A process occurring under conditions of constant volume and temperature[**?**].

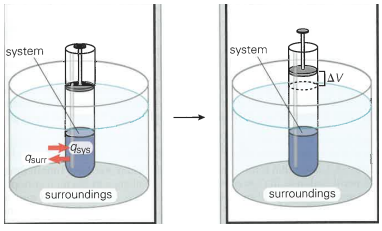


Figure 5.8: (b) A process occurring under the conditions of constant pressure and temperature.

From Eq. (**??**), we see that $dG = 0$ when T, P, N are CONSTRAINED by a reservoir. In other words, S, V and P adjust themselves to make G EXTREMAL, actually MINIMAL see next section.

In short:

1. For processes occuring under the condition of constant volume, use the free energy $F = U - TS$, see case (a) of Fig. **??**.

2. For processes occuring under the condition of constant pressure, use the Gibbs free energy $G = F - PV$, see case (b) of Fig. **??**.

Remark 3 *An important question in thermodynamics is to isolate the control parameters and the companion parameters which adjust themselves by (Gibbs) free energy minimization. For an intensive parameter determined by the experimental conditions (force or pressure), there is always an extensive variable that adjusts (length or volume). The reciprocal is also true. Minimizing the wrong free energy leads to non-sense. The following example illustrate this point.*

*Consider Fig. **??**. A polymer is grafted to a solid surface at one en point. A bead is bound to the other end point. The bead can be observed under the microscope because of its size and the elongation R can be recorded. On can also apply a force F to the bead so that the polymer can be stretched. What the characteristic force-extension curve $R = R(F)$?*

To answer we need two things. First, the correct free energy. Second our minimization principle. Assume that the polymer behaves as a spring. Its potential energy has therefore the form $1/2kR^2$, where k is some elastic modulus. The control parameter is the force. The work done by the force is FR, so we consider the Gibbs free energy

$$G = \frac{1}{2}kR^2 - FR \tag{5.56}$$

Then, the elongation minimizes G. Plotting G as a function of R shows that G has indeed a minimum at some $R_e = F/k$. This is the equilibrium and one finds that at equilibrium G is independent of R, since R is fixed by the force. Note that if we would have minimized $1/2kR^2$ without adding the work done by the force, the result would have been meaningless, i.e. $R = 0$.

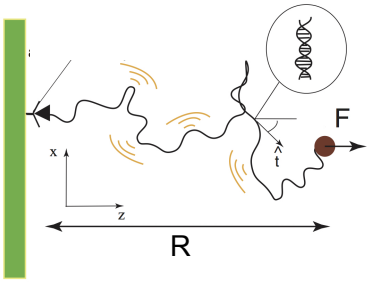


Figure 5.9: A single molecule experiment using a bead trapped in an optical trap.

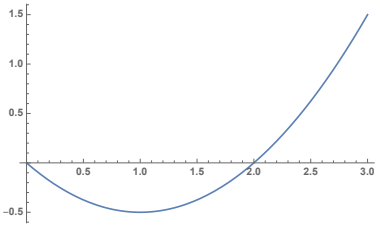


Figure 5.10: Plot of $1/2kx^2 - Fx$ with the minimum at $x = F/k$.

5.9 *Minimum principle*

We illustrate two points:

1. The free energy minimization is an alternative of the entropy maximization.

2. The minimization of the free energy reflects the competition between energy and entropy.

The enthalpy of the system is given by:

$$H_{sys} = U_{sys} + PV_{sys} \tag{5.57}$$

According to this equation, an infinitesimal change in the enthalpy is given by

$$dH_{sys} = dU_{sys} + PdV_{sys} + V_{sys}dP \tag{5.58}$$

If this change is made under constant pressure, then $dP = 0$ and

$$dH_{sys} = dU_{sys} + PdV_{sys} \tag{5.59}$$

Using

$$dS_{sur} = \frac{1}{T}dU_{sur} + \frac{P}{T}dV_{sur} \tag{5.60}$$

with

$$\begin{aligned} dU_{sur} &= -dU_{sys} \\ dV_{sur} &= -dV_{sys} \end{aligned} \tag{5.61}$$

we get

$$dS_{sur} = -\frac{1}{T}dU_{sys} - \frac{P}{T}dV_{sys} \tag{5.62}$$

Comparing with (**??**), we get the following for the entropy change of the surrounding when the process occur under constant pressure

$$dS_{sur} = -\frac{1}{T}dH_{sys} \tag{5.63}$$

which means that the entropy changes of the surrounding is equal to the heat transferred to the system.

For the process at constant pressure and constant temperature to occur spontaneously, the total entropy must increase

$$dS_{total} = dS_{sys} + dS_{sur} \geqslant 0 \tag{5.64}$$

which means:

$$dH_{sys} - TdS_{sys} \leqslant 0 \tag{5.65}$$

We now define the Gibbs free energy

$$G = H - TS \tag{5.66}$$

As the entropy and the enthalpy, G is a state function.

The change in Gibbs free energy is the amount of energy (or heat) that can be converted to work. An infinitesimal change dG is given by

$$dG = dH - SdT - TdS \tag{5.67}$$

At constant temperature

$$dG = dH - TdS \tag{5.68}$$

and using (**??**), we find that the Gibbs free energy decreases

$$dG \leqslant 0 \quad \text{at constante pressure and temperature} \tag{5.69}$$

Thus, a spontaneous process at constant temperature and pressure always involve a decrease in Gibbs free energy. It follows that the Gibbs free energy is minimum at equilibrium, see fig. **??**.

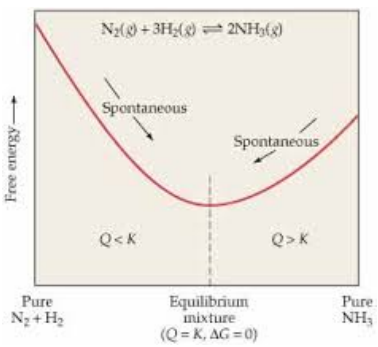


Figure 5.11: Illustration of the Gibbs free energy change during a chemical reaction. The reaction evolves till the system reaches the minimum equilibrium point

Exercice 5.6 EQUIVALENCE OF THE BOLZMAN ENTROPY AND OF THE STATISTICAL ENTROPY

Consider a collection of N molecules distributed among t conformational states. Each molecule can occupy a conformational state j, $j = 1, 2, \ldots t$. Let N_j the number of molecules in the state j. We have:

$$\sum_{1 \leqslant j \leqslant t} N_j = N \tag{5.70}$$

Recall that In the lecture we have defined the Bolzmann entropy as

$$S = k_B \ln W \tag{5.71}$$

where W is the multiplicity of the system. This follows naturally from the idea that a system evolves naturally from less probable states to more probable ones (a macroscopic state with high multiplicity is more likely to be observed).

1. *What the multiplicity of the distribution of N molecules ?*

2. *Use*

$$\ln N_j! = N_j \ln N_j - N \tag{5.72}$$

for all N_j and show

$$W = \frac{N^N}{N_1^{N_1} N_2^{N_2} \ldots N_t^{N_t}} \tag{5.73}$$

3. *Let*

$$p_i = \frac{N_i}{N} \tag{5.74}$$

be the fraction of the total number of molecules found in level i. Show

$$S = N k_B \sum_{1 \leqslant j \leqslant t} p_j \ln p_j \tag{5.75}$$

For a TYPICAL *configuration, $p_i = N_i/N$ is the probability that a molecule is in conformational stet j. This last expression is the statistical definition of entropy we shall use later on and this exercice demonstrates that the definition of Bolzmann entropy is equivalent to the definition of statistical entropy.*

5.10 The statistical and thermodynamic definitions of entropy are equivalent

5.10.1 The work done in an near-equilibrium process is related to the change in entropy

Consider a volume expansion $V_1 \rightarrow V_2$ which occurs in a series of infinitesimally small steps. The work done by the experimentalist is

$$dW = -pdV \tag{5.76}$$

so that for $dV < 0$, we have $dW > 0$. The process being quasi-static, we van apply the ideal gas law

$$PV = nRT \tag{5.77}$$

This means

$$W = -\int_{V_1}^{V_2} \frac{nRT}{V} dV = -nRT \ln \frac{V_2}{V_1} \tag{5.78}$$

We assume also an isothermal process. This means that the energy of the gas cannot change during the process. In accordance with the fist law which states

$$dU = dw + dq \tag{5.79}$$

the system takes heat from the surrounding

$$W + Q = 0 \implies Q = nRT \ln \frac{V_2}{V_1} \tag{5.80}$$

Using the thermodynamic definition of entropy $\Delta S = Q/T$, we get

$$\Delta S = nR \ln \frac{V_2}{V_1} \tag{5.81}$$

5.10.2 Equivalence between the two definitions

To analyse the statistical entropy, we consider again a container divided into M boxes. For large N et M (N is number of molecules), we use Stirling formula to get

$$\ln W = N \ln \frac{M}{N} \tag{5.82}$$

The volume V_1 is related to M by $V_1 = Mv_0$, where v_0 is the volume of a box (equal to to the volume of one molecule). So, for system 1

$$S_1 = k_b N \ln \frac{V_1}{Nv_0} \tag{5.83}$$

and

$$\Delta S = S_2 - S_1 = Nk_b \ln \frac{V_2}{V_1} \tag{5.84}$$

Or $N = nN_A$, where N_A is the Avogadro number. We define $R = N_A k_b$. Both definitions, see Eqs. (**??**) and (**??**) give the same result. These definitions are, therefore, equivalent.

6

Maximum work and Gibbs free energy: coupling work to ATP hydrolysis

Our discussion has so far focused on a particular kind of work involving changes in volume. This is called "expansion" work. The system can, however, do other kind of works without changing the volume (in the sense defined below, the system is can be either a transporter or a motor protein). This includes electrical work, in which charges move against a gradient of electrical potential, and chemical work, where the free energy change is due to change in the number of molecules. The exquisite ability to extract work for a chemical reaction a landmark property of biological systems.

Figure 6.1: Even at rest, a human body requires as much power as a 100-watt lightbulb, from [**?**].

Basically, we rely on mitochondria to synthesis ATP the energy is stored from the synthesis of ATP from ADP and a phosphate. This energy can be released from ATP hydrolysis, a reaction that is used by a myriad energy requiring enzymes that maintain cellular function.

As seen in Table **??**, there are many possible ways to perform work. Consider what happens to the free energy when a small number of molecules moves from outside to the inside of the cell. Let us say that the number of moles inside changes as $n \rightarrow n + dn$. For a mechanical displacement with a force F and a displacement dr, we have

$$\Delta G = \int F dr \tag{6.1}$$

What is the equivalent of the MECHANICAL WORK (**??**) for our CHEMICAL WORK which consists in transferring molecules ? If $\Delta\mu$ is the change in chemical potential between the outside and the inside, the equivalent of (**??**) is

$$\Delta G = \int \Delta\mu \, dn \tag{6.2}$$

Th work is known as the CHEMICAL WORK. Note that there is a close relationship between the change in free energy and the amount of work done on the system. Actually, the change in free energy in a process equal the maximum amount of work that can done or extracted in a process.

Table 6.1: Different types of works that can be done by a system.

Type of work	Intensive variable	Extensive variable	Work
Mechanical	Force, F	Change in distance, dr	$W = \int F dr$
Expansion	Pressure, P	Change in Volume, V	$W = \int P dV$
Electrical	Voltage Difference, ΔV	Change in charge , dq	$W = \int \delta V q$
Surface	Surface tension, γ	Change in surface area, dA	$W = \int \gamma dA$
Chemical	Chemical potential difference, $\Delta\mu$	Change in the number of molecules, dn	$W = \int \Delta\mu \, dn$

6.1 An example

Consider a kinesin motor protein moving a cargo vesicle along a microtubule track. This motor protein is able to perform work which is equal to

$$dw = \vec{F}.\vec{dr} \tag{6.3}$$

for a small displacement dr (corresponding to a "step" size). If the motor protein "walks" at constant speed, the energy dissipated is equal to the work done by the protein. In the preceding equation, the force $\vec{F}$ is the resistive force due to friction and viscositywhich counterbalances exactly the generating force of the kinetsin. In other words, one can extract work from the kinesin motor protein. The movement of the vesicle is powered by the hydrolysis of ATP within the motor domain of the kinesin protein and the value of the free energy change for hydrolysis

$$\Delta G_{\text{ATP}} = -28\,\text{kJ.mol}^{-1} \tag{6.4}$$

is NEGATIVE and sets the limit of work that can be done (extracted) from the system. Recall the convention $dw < 0$ for work done by the system (extracted from the system). Since $\vec{F}$ is resistive, the vector product is negative indeed (in the opposite direction of the movement). Although $\Delta G_{\text{ATP}} < 0$, ATP hydrolysis is not spontaneous because of a high energy barrier and this process is controlled in cells by a number of kinase proteins.

This said, it is important to remember that a way to transform free energy into work is to couple a chemical reaction to a mechanical displacement. This has measured in single molecule experiments[**?**] and can be summarized as follows for a kinesin performing a 8-nm step per ATP molecule hydrolysed

$$\text{Original Position} + \text{ATP} \longrightarrow (\text{Original Position} + 8\,\text{nm}) + \text{ADP} + \text{P}_i \tag{6.5}$$

It should be noted that the difference in energy is between the total sum of the right and the total sum of the left member of this equation.

Figure 6.2: A kinesin protein walking on a microtubule filament

6.2 Maximum work that can be extracted

It will be useful to derive the conditions imposed by thermodynamics on the maximum work extracted from the hydrolysis of ATP.

Consider a system coupled to a surrounding. In the preceding example, the system is the sum of the ATP bound molecule with the motor protein. As before, we have for the total variation of entropy

$$dS_{sys} + dS_{surr} \geqslant 0 \tag{6.6}$$

with

$$dS_{surr} = -\frac{dq}{T} \tag{6.7}$$

where dq is the heat transferred from the surrounding to the system (when the surrounding gives heat, its entropy decreases).

From

$$dU = dw + dq \tag{6.8}$$

One gets

$$dS_{surr} = -\frac{1}{T}\left(dU - dw\right) \tag{6.9}$$

and

$$T\left(dS_{sys} + dS_{surr}\right) = TdS_{sys} - dU + dw \tag{6.10}$$

For isothermal processes without expansion work (i.e. no change in volume), this gives

$$-dG + dw \geqslant 0 \quad \text{or} \quad -\Delta G_{\text{ATP}} + \Delta w \geqslant 0 \tag{6.11}$$

Since ΔG and Δw are both negative, we have in absolute value

$$|\Delta G_{\text{ATP}}| \geqslant |\Delta w| \tag{6.12}$$

Thus the maximum work that can be extracted from the process is equal to the change in the Gibbs free energy for ATP hydrolysis.

Energy is the ability to do work: How do we convert chemical energy into mechanical work ? The trick is to couple a reaction to a mechanical process (rotation, translation, diffusion etc.).

Consider the hydrolysis of ATP

$$\text{ATP} + \text{H}_2\text{O} \rightleftharpoons \text{ADP} + \text{P}_i + \text{H}_2\text{O} \tag{6.13}$$

where P_i represents the phosphate ion (inorganic). In order to determine whether the reaction will proceed spontaneously from left to right, we need to determine the sign of the total change in energy ΔG

$$\begin{aligned}\Delta G = \int_{\text{reactants}}^{\text{products}} dG &= G(\text{products}) - G(\text{reactants}) \\ &= G(\text{ADP} + \text{P}_i + \text{H}_2\text{O}) - G(\text{ATP} + \text{H}_2\text{O})\end{aligned} \tag{6.14}$$

Since the free energy of a molecule changes with temperature, pressure, and wether it is pure or in mixture, one needs to know the conditions for which a free energy change is reported. The free energy change is usually reported for the standard state (molar free energy, i.e. for one mole) and for ATP hydrolysis is

$$\Delta G = -28\text{kJ.mol}^{-1}$$

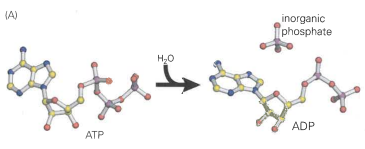


Figure 6.3: ATP loses its terminal phosphate group upon hydrolysis. This reaction occurs rapidly in the forward direction when CATALYZED.

So the reaction will proceed spontaneously to the right, because the free energy of ATP in water is higher than the free energy of ADP and P_i. However, the energy barrier along the reaction coordinate is so high that this reaction cannot happen spontaneously. We need a catalyser, i.e. a molecule which lowers the energy barrier as seen below.

As said before, the way to transform free energy into work is to couple the ATP hydrolysis to an other chemical or mechanical reaction. Then the maximum chemical or mechanical work which can be extracted is bounded from above by the free energy change is ATP hydrolysis.

Consider, for example, the maltose transporter with the reaction

$$\begin{aligned} &H_2O + ATP\,(\text{in}) + \text{Maltose}\,(\text{out}) \\ &\longrightarrow ADP + P_i + \text{Maltose}\,(\text{in}) \end{aligned} \tag{6.15}$$

where the maltose is transported from the outside of the cell to the inside by an enzyme which uses ATP hydrolysis[1], see Fig. **??**. The cycle proceeds into 4 steps:

1. ATP binds to the inner face of the membrane and maltose binds to the outer face. This is a high energy conformation of the transporter.
2. The transporter relaxes this high energy conformation by moving the maltose inside the barrel.
3. Then, ATP can be hydrolysed resulting in the formation of ADP. This is why the maltose transporter is an enzyme which catalyse this reaction.
4. This conformation is unstable and relaxes by releasing the maltose molecule in the inside of the cell (with ADP + P_i).

In short, the gain in (chemical) energy due the hydrolysis of ATP is used to drive a conformational change in the transporter. Coupling the transporter molecule to ATP hydrolysis gives here a way to perform chemical work (the maltose molecule has been transferred from the outside to the inside of the cell). This is this conformational change which allows the maltose molecule to be transported through the barrel.

The next question is far from trivial: can we increase the concentration of maltose inside the cell so that the cycle will run the other way around. In that case, the energy provided would be the increase of entropy due to the maltose molecules flowing outside the cell (remember $F = U - TS$). By the same token, this would provide a way to synthesize ATP from ADP. The problem is that we cannot increase the concentration of maltose to infinity without reaching the sedimentation limit. The F-1ATPase motor protein uses this strategy to synthesize ATP. This protein is molecular turbine machine using protons flux. If the flux is driven one way, the machine synthesize ATP and the machine can use ATP to drive the flux of protons the other way.

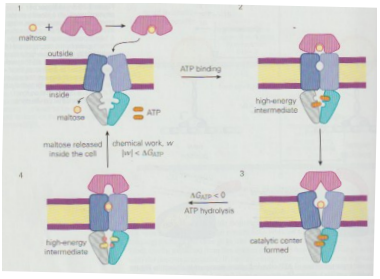


Figure 6.4: The maltose transporter which couples transport of maltose molecules across the membrane with ATP hydrolysis.

[1] Maltose = 2 glucose molecules together

7
Entropy of mixing and chemical potential

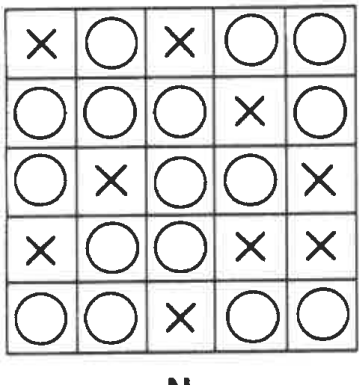


Figure 7.1: Lattice model to calculate the entropy of mixing.

We are concerned with the thermodynamics of self-assembly of molecules (polymers, surfactants, phospholipids and so on). We start by considering the mixing of two lipid species, or solute/solvant, on a flat 2D membrane which reflect the behavior of the miscibility of sucrose into water.

The simplest approach to calculate the entropy of mixing of N_A molecules A with N_B molecules B is to adopt a coarse-grained or lattice model. In that case, we divide the membrane into $N = N_A + N_B$ compartments (little cells). Molecules interchanges positions by diffusion. The conformational probability of the last section is replaced by the probability to distribute molecules among the different compartments. This is the origine of the mixing entropy.

Let us distribute N_A of A molecules in N compartments. Since the A molecules are indistinguishable, there are

$$\frac{N!}{N_A!\,(N-N_A)!} \tag{7.1}$$

ways to do it. All that remains is to place the B molecules. Since the B molecules are also indistinguishable, there is only one way. Thus

$$\Omega = \frac{N!}{N_A!\,(N-N_A)!} = \frac{N!}{N_A!N_B!} \tag{7.2}$$

This expression is exact, but working with factorial is clumsy. To go ahead, use the Stirling approximation

$$\ln(x!) \approx x\,(\ln x - 1) \quad x \gg 1 \tag{7.3}$$

and get

$$\begin{aligned} S &= -k\left[\frac{N_A}{N}\ln\frac{N_A}{N} + \frac{N_B}{N}\ln\frac{N_B}{N}\right] \\ &= -k\left[\phi_A \ln\phi_A + (1-\phi_A)\ln(1-\phi_A)\right] \end{aligned} \tag{7.4}$$

where $\phi_A = N_A/N$ is the fraction of surface occupied by the A molecules. We see that the mixing entropy depend sonly on the A molecule and, from now on, it is simpler to drop the A and to take $\phi_A = \phi$.

7.1 Chemical potential

For a lattice model, it is much more convenient to work at fixed total number of compartments. This is equivalent to work at a given volume and the appropriate thermodynamic potential is the free energy

$$F = U - TS \tag{7.5}$$

The chemical potential per unit surface area is

$$\mu = \left(\frac{\partial F}{\partial \phi}\right)_T \tag{7.6}$$

For ideal solutions, there is no energy $U = 0$. The free energy is purely entropic. Taking the derivative of the ln, we get:

$$\mu = kT \ln \frac{\phi}{1-\phi} \tag{7.7}$$

Ideal solutions makes sense in the low density limit. In the hight density limit, molecules start interacting and the ideal solution concept is meaningless. For this reason, we take the small ϕ limit so that

$$\mu = +\mu_0 + kT \ln \phi \tag{7.8}$$

where μ_0 is the chemical potential of a reference state. For a 3D-problem, the surface fraction is replaced by the volume fraction and ϕ is usually replaced by the concentration c.

For any type of gas A^+B (real or perfect) the partial pressure of the gas A is defined as :

$$p_A = x_A p \tag{7.9}$$

where x_A is the mole fraction of A.

$$x_A = \frac{N_A}{N_A + N_B} \quad x_B = \frac{N_B}{N_A + N_B} \tag{7.10}$$

The total pressure is sum of the partial pressures

$$p_A + p_B = p \tag{7.11}$$

For a gas, the chemical potential is generally written in terms of the of the partial pressures

$$\begin{aligned} \mu^A &= \mu_0^A(T,P) + kT \ln p_A/p \\ \mu^B &= \mu_0^B(T,P) + kT \ln p_B/p \end{aligned} \tag{7.12}$$

where $\mu_0^A(T,P)$ is the chemical potential of the A or B component in the PURE phase.

Note that the chemical potential for a ideal gas is

$$\mu(p) = \mu_0 + kT \ln p \tag{7.13}$$

where μ_0 is the chemical potential of the reference state where $p = 1$ atm.

Exercice 7.1 *Recall that as a consequence of the surface tension the pressure difference across a curved interface is*

$$\Delta p = \gamma \left(\frac{1}{R_1} + \frac{1}{R_2} \right) \tag{7.14}$$

where $R_{1,2}$ are the two radii of curvature. This expression reduces to

$$\Delta p = 2\frac{\gamma}{R} \tag{7.15}$$

for a spherical droplet. As a result, on expects that the vapor pressure over of small liquid droplet is higher than over a flat surface.

Consider a droplet of gas phase with radius r. The surface tension is γ.

1. *What is the increase in free energy when r increases by dr ? (since dr is small, do this calculation to first order in dr).*
2. *To increase r by dr, we need to transfert molecules from the liquid phase. Let dn be the number of moles transferred from the liquid phase to droplet. If the liquid phase is at pressure p_0 and the gaz phase in the droplet at pressure p, what is the corresponding change in Gibbs free energy ?*
3. *Let M be the molar mass and ρthe density of the liquid phase. What is the relation between dn and dr ?*
4. *Deduce the Kelvin equation*

$$RT \ln \frac{p}{p_0} = \frac{2\gamma M}{\rho r} = 2\gamma \frac{V_m}{r} \tag{7.16}$$

where the molar volume V_m is defined as M/ρ.

If $V_m \approx 18.1$ ml/mol (T = 300 K) , $\gamma = 72\,10^{-3}$ N.m^{-1} (water):

$$\frac{p}{p_0} = Exp[1/r] \tag{7.17}$$

where r is in nM.

An important example of this phenomenon is to be found in the aging of colloidal dispersion (referred to as Oswald ripening).

7.2 Osmosis: balancing entropy versus mechanics

Consider a system : solute (s, with N_s molecules) + solvant (H_2O with N_{H_2O} molecules). We calculate the chemical potential of the solute as

$$\mu_s = \frac{\partial G_{total}}{\partial N_s}\Big|_{T,p} \tag{7.18}$$

where the total Gibbs energy is the sum of:

1. The Gibbs energy of the solvant;
2. The internal energy of the solute;
3. The mixing entropy.

This means:

$$G_{total} = N_{\mathrm{H_2O}}\mu^0_{\mathrm{H_2O}}(T,p) + N_s\epsilon_s - TS_{mixing} \tag{7.19}$$

Taking the derivative, we have the chemical potential per solute molecule

$$\mu_s(T,p) = \epsilon_s + kT\ln\frac{c}{c_0} \quad \text{where} \quad c = \frac{N_s}{V_{Box}} \tag{7.20}$$

and $c_0 = N_{\mathrm{H_2O}}/V_{Box}$ is a reference concentration for which we chose to take $\mu_s(T,P) = 0$.

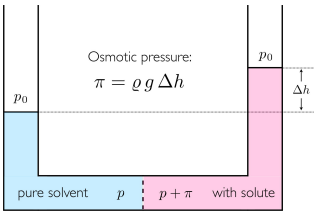


Figure 7.2:

Consider now a bacterium overcrowded in the interior with components. The exterior is at much mower concentration in these components. Let $N_{i,e}$ be the concentration at the inside and in the outside. The system + the surrounding being isolated:

$$N_e + N_i = \text{const} \quad \text{, which means} \quad dN_i = -dN_e \tag{7.21}$$

The difference in Gibbs free energy is therefore

$$dG = (\mu_i - \mu_e)dN_i \tag{7.22}$$

must decrease and $\mu_i - \mu_e$ is the driving force for mass transport. The difference in solute concentration leads to a mechanical force called the osmotic pressure. Cells are able to prevent swelling due to this osmotic pressure and consume a lot of energy to do that.

We now proceed to derive the osmotic pressure difference. Since the membrane is permeable to water (and not to other stuff), we have equality of the chemical potential for water molecules between subsystems i (interior) and e (exterior)

$$\mu^e_{\mathrm{H_2O}} = \mu^i_{\mathrm{H_2O}} \tag{7.23}$$

Recall the entropy of mixing,

$$S_{mix} = -k_B\left[N_{\mathrm{H_2O}}\ln\frac{N_{\mathrm{H_2O}}}{N_{\mathrm{H_2O}}+N_{\mathrm{s}}} + N_{\mathrm{s}}\ln\frac{N_{\mathrm{s}}}{N_{\mathrm{H_2O}}+N_{\mathrm{s}}}\right] \tag{7.24}$$

Since the ratio $N_{\mathrm{s}}/N_{\mathrm{H_2O}}$ is small, we have

$$\frac{N_{\mathrm{H_2O}}}{N_{\mathrm{H_2O}}+N_{\mathrm{s}}} = \frac{N_{\mathrm{H_2O}}+N_{\mathrm{s}}-N_{\mathrm{s}}}{N_{\mathrm{H_2O}}+N_{\mathrm{s}}} \approx 1 - \frac{N_{\mathrm{s}}}{N_{\mathrm{H_2O}}} \tag{7.25}$$

and

$$\frac{N_{\mathrm{s}}}{N_{\mathrm{H_2O}}+N_{\mathrm{s}}} \approx \frac{N_{\mathrm{s}}}{N_{\mathrm{H_2O}}} \tag{7.26}$$

Finally, we can use

$$\ln(1-\epsilon) = -\epsilon \quad \text{with} \quad \epsilon = \frac{N_{\mathrm{s}}}{N_{\mathrm{H_2O}}} \tag{7.27}$$

so that the mixing entropy is very well approximated by

$$S_{mix} \approx -k_B\left[N_{\mathrm{s}}\ln\frac{N_{\mathrm{s}}}{N_{\mathrm{H_2O}}} - N_{\mathrm{s}}\right] \tag{7.28}$$

Finally, from **??**, the chemical potential of the water molecules is

$$\mu^i_{H_2O}(T, p_i) = \mu^0_{H_2O}(T, p_i) - kT\frac{N_s}{N_{H_2O}} \tag{7.29}$$

Since water can pass through the membrane, we have equality of the chemical potentials on both sides. On the outside of the membrane, there is no solute, so that the chemical potential is the one of the reference state at p_e

$$\mu^e_{H_2O}(T, p_e) = \mu^0_{H_2O}(T, p_e) \tag{7.30}$$

and

$$\mu_{H_2O}(T, p_e)^0 = \mu^0_{H_2O}(T, p_i) - \frac{N_s}{N_{H_2O}}kT \tag{7.31}$$

so that $p_e \neq p_i$ for this equality to hold. We can, however, assume that the difference $p_e - p_i$ is small, so that we can Taylor expand the left hand-side

$$\mu_{H_2O}(T, p_e) = \mu_{H_2O}(T, p_i) + (p_e - p_i)\frac{\partial \mu}{\partial p} \tag{7.32}$$

Following the definition of the chemical potential

$$\mu = \frac{\partial G}{\partial N} \implies \frac{\partial \mu}{\partial p} = \frac{\partial}{\partial N}\left[\frac{\partial G}{\partial p}\right] \tag{7.33}$$

From

$$dG = -SdT + Vdp + \mu dN \implies V = \frac{\partial G}{\partial p} \tag{7.34}$$

So $\mu = pv$, where v is the volume per molecule ($v = V/N_{H_{20}}$). Finally,

$$(p_i - p_e)\frac{\partial \mu_{H_2O}}{\partial p} = \frac{N_s}{N_{H_2O}}kT = \frac{N_s}{V}kT \tag{7.35}$$

which is known as the Van't Hoff law.

Exercice 7.2 *Consider Fig.* **??**. *Discuss why the right column of the U-tube raises higher than the column on the left.*

7.3 Nerst Potential: Balancing entropy versus electrostatic

Exercice 7.3 MEMBRANE AND ELECTROCHEMICAL CELLS: *The concept of chemical potential is very general and can be extended to systems in an electrical field. Recall the definition of the Faraday constant: $F = N_A e$ (N_A Avogadro's number, e electric charge). Consider two compartments, say i (for interior of the cell) and e (for exterior of the cell), at electric potentials $\varphi_{1,2}$. The electrical potentials are assumed to be homogenous in both compartments. Take $k_B T = 4.3\,10^{-21}$ J for a human body, so that $kT/e \approx 25$ mV (check).*

1. *What is the electrochemical potential $\tilde{\mu}_{i,e}(\phi)$ for a ion with charge Ze in the two compartments ?*

2. *Assume that the membrane is permeable to K^+, but not to Cl^-. What is the condition for equilibrium ? Do we have one or two conditions ?*

3. *Assume the concentrations are* $0.1M$ *on left and* $1M$ *on the right compartment. What is the voltage drop* $\varphi_i - \varphi_e$ *across the membrane ?*

4. *The typical voltage drop across a membrane is* $-90mV$ *(the interior of a cell is at lower potential). Assume the concentration of* Na^+ *and* Ca^{2+} *as given in table below (measured values). Show that the calculated values is in sharp contradiction with the measured value. Biologists should explain why.*

Exercice 7.4 1. *Consider now the much weaker gravitational potential field (gravity constant g). Assume that the chemical moiety has molar mass M. What is the gravitational energy of thin slice of material at height h ? Check your result by computing the vectorial force.*

2. *Assume now that this chemical compound is a perfect gaz. Compute the chemical potential at height h. Start to derive this result with the concentration at height h and transform your result using the pressure .*

3. *What is the condition for equilibrium on the chemical potential ?What is the pressure at height h (consider that* $p(h = 0)$ *is known).*

	K^+	Na^+	Ca^{2+}
Intracellular concentration	155 mM	12 mM	10^{-4} mM
Extracellular concentration	4 mM	145 mM	1.5 mM
Nerst potential (calculated)	−98 mV	67 mV	130 mV

Table 7.1: Ion concentrations and the Nerst potential for small ions within the cell. The Nerst potential corresponds to the calculated value. For sodium and potassium, the value of the Nerst potential has the wrong sign.

7.4 Ion channels and neuronal dynamics

8
Surface phenomena

8.1 Capillary condensation

Consider a vapor, ie. water, in contact with a solid surface. If the corresponding liquid wets the surface, the vapor will have a tendency to form a wetting film. At a given T, this film will be formed at a vapor pressure p LOWER than the bulk saturation pressure p_0. The relative humidity is is defined by the ratio p/p_0, so that 100% humidity means that the vapor is in equilibrium with liquid (p is actually the partial pressure of the vapor phase).

The chemical potential of the vapor is (per mole)

$$\mu_g = \mu_g^0 + RT \ln p \tag{8.1}$$

while the chemical potential of the condensed bulk liquid is

$$\mu_l = \mu_g^0 + RT \ln p_0 \tag{8.2}$$

The free energy change in forming a liquid film of thickness δ of an area A involves a transfer from vapor to liquid of $\delta A/V_L$ moles, where V_L represents the molar volume of the liquid. There is also a change in surface energy

$$(\gamma_{lv} + \gamma_{sl} - \gamma_{sv})\, A \tag{8.3}$$

The free energy change is therefore

$$\frac{\delta A}{V_L} RT \ln \frac{p_0}{p} + (\gamma_{lv} + \gamma_{sl} - \gamma_{sv})\, A \tag{8.4}$$

and this free energy energy change is zero when the liquid pressure is such that

$$RT \ln \frac{p_0}{p} = \frac{V_L}{\delta} \left(\gamma_{sv} - \gamma_{sl} - \gamma_{lg} \right) \tag{8.5}$$

Surface condensation occurs if the liquid wets the surface. The right-hand side is positive, and the the pressure $p < p_0$. The problem with this derivation is that we have treated the thickness of the film δ as given. Going further needs to discuss intermolecular forces in details.

Even for a liquid that does not wet the surf ace, condensation with $p < p_0$ can occurs if the surface arrangement is favorable. Consider two planar parallel surfaces with a gap of thickness h in equilibrium with a bulk vapor phase. If the geometry of the condensate

is a cylinder the number of mole in the condensate is hA/V_L. Comparing the two situations where the gap is either filled with water or with vapor, the free energy change in the condensation is

$$\Delta G = \frac{hA}{V_L} RT \ln \frac{p_0}{p} + 2(\gamma_{sl} - \gamma_{sv})A \tag{8.6}$$

where the term γ_{lg} is absent since the liquid fill completely the interstice. The factor arises owing to the presence of two interfaces. Condensation occurs at the threshold pressure where $\Delta G = 0$. This means

$$RT \ln \frac{p_0}{p} = \frac{2V_L}{h} (\gamma_{sl} - \gamma_{sv}) = \frac{2V_L}{h} \gamma_{lv} \cos\theta \tag{8.7}$$

An interesting consequence of this formula is the change in relative humidity when we compare a wetting surface for which θ is small, $\cos\theta = 1$, with a hydrophobic surface for which $\theta > \pi/2$ (therefore, $\cos\theta < 0$). A surface has always cracks or pores at the microscopic level and this problem gives the conditions for drying the surface. If the liquid wets the surface, il will take a vapor pressure less than the equilibrium liquid-vapor pressure to dry the surface. For an hydrophobic surface where $\cos\theta < 0$, il will take a vapor pressure larger than the equilibrium pressure to have a film, so that drying will occur even at the equilibrium p_0.

8.2 Langmuir adsorption

9
Non-ideal solutions: Binary solutions

The phase behavior of a lipid system depends on the pressure, temperature, and exact membrane composition. The maximum number of phases P that can coexist in a given system is determined by the Gibbs phase rule

$$P = C - F + 2 \tag{9.1}$$

Here C is the number of components and F denote the number of independent intensive variables. For a binary system, $C = 2$ and $F = 2$ (temperature and pressure), and hence $P = 2$. In a binary system only two coexisting phases are possible. In a ternary system (cholesterol, saturated lipid and unsaturated one), coexistence of 3 phases are possible. Compositions for a ternary system are commonly represented using a triangle as in Fig. **??** and an example is shown in Fig. **??**. Other examples in biology are lipid rafts for celle membranes whose biological function is still a matter of debate.

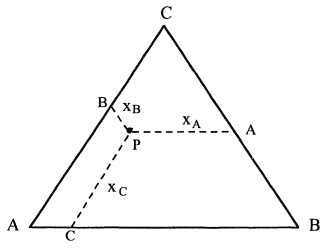


Figure 9.1: The composition of a ternary system consisting of components A, B, and C can be represented on a triangular graph because $x_A + x_B + x_C = 1$. The composition corresponds to a point P inside an equilateral triangle of unit side length. The mole fraction are the lengths of the line drawn parallel to the sides of the triangle. For ternary systems, see [**?**].

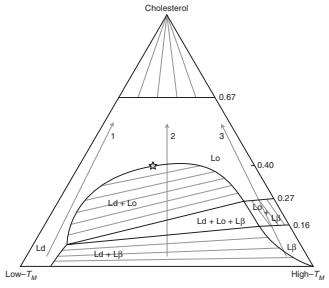


Figure 9.2: Illustrative phase diagram for a ternary lipid mixture containing low- and high-melting temperature lipids and cholesterol[**?**].

9.1 Introduction to the mixing free energy

Due to the near incompressibility of liquids the energy and enthalpy differ by a constant term pV. Therefore, if we compare two states at the same pressure, the enthalpy change is equal to the energy change

$$\Delta H = \Delta U \tag{9.2}$$

It follows that the changes in Helmhotz free energy equal changes in Gibbs free energy. The thermodynamic internal energy U equals the total intermolecular interaction

$$E = \sum_{i>j}^{\text{All molecules}} w_{i,j} \tag{9.3}$$

For the mixing of two pure liquids into a randomized mixture

$$\Delta E_{mixing} = E_{mixing} - E_0 \tag{9.4}$$

where E_0 is the energy of unmixed liquid. Assume $E_0 = 0$ to make things simple.

To calculate ΔE_{mixing}, we define w_{AB} as the interaction energy for a pair of nearest neighbor compartment. If two neighboring

compartments are occupied by a A and B molecule, respectively, the mixing energy for this pair is

$$w_{AB} \tag{9.5}$$

The mixing energy is thus

$$\Delta E_{mixing} = w_{AB} p_{AB} \tag{9.6}$$

where p_{AB} is the probability to have a nearest neighbor A−B pair. The probability that a compartment is occupied by a type A molecule is N_A/N. Given that a compartment is occupied is by a type A molecule, the probability that one its z neighbor is occupied by a type B molecule is N_B/N. Therefore, the probability for a compartment to have a A−B bond is

$$z \frac{N_A}{N} \frac{N_B}{N} \tag{9.7}$$

The last equation is the mixing energy per compartment. To have the total the total mixing energy, we sum up over all compartments

$$\Delta E_{mixing} = \sum_{\text{All compartments}} w_{AB} z \frac{N_A}{N} \frac{N_B}{N} \tag{9.8}$$

The term in the sum is the same for all compartments. Therefore,

$$\Delta E_{mixing} = N w_{AB} z \frac{N_A}{N} \frac{N_B}{N} \tag{9.9}$$

This equation is known as the Flory-Huggins theory to investigate binary systems.

Exercice 9.1 *The purpose of this exercise is to study the phase transition phenomenon for binary solutions. One considers a mixture of* A *and* B *lipids. As before, we imagine that the membrane can be divided into N cells which contain either* A *or* B *lipids (one per each cell). The total number of* A *lipids is N_A and the total number of lipids of type* B *is N_B. The lattice is supposed to be a square lattice with coordination number $z = 4$ (number of nearest neighbors). Because of the afore mentioned constraint, we have $N = N_A + N_B$.*

1. *In this problem, we will follow a mean-field approach where all quantities are average quantities. This allows us to use occupancy probabilities. Assuming N_A A lipids with N_B for B-lipids, what are the probabilities for a cell to be occupied by a A lipid or a B lipid ?*

2. *Given that a compartment is occupied is by a type* A *molecule, the probability that one its z neighbor is occupied by a type* B *molecule is N_B/N. What is the probability for a compartment to have a* A−B *bond as a function of z ?*

3. *To calculate the enthalpy of mixing ΔE_{mixing}, we define w_{AB} as the interaction energy for a pair of nearest neighbor compartment. What is, on average, the mixing enthalpy per cell due to this interaction anergy ?*

4. *Till now, we have assumed that the contact energy w_{AA} for a* AA *pair or w_{BB} for a* BB *pair is zero. We want to know how the previous equation is modified when $w_{AA} \neq 0$, or $w_{BB} \neq 0$. To do this, we have to count the number n_{AA} of* AA *pairs and the number n_{BB} of* BB *pairs.*

   Given that a A *molecule is either engaged in* AA *or a* AB *pair, zN_A is the total number of pairs where* A *molecules are engaged. Give zN_A as a function of n_{AA} and n_{AB}. Give zN_B as a function of n_{BB} and n_{AB}*

5. *Show that the total mixing energy becomes (sum over all cells) :*

$$E_{Mixing} = Nz\frac{N_A}{N}\frac{N_B}{N}\left(w_{AB} - \frac{1}{2}w_{AA} - \frac{1}{2}w_{BB}\right) + E_0 \tag{9.10}$$

   where

$$E_0 = \frac{1}{2}zw_{AA}N_A + \frac{1}{2}zw_{BB}N_B \tag{9.11}$$

   is the energy of the pure states.

6. *Give the mixing entropy for a system of N_A and N_B lipid molecules distributed among $N = N_A + N_B$.*

7. *Show that the mixing free energy can be expressed as*

$$\begin{aligned}\Delta G_{mixing}(T,p,N_A,N_B) = {} & N_A\mu_A^0(T,P) + N_B\mu_B^0(T,P) + \\ & N_Ak_BT\ln\left(\frac{N_A}{N_A+N_B}\right) + N_Bk_BT\ln\left(\frac{N_B}{N_A+N_B}\right) \\ & + \lambda\frac{N_AN_B}{N_A+N_B}\end{aligned} \tag{9.12}$$

   where λ is a parameter. Give λ as a function of the other parameters.

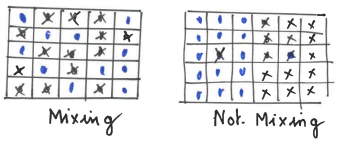


Figure 9.3: A−B binary solution. At high temperature, entropy rules with perfect mixing for the A and B molecules. At lower temperature, the energy of contact between the A and B atoms wins. Phase separation occurs between a B rich phase and a A rich phase (i.e. B poor phase).

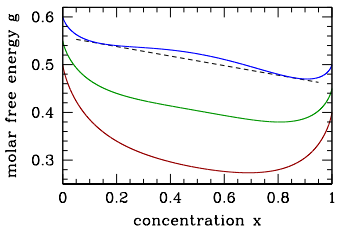


Figure 9.4: Gibbs free energy per particle for a binary solution as a function of concentration $x = x_A$ of the A species . Dark red curve is for $T > T_c$ and blue red curve is for $T < T_c$. The Gibbs free energy is not convex for $T < T_c$ indicating an instability towards phase separation between a A rich phase and a A poor phase. The dotted line is the double tangent construction giving the concentration of A molecule in the rich and poor phase.

8. *As usual the state of the system is the state which minimizes the Gibbs free energy. We have $N = N_A + N_B$. For $\lambda > 0$, what kind of phase the term*

$$\lambda \frac{N_A N_B}{N_A + N_B}$$

does favor ? Discuss the competition between the mixing entropy term and this term as a function of the temperature ?

9. *Define the variable $x = x_A = N_A/(N_A + N_B)$. What is x_B as a function of x ?*

10. *Define*

$$g(T, p, x) = G(T, p, x)/(N_A + N_B) = \frac{1}{N} G(T, p, x) \tag{9.13}$$

Write $g(p, T, x)$ as a function of x.

11. *In order for the system to be stable into relatively A-rich and B-rich regions, we consider the plots of $G(T, P, x)$ as a function of x for different temperatures T as in Fig. **??**. What happens if G has the shape of the upper blue curve ? (Remember that for the system to be stable against any fluctuation Δx, $g(x - \Delta x) + g(x + \Delta x) \leqslant 2g(x)$. The last inequality means that $g(x)$ must be a convex function of x. To answer this question, consider the total Gibbs free energy and divide the system in two).*

12. *Consider again Fig. **??**. Identify on x axis the pure* A *system and the pure* B *system. Draw an arrow to sketch the experimental protocol when the system is quenched from high to low temperatures.*

13. *Since x_A is the only variable, we can simplify our notation and take $x_A = x$. Show*

$$\begin{aligned} g(T, p, x) = {} & x\mu_A^0(T, P) + (1 - x)\mu_B^0(T, P) \\ & + kT\left[x \ln x + (1 - x)\ln(1 - x)\right] \\ & + \lambda x(1 - x) \end{aligned} \tag{9.14}$$

14. *In order for the system to be stable against phase separation, we must have that $g(T, p, x)$ to be a convex function of x. Thus, we must calculate the second derivative. Show :*

$$\frac{\partial^2 g}{\partial x^2} = k_B T \left[\frac{1}{x} + \frac{1}{1 - x}\right] - 2\lambda(1 - 2x) \tag{9.15}$$

15. *The solution of the equation $\partial^2 g/\partial x^2 = 0$ gives a condition $T^*(x)$ known as the spinodal. What is the maximum value achieved by the function $x(1 - x)$ for $0 \leqslant x \leqslant 1$?*

Deduce that the system phase separates if $T < T^* \leqslant k_B/2\lambda$. Conclude from question 1. In this case the two phases are said to immiscible, or, equivalently, there exists a SOLUBILITY GAP.

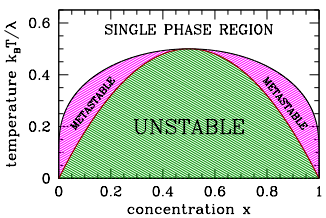


Figure 9.5: Phase diagram for the binary system. The black curve is the coexistence curve, and the dark red curve is the spinodal. A-rich material is to left and B-rich to the right.

16. *If two phases coexist, they must have equal chemical potential (as well as same temperature and pressure, which is why G is a useful function). The chemical potentials associated with each component are*

$$\mu_i = \frac{\partial G}{\partial N_i}, i = A, B \tag{9.16}$$

where the partial derivatives are taken with all other variables constant. Using

$$\mu_i = \frac{\partial [Ng]}{\partial N_i} \qquad i = A, B \tag{9.17}$$

and

$$\frac{\partial g}{\partial N_i} = \sum_k \frac{\partial g}{\partial x_k} \frac{\partial x_k}{\partial N_i} \tag{9.18}$$

where the sum runs over $k = A$ and $k = B$, show

$$\mu_i = g + \frac{\partial g}{\partial x_i} - \sum_k x_k \frac{\partial g}{\partial x_k} \qquad i = A, B \tag{9.19}$$

which shows that $\mu_i \neq \frac{\partial g}{\partial x_i}$ as one would have naively expected.

17. *In our problem, the total number of particles is conserved $N = N_A + N_B$. Deduce*

$$g = \sum_{i=A,B} x_i \mu_i \tag{9.20}$$

18. *Since $x_A + x_B = 1$, x_A and x_B are not independent. We take x_A as the independent variable. Show that the chemical potential are*

$$\begin{aligned} \mu_A &= g + \frac{\partial g}{\partial x_A} - x_A \frac{\partial g}{\partial x_A} \\ \mu_B &= g - x_A \frac{\partial g}{\partial x_A} \end{aligned} \tag{9.21}$$

where g and its derivative are now functions of x_A only.

19. *Consider the coexistence of two phases 1 and 2. Let $x_{A,1}$ the concentration of A in the phase number 1 and $x_{A,2}$ the concentration of A in phase number 2. For the B molecules, we have $x_{B,1}$ or $x_{B,2}$.*

The phases can coexist if the chemical potential of the two components in both phases are equal

$$\begin{aligned} \mu_A(x_{A,1}) &= \mu_A(x_{A,2}) \\ \mu_B(x_{A,1}) &= \mu_B(x_{A,2}) \end{aligned} \tag{9.22}$$

Show that this condition implies

$$\frac{\partial g}{\partial x}|_{x=x_{A,1}} = \frac{\partial g}{\partial x}|_{x=x_{A,2}} = \frac{g(x_{A,2}) - g(x_{A,1})}{(x_{A,2} - x_{A,1})} \tag{9.23}$$

This condition is known as the double tangent, see Fig. **??**.

20.

21. *From the Maxwell construction, show that the two phases coexist if temperature and concentration are related by*

$$T_{\text{coex}}(x) = \frac{\lambda}{k_B} \frac{1 - 2x}{\ln\left[\frac{1-x}{x}\right]} \tag{9.24}$$

22. *Consider the phase diagram of Fig.* **??**. *Find on which line of this diagram are located the points with the double tangents of Fig.* **??**.

9.2 *Non-ideal solutions: Polymer solutions, the Flory-Huiggins theory for polymers*

Up to now we have considered ideal solutions. This approximation may be correct for gas, but solutions are very, very non-ideal. As a first example of non-ideal solutions, we concentrate on the case where the solvent and the solute are not of the same size. This is the case for polymer solutions where the solute is assumed to be a macromolecule composed of N monomeric units, where N is a large number. An other case non-ideal solutions is the case of electrolyte solutions (Coulomb forces are not weak).

Implicit in many of our solution thermodynamic equations is the assumption that the solute and solvent particles are of similar sizes and occupy similar volumes. A good example is the entropy of mixing. If we mix gas A in voule V_A and gas B in volume V_B the final volume occupied by both gases is $V_A + V_B$. The entropy change is

$$\Delta S_{mixing} = -k\left[n_A \ln \frac{V_A}{V_A + V_B} + n_B \ln \frac{V_B}{V_A + V_B}\right] \tag{9.25}$$

with volume fractions defined as:

$$\phi_A = \frac{V_A}{V_A + V_B} \quad \phi_B = \frac{V_B}{V_A + V_B} \tag{9.26}$$

A polymer solution can be visualized in the same way as a regular solution: the solvent and solute occupy a lattice. The difference is that the polymer occupies more than a single lattice site. We assume each monomer occupies a lattice site as shown below, where each monomer is a dark circle and the monomers are connected into a polymer. The solvent molecules are shown as open circles. Actually, what counts is the center of mass of the molecule.

Suppose the lattice has M sites, M plays the role of the total volume. There are N_p polymer molecules each with N monomer units and N_s solvent molecules. Therefore, $M = NN_p + N_s$. We now define the solvent and polymer volume fractions:

$$\phi_s = \frac{N_S}{M} \quad \text{and} \quad \phi_p = \frac{N_p N}{M} \tag{9.27}$$

The total entropy of mixing a the polymer and a solvent is

$$\Delta S_{mixing} = -k\left[N_s \ln \phi_s + N_p \ln \phi_p\right] \tag{9.28}$$

so the entropy per site is q

$$\frac{\Delta S_{mixing}}{M} = -k\left[\phi_s \ln \phi_s + \frac{\phi_p}{N} \ln \phi_p\right] \tag{9.29}$$

which is the usual entropy of mixing is $N = 1$.

This formula is far from trivial because of the $N_p \ln \phi_p$ term (one should expect $N_p N$ instead of N_p). The simplest way to understand that its correct is to note that the mixing entropy should be proportional to the total number of chains, N_p (only the center of mass of

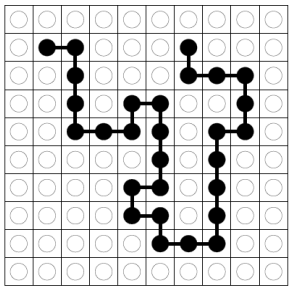


Figure 9.6: Flory model for a polymer. Each mer occupies a single compartment and the chain is visualized as a random walk.

the chains counts when we place the chain on a lattice), but the volume fraction should be the one of the monomers (thus the ϕ_p term within the Log). De Gennes writes this formula with the symmetric form

$$\frac{\Delta S_{mixing}}{M} = -k\left[\phi_s \ln \phi_s + \frac{\phi_p}{N} \ln \frac{\phi_p}{N}\right] \tag{9.30}$$

10
The Bolzmann-Gibbs distribution

10.1 Statistical entropy

Proteins can adopt many conformational states as a function of generalized forces. For example, Fig. **??** schematizes different types of ionic channels with two conformational states: open and closed. Recording the ionic current in a patch clamp experiment allows to measure the probability $p_{i=1,2}$ to be in one of the conformational states.

With this example in mind, consider a hypothetic protein with Ω conformational states. First, we define the probabilistic entropy as[1]

[1] This godlike contraption is due to Shannon in the 40th.

$$S = -k \sum_{i=1}^{i=\Omega} p_i \ln p_i \tag{10.1}$$

where p_i is the probability to find the system in state i. This definition is equivalent to well-known formula[2]

[2] This other godlike contraption is due to Bolzmann in 1897.

$$S = k \ln \Omega \tag{10.2}$$

where k is the Bolzmann constant and where Ω stands for the number of microscopic states accessible to the system under given constraints. To go from the first equation to the second one, take $p_i = 1/\Omega$. So, when all microscopic states have equal probability, the Bolzmann definition is equivalent to the probabilistic definition. Proteins, however, like other systems have many conformational states which differ in energy, so that the probabilities are not equal.

Does the probabilistic entropy agree with the thermodynamic entropy ? To answer this equation, we should do statistical physics and this is not our purpose. Here it suffices to show that the entropy defined this way is an extensive property.

Exercice 10.1 *Suppose that we have two proteins A and B with N and M conformational states. The entropy of for each protein is*

$$S_A = \sum_{1 \leqslant i \leqslant N} p_i \ln p_i \quad S_B = \sum_{1 \leqslant j \leqslant M} p_j \ln p_j \tag{10.3}$$

Consider now the ensemble $A + B$. Each state (i, j) of the ensemble is the product of the state i of the protein A with the state j of protein B.

1. *What is the probability $p_{i,j}$ to observe the microstates i and the j ?*
2. *The conformations of the two molecules are independent so that the joint probability is the product of the probabilities. What is the entropy for the combinaison C of A and B ?*
3. *Check that the entropy is extensive indeed*

$$S_{A+B} = S_A + S_B \tag{10.4}$$

10.2 Bolzmann-Gibbs distribution

Consider again an hypothetical molecule with Ω conformational states. The Bolzmann-Gibbs distribution is the distribution probability to observe the molecule in state i

$$p_i = \frac{1}{Z} e^{-E_i/kT} \quad i = 1, \ldots, \Omega \tag{10.5}$$

Since

$$\sum_i p_i = 1 \tag{10.6}$$

the normalization constant is equal to

$$Z = \sum_{1 \leqslant i \leqslant \Omega} e^{-\beta E_i} \quad \beta = 1/k_B T \tag{10.7}$$

This normalization constant is called the partition sum.

Where (**??**) does come from ? Here it suffices to say that if we fix the mean energy

$$< E >= \sum_i p_i E_i \tag{10.8}$$

Then the Bolzmann distribution is the one which MAXIMIZES the entropy. Since the entropy measures (returning to our physical intuition) the randomness or disorder of the system, the Bolzmann distribution is the 'most random' or 'least structured' distribution that can generate the mean energy.

Exercice 10.2 *One of the principal result in statistical mechanics states that that the average energy associated with every degree of freedom is $1/2k_BT$. This statement is the known as the equipartition of energy. Assume that the cost of energy of a hypothetical protein is $E = 1/2kx^2$, where x is the elongation of the protein in the x-direction.*

1. *Check this result.*
2. *What is the mean energy for a two-dimensional deformation $E = 1/2k(x^2 + y^2)$ and a three-dimensional case $E = 1/2k(x^2 + y^2 + z^2)$*

Exercice 10.3 *We are going to show that the open probability of an ion channel depend on membrane tension.*

1. *Consider first a two-states model where the channel is either closed or open. We label the state of the channel via a variable σ and when $\sigma = 0$, the channel is closed, but when $\sigma = 1$, the channel is open. For the case for which there is no external driving force, the energy $E(\sigma)$ is a function of the internal state $\sigma = 0, 1$. We write:*

$$E(\sigma) = \sigma\epsilon_0 + (1 - \sigma)\epsilon_1 \tag{10.9}$$

   What are ϵ_0 and ϵ_1?

2. *What is the probability to observe the channel in the open state et what is the probability to observe the channel in the closed state ?*
3. *When a bacterial cell is subjected to osmotic shock, the resulting flow of water across the cell membrane results in osmotic tension. The channels reply by opening. We thus introduce the energy as a function of the applied tension τ as*

$$E(\sigma) = \sigma\epsilon_0 + (1 - \sigma)\epsilon_1 - \sigma\tau\Delta A \tag{10.10}$$

   where the term $\sigma\tau\Delta A$ favors the open state and reflect the fact that membrane tension favors the open states. What is the probability p_{open} to observe the channel in the open state ? Draw a graph of p_{open} as a fun function of σ ?

4. *What is σ ? Conclude.*

Exercice 10.4 *Consider the mixing entropy*

$$S(n) = k_B \left[N \ln N - n \ln n - (N - n) \ln(N - n)\right] \tag{10.11}$$

Suppose that one solute molecule is removed from solution by binding to a protein receptor. The change in free energy has two contributions. The first is associated with the enthalpy binding, the second is the change in entropy due to the change of $n \to n - 1$ molecules in the solution.

1. *If the binding energy is ϵ, give the change in free energy as a function of the concentration $c = n/N$. Call this result ΔE.*
2. *Recall Bolzmann's law for a macro-molecule with $j = 1, 2, \ldots N$ internal states*

$$p_j = e^{-\beta E_j}/Z \quad j = 1, 2, \ldots N \tag{10.12}$$

   Compute Z (recall that probabilities have to be normalized).

3. *One application of the chemical potential is to ligand-gated ion channels. Suppose that the ion channel receptor can be in two states : unbound by a ligand (C) or bound by a ligand (o). Give p_C and p_O as a function of ΔE.*

4. *As shown in Fig.* **??**, *these probability are experimentally accessible. Using single molecule devices which mesure the electrical current passing through a ionic canal (patch-clamp), one mesures the time spent t_{open} in the open conformation. Assume that $t_{\text{open}} + t_{\text{close}}$ is the time of observation. What is p_O as a function of these two times ?*

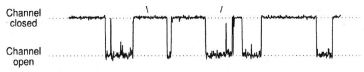


Figure 10.1: The opening of a ionic ion-channel is all-or-none and is a stochastic event. The probability for channel opening is the fractional time passed in the open conformation. Such experimental results are routine using patch-clamp setups.

Exercice 10.5 *In this exercice we will explore simple thermodynamic model for gene or protein regulation, by studying how the concentration of a transcription factor (TF) relates to the to promoter occupancy. A TF is present in solution at concentration c in the cell. On the DNA, there is a single specific binding site that can be empty or occupied by this TF. When the site is occupied, the regulated gene will transcribed into mRNA, see Fig.* **??**. *The problem of regulation by agonist*[3] *is central in biology*[4]

Suppose that a site is occupied of empty. The different states of this site are therefore labeled by a number $n = 0, 1$. We assume that the unoccupied state has zero energy.

1. *Assume that there is a binding energy E favoring the occupied state, relative to the reference energy 0 in the unbound state. But in order to occupy the state, one needs to remove one molecule of TF from the solution. Let μ be the chemical potential of TF. What is the energy cost of removing a single TF molecule from the solution ?*

2. *What is the probability for this site to be occupied ?*

3. *What is the partition sum Z ?*

4. *Show that we can write*

$$P(n = 1) = \frac{c}{c + K_d} \tag{10.13}$$

and give K_d as a function of E. Plot $P(n = 1)$ as a function of c.

5. *In the limit of relatively large concentrations, we can treat the concentrations c as a continuous variable and describe the regulatory process by a differential equation. If becomes n a number between 0 and 1, we can interpret n as the "probability of the site" to be occupied, we write*

$$\frac{dn}{dt} = k_+ c(t)(1 - n) - k_- n \tag{10.14}$$

where k_+ is the on-rate and k_- is the off-rate. Interpret this equation. Give k_-/k_+ as a fucntion of E.

6. *Suppose now that we make a model somewhat more complicated. We consider 2 binding sites and consider the 4 possible values (00, 01, 10, 11). Suppose moreover that there is* COOPERATIVITY *- if both sites are occupied there an additional favorable energy contribution ϵ to the total energy energy of the state (11). What is the partition sum of the system ?*

[3] Recall the definition of an agonist in biochemistry: A substance that attaches to a receptor and directly causes a response in the organism.

[4] There are many drugs that act as agonists ligands (L) which means they "turn on" their target receptor (RL) so that it induces its normal downstream signalling. Examples of such drugs include: growth hormones, insulin, steroids and G-protein coupled Recetor(GCPR) ligands such as morphine (opiods), neurotransmitters and scent/aroma compounds. In general you can improve the potency of these drugs by improve their binding dissociation constant K_d for their receptor.

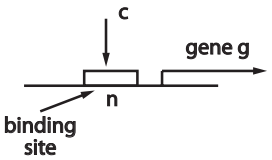


Figure 10.2: The simplest regulatory graph, where an input transcription factor at concentration *c* regulates the output expression level of *mRNA* by binding to a binding site *n*, which can be empty or occupied.

7. *What is $p(11)$?*

8. *When $\epsilon \ll \mu - E$, i.e. when the gain in energy ϵ is larger that the favorable energy $\mu - E$ of transferring one molecule in an empty site, we can assume*

$$e^{-E+\mu} \ll e^{-2E-\epsilon+2\mu} \tag{10.15}$$

show

$$P(11) = \frac{c^2}{c^2 + (K_d')^2} \tag{10.16}$$

and give K_d'.

9. *In molecular biology, Hill functions (or sigmoidal functions) are defined as*

$$f(c) = \frac{c^h}{c^h + K_d^h} \tag{10.17}$$

where h is known as the Hill coefficient. We have seen how such phenomenological curves arise in thermodynamics. Assume for simplicity $K_d = 1$ and plot the occupancy $f(c)$ as a function of c for increasing values of the Hill coefficient h.

Exercice 10.6 *Consider a molecule with $1 \leqslant n \leqslant N$ internal states.*

1. *Since the internal energy is a random variable, it is of interest to compute the mean $< E >$. Call*

$$Z = \sum_n \exp\{[-\beta E_n]\} \quad \beta = \frac{1}{kT} \tag{10.18}$$

Show:

$$< E >= -\frac{\partial Z}{\partial \beta} \tag{10.19}$$

2. *The specific heat is the energy to increase the the temperature by one units. In other term: $C_V = \partial < E > /\partial T$. Show that the specific heat is related tot he fluctuations of E (second cumulant)*

$$C_V = \frac{1}{kT^2}\left[< E^2 > - < E >^2\right] \tag{10.20}$$

This result is general. Response functions, i.e. how a system responds to an external perturbation, are related to the fluctuations of the quantity coupled to the perturbation.

Exercice 10.7 INTRODUCTION TO THE DEBYE-HÜCKEL THEORY: *Surfaces of nanoparticles in solvent are electrically charged. This is is due to:*

1. *Ionization of surface groups;*

2. *Adsorption of ions to previously uncharged surfaces;*

3. *Charge transfert: Acid-Base reaction for example.*

Interactions that occur between fixed charges at surface and those which are free in solution play an important role. Charged surface are characterized by:

- *The density σ of surface charges;*
- *An electrical potential Φ_0.*

We assume that the adjacent solution contains electrolyte and is characterized by bulk concentration (i.e. number of molecules per unit volume) c_{ion}. Let z_i be the ion valency. We want to determine the relationship between σ and Φ_0 and also how the potential and the distribution of ions varies with distance from the charged interface.

We consider negatively charged wall that is infinite in the x and y direction. The distance from the charged surface is z. The charge density on the wall is σ. Let $\Phi(z)$ be the electrical potential. Because of Gauss's law

$$\frac{d\Phi}{dz} = -\frac{\sigma}{\epsilon_0 \epsilon_r} \tag{10.21}$$

The adjacent solution contains positively charged and negatively charged ions in equal quantity with homogeneous density c_0 when $\phi(z) = 0$. We assume that the ions bare a charge $\pm z_i e$.

1. *Because the ions in solution are free and respond to the electrical fields, the solution's charge distribution is not independently known. In addition to the electrostatic interaction energy, we must also consider the entropy associated withe the solution's ion distribution. The electrostatic interaction favors an ordered and well localized ion arrangement, but entropy strives to generate a random distribution. Recall that this compromise between entropy and energy results in the Bolzmann distribution.*

   The potential energy of a charge q in an an electrical potential $\Phi(z)$ is $q\Phi(z)$. Check this formula using the relation between the electrical field $\mathbf{E}$ and the electrical potential $\Phi(z)$. It suffices to compute the force due to the electrical field (remember $\mathbf{E} = -\nabla\Phi$).

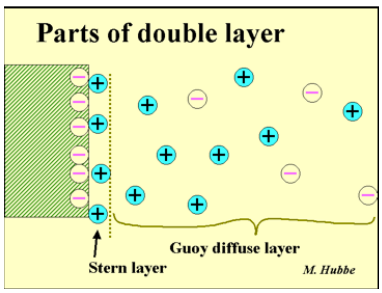


Figure 10.3:

2. *Calculate $c_{\pm}(z)$ as a function of $\Phi(z)$ (use Bolzmann law).*
3. *In electrostatics, the Poisson equation gives the relationship between the electrical charges and the electrical potential $\Phi(z)$. It takes the form (ϵ_r is the relative permittivity of the water, $\epsilon_r = 80$)*

$$\Delta\Phi(z) = -\frac{\rho_{\text{free ions}}(x)}{\epsilon_0 \epsilon_r} \tag{10.22}$$

   and show

$$\frac{d^2\Phi}{dz^2} = -\frac{e}{\epsilon_0 \epsilon_r} \sum_i z_i c_0 \exp\left\{-\frac{-z_i e\Phi}{kT}\right\} \tag{10.23}$$

   where each ion "i" (concentration c_0) carries a charge z_i (ion valency). Typically (i.e. $z_i = 1$ for NaCl in solution)

4. *Use the identity*

$$\frac{d}{dz}\left(\frac{df}{dz}\right)^2 = 2\frac{d^2 f}{dz^2}\frac{df}{dz} \tag{10.24}$$

   to show that the potential $\phi(z)$ solves the differential equation:

$$\Delta\Phi(z) = +\frac{2ez_i c_0}{\epsilon_0 \epsilon_r} \sinh\left[\frac{z_i e\Phi(z)}{kT}\right] \tag{10.25}$$

This equation is known as the Poisson-Bolzmann equation. There is fundamental approximation involved in this derivation. We have neglected the electrical potential due to the ions and have only considered the external potential due the charges on the surface.

5. *Without solving this equation, show that there exists a characteristic length scale l_p which enters into the problem. What is your interpretation ?*

6. *To solve this equation we need appropriate boundary conditions. Electro-neutrality requires that the surface charge be fully neutralized by ions in solution, and at sufficiently large distance $\mathbf{E} = \mathbf{0}$. What is the condition on $d\Phi/dz$ as $z \to +\infty$?*

7. *The other condition is similar to the condition governing the electrical field inside a capacitor. What is*

$$\frac{d\Phi}{dz}|_{z=0} = ? \tag{10.26}$$

8. *Assume*

$$\sinh\left[\frac{z_i e\Phi(z)}{kT}\right] \approx \frac{z_i e\Phi(z)}{kT} \tag{10.27}$$

and solve the differential equation. Give l_p. What is the physical interpretation of l_p ? Are electrostatic interaction relevant in cells and if yes at which scale ?

9. *Assume that the ions come from the dissociation of* NaCl *(0.15 M). What is the order of magnitude of l_p ? (For future reference, $l_p^{-1} = 0.3/c_0^{1/2}$ where c_0 is in Mol) (hints: $kT = 4.110^{-21} J$, $\epsilon_r = 78.5$, $\epsilon_0 = 8.8510^{-12} F/m$)*

11
Electrostatic interactions, Van der Waals interaction, DLVO theory for colloidal dispersions

Competition between attractive van der Waals and repulsive double-layer (electrostatic) forces determine the stability of colloidal systems.

11.1 Debye-Hckel theory

Surfaces of nanoparticles in solvent are electrically charged. This is is due to:

1. Iononization of surface groups;
2. Adsorption of ions to previously uncharged surfaces;
3. Charge transfert: Acid-Base reaction for example.

Interactions that occur between fixed charges at surface and those which are free in solution play an important role. Charged surface are characterized by:

- The density σ of surface charges;
- An electrical potential Φ_0.

We assume that the adjacent solution contains electrolyte and is characterized by bulk concentration (i.e. number of molecules per unit volume) c_{ion}. Let z_i be the ion valency. We want to determine the relationship between σ and Φ_0 and also the potential and the distribution of ions varies with distance from the charged interface.

Exercice 11.1 *We consider negatively charged wall that is infinite in the x and y direction. The distance from the charged surface is z. The charge density on the wall is σ. Let $\Phi(z)$ be the electrical potential. Because of Gauss's law*

$$\frac{d\Phi}{dz} = -\frac{\sigma}{\epsilon_0 \epsilon_r} \tag{11.1}$$

The adjacent solution contains positively charged and negatively charged ions in equal quantity with homogeneous density c_0 when $\phi(z) = 0$. We assume that the ions bare a charge $\pm z_i e$.

1. *Because the ions in solution are free and respond to the electrical fields, the solution's charge distribution is not independently known. In addition to the electrostatic interaction energy, we must also consider the entropy associated withe the solution's ion distribution. The electrostatic interaction favors an ordered and well localized ion arrangement, but entropy strives to generate a random distribution. Recall that this compromise between entropy and energy results in the Bolzmann distribution.*

   The potential energy of a charge q in an an electrical potential $\Phi(z)$ is $q\Phi(z)$. Check this formula using the relation between the electrical field $\mathbf{E}$ *and the electrical potential* $\Phi(z)$

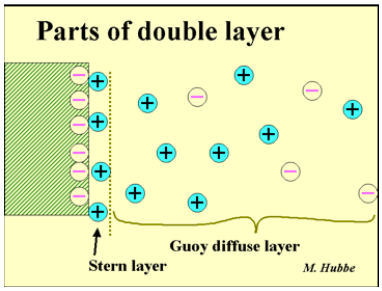


Figure 11.1:

2. *Calculate $c_{\pm}(z)$ as a function of $\Phi(z)$ (use Bolzmann law).*

3. *The Poisson equation gives the relationship between the electrical charges and the electrical potential $\Phi(z)$. It takes the form*

$$\Delta\Phi(z) = -\frac{\rho_{free\,ions}(x)}{\epsilon_0\epsilon_r} \tag{11.2}$$

   and show

$$\Delta\Phi(z) = +\frac{2ez_ic_0}{\epsilon_0\epsilon_r}\sinh\left[\frac{z_ie\Phi(z)}{kT}\right] \tag{11.3}$$

   This equation is known as the Poisson-Bolzmann equation. There is fundamental approximation involved in this derivation. We have neglected the electrical potential due to the ions and have only considered the external potential due the charges on the surface.

4. *Without solving this equation, show that there exists a characteristic length scale l_p which enters into the problem. What is your interpretation ?*

5. *To solve this equation we need appropriate boundary conditions. Electro-neutrality requires that the surface charge be fully neutralized by ions in solution, and at sufficiently large distance* $\mathbf{E} = \mathbf{0}$*. What is the condition on $d\Phi/dz$ as $z \to +\infty$?*

6. *The other condition is similar to the condition governing the electrical field inside a capacitor. What is*

$$\frac{d\Phi}{dz}|_{z=0} = ? \tag{11.4}$$

7. *Assume*

$$\sinh\left[\frac{z_ie\Phi(z)}{kT}\right] \approx \frac{z_ie\Phi(z)}{kT} \tag{11.5}$$

   and solve the differential equation. Give l_p. What is the physical interpretation of l_p ?

8. *Assume that the ions come from the dissociation of* NaCl *(0.1 M). What is the order of magnitude of l_p ? (For future reference, $l_p^{-1} = 0.3/c_0^{1/2}$)*

11.2 *Zeta potential*

Zeta potential is the charge that develops at the interface between a solid surface and its liquid medium. This potential, which is measured in MilliVolts, may arise by any of several mechanisms. Among these are the dissociation of ionogenic groups in the particle surface and the differential adsorption of solution ions into the surface region. The net charge at the particle surface affects the ion distribution in the nearby region, increasing the concentration of counterions close to the surface. Thus, an electrical double layer is formed in the region of the particle-liquid interface.

This double layer (upper part of figure) consists of two parts: an inner region that includes ions bound relatively tightly to the surface, and an outer region where a balance of electrostatic forces and random thermal motion determines the ion distribution. The potential in this region, therefore, decays with increasing distance from the surface until, at sufficient distance, it reaches the bulk solution value, conventionally taken to be zero. This decay is shown by the lower part of the figure and the indication is given that the zeta potential is the value at the surface of shear.

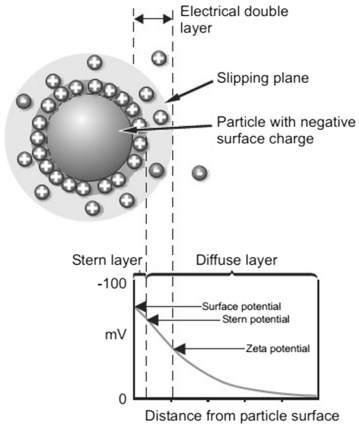


Figure 11.2:

In an electric field, as in microelectrophoresis, each particle and its most closely associated ions move through the solution as a unit, and the potential at the surface of shear between this unit and the surrounding medium is known as the zeta potential. When a layer of macromolecules is adsorbed on the particles surface, it shifts the shear plane further from the surface and alters the zeta potential.

Zeta potential is therefore a function of the surface charge of the particle, any adsorbed layer at the interface, and the nature and composition of the surrounding suspension medium. It can be experimentally determined and, because it reflects the effective charge on the particles and is therefore related to the electrostatic repulsion between them, the zeta potential has proven to be extremely relevant to the practical study and control of colloidal stability and flocculation processes.

11.3 *Electrostatic interaction between two plane surfaces*

11.4 *Van der Waals interaction*

Competition between attractive van der Waals and repulsive double-layer forces determines the stability or instability of colloidal systems.

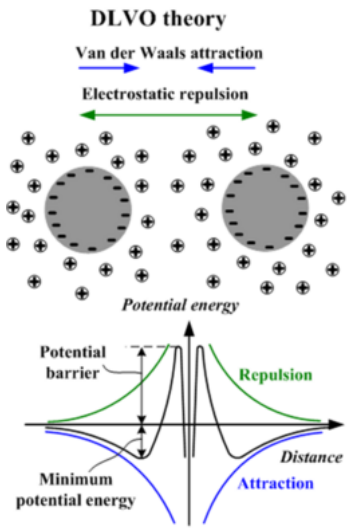


Figure 11.3: . DLVO theory: The total interaction potential between two colloidal particles is the sum of the attractive Van de Waals interaction and the repulsive electrostatic repulsion.

12
Brownian motion and random walk

12.1 *Introduction*

A polymer chain is a chain of several polyatomic units called monomers and look like a cooked spaghetti. In this chapter we will look at static or time averaged properties of polymers by employing different models. In particular we will investigate the end-to-end distance and the radius of gyration (i.e. its averaged size in solution) as a function of the number of monomers (index of polymerization). In this chapter, chains are "ideal", meaning that self-avoidance effects are neglected (two monomers can occupy the same place). We will limit ourselves ti polymer in good solvents where the interaction between the monomers and the solvent molecules are attractive.

12.2 *The central limit theorem*

The normal random variable has probability distribution

$$f(x) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left\{\left[-\frac{(x-\mu)^2}{2\sigma^2}\right]\right\} \tag{12.1}$$

The mean is μ and the variance is σ^2. As $\sigma \to 0$, the random variable is almost sure. With these definitions, (**??**) is normalized to 1, so that the $\sigma \to 0$ limit gives the δ-Dirac distribution (where all the 'mass' is concentrated on one point on the x axis .

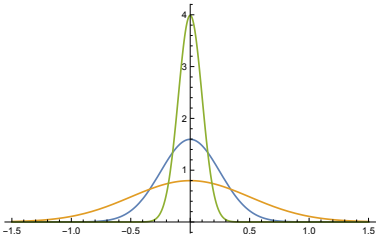


Figure 12.1: The normal distribution tends to a Dirac distribution as $\sigma \to 0$ (peaked at one point).

The generalization to N variables is straightforward

$$P(\mathbf{x}) = P(\{x_i\}) = \frac{1}{\sqrt{(2\pi)^N \det C}} \exp\left\{\left[-\frac{1}{2}\mathbf{x}^T \cdot C^{-1} \cdot x\right]\right\} \tag{12.2}$$

where $\mathbf{x}^T$ is the transpose of the vector $\mathbf{x}$ with dimension N.

For example, we can consider a vector in d-dimension ($d = 1, 2, 3$) with components $(r_1, r_2, \ldots r_d)$ on a vector basis (orhonormal) $\hat{\mathbf{u}}_1, \hat{\mathbf{u}}_2, \ldots \hat{\mathbf{u}}_d$

$$\mathbf{R} = r_1\hat{\mathbf{u}}_1 + r_2\hat{\mathbf{u}}_2 + \ldots r_d\hat{\mathbf{u}}_d \tag{12.3}$$

The vector $\mathbf{R}$ is said to normally distributed if r_1, $r_2, \ldots r_d$ are nor-

mally distributed (mean μ_i, variance σ_i)

$$P(\mathbf{R}) = \frac{1}{\sqrt{(2\pi)^d \sigma_1^2 \sigma_2^2 \dots \sigma_d^2}} \exp\left\{\left[-\sum_{i=1,2,\dots d} \frac{(r_i - \mu_i)^2}{2\sigma_i^2}\right]\right\} \tag{12.4}$$

or

$$P(\mathbf{R}) = \frac{1}{\sqrt{(2\pi)^d \sigma^{2d}}} \exp\left\{\left[-\frac{1}{2\sigma^2}\sum_{i=1,2,\dots d} (r_i - \mu)^2\right]\right\} \tag{12.5}$$

in the usual case where all σ_i and μ_i are equal to σ or μ.

Exercice 12.1 *If you have not done before, the following trick is useful. To calculate*

$$\int_{-\infty}^{+\infty} dx \exp\left\{\left[-\alpha x^2\right]\right\}$$

Evaluate first

$$\left[\int_{-\infty}^{+\infty} dx \exp\left\{\left[-\alpha x^2\right]\right\}\right]^2 = \int_{-\infty}^{+\infty} dx \exp\left\{\left[-\alpha x^2\right]\right\} \int_{-\infty}^{+\infty} dy \exp\left\{\left[-\alpha y^2\right]\right\} \tag{12.6}$$

and use polar coordinates. Don't forget

$$\int\int dxdy \dots = \int_0^{2\pi} d\phi \int_0^{\infty} dr \dots \tag{12.7}$$

While you are at it, take the derivative with respect to α to calculate $< x^2 >$.

In his most restrictive form, the central limit theorem goes as follows:

Let X_1, X_2, $X_3, \dots$, X_n be a sequence of n and identically distributed variables having each finite value of expectation μ and variance σ^2. Form

$$Y_n = \frac{\sum_{i=1,n} X_i - n\mu}{\sigma\sqrt{n}} \tag{12.8}$$

The distribution for Y_n approaches the standard distribution as $n \to \infty$.

12.3 One-dimensional random-walk

A polymer chain can be seen as a random walk. Here we define what we mean by that and consider the stochastic movement of particles on a lattice. We reduce the problem to its barest essential and consider the motion of particles along one axis only. All particles start at time $t = 0$ at the origin and execute a random walk according to the following rule :

1. Each particle steps to the right or to the left once every τ seconds with a velocity $\pm v_x$. The corresponding distance travelled without changing direction is thus $\delta = v_x \tau$.

2. the probability from going to right is 1/2, and the probability of going to the left at each step is 1/2. The particle by interacting with the water molecule forgets the preceding journey. The walk is not biased.

3. Each particle moves independently of all other particles. There is no interaction among particles.

The motion of one single particle is not of interest, since we cannot predict what it will be. This is an example of a random process (stochastic process). We want to characterize the PROBABILITY to be at a certain distance after N steps. In $d = 2$ or $d = 3$, the path taken by our stochastic molecules correspond to one configuration of a polymer chain with N mers. What we want to do is to average over the configurations of a polymer.

The consequences of this random walk picture are striking :

1. On average, the particle goes nowhere. the mean displacement is zero $< x >= 0$.

2. On average, the root-mean-square displacement is proportional to the square-root of the time and NOT to the time $\sqrt{< x^2 >} \propto t$. This point will be discussed later on in a next chapter.

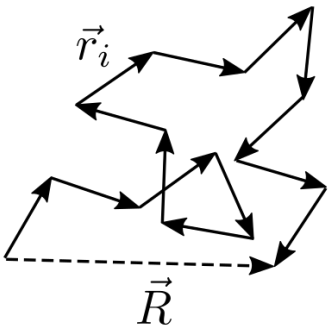


Figure 12.2:

We consider an ensemble of Z particles. Let $x_i(N)$ the displacement of ith particule after the Nth step. We have

$$x_i(N) = x_i(N-1) \pm l \tag{12.9}$$

For half of the particles, the $+$ sign will apply and for the other half, we will choose the $-$ sign.

On average

$$< x(N) >= \frac{1}{Z} \sum_{i=1,Z} x_i(N) \tag{12.10}$$

which means

$$\begin{aligned} < x(N) > &= \frac{1}{Z} \sum_{i=1,Z} [x(N-1) \pm l] \\ &=< x(N-1) > \end{aligned} \tag{12.11}$$

Therefore : One average, the particle goes nowhere. The distribution which characterizes the spreading is symmetrical withe respect to the origin.

We compute the root-mean square displacement. For the ith particle, we take the square

$$x_i(N)^2 = x_i(N-1)^2 \pm 2l x_i(N-1) + l^2 \tag{12.12}$$

and compute the mean

$$\begin{aligned} < x(N)^2 > &= \frac{1}{Z} \sum_{i=1,Z} < x(N)^2 > \\ &=< x^2(N-1) > +l^2 \\ &=< x^2(N-2) > +2l^2 \\ &=< x^2(N-3) > +3l^2 \\ &= \dots \end{aligned} \tag{12.13}$$

which means :

$$< x^2(N) >= Nl^2 \tag{12.14}$$

Consider now the bond vectors $\mathbf{u}(\mathbf{i}) = \mathbf{x}(\mathbf{i}+\mathbf{1}) - \mathbf{x}(\mathbf{i})$. A bond vector corresponds one mer in our polymer analogy. Then the $\mathbf{u}(\mathbf{i})$ are independent random variables with:

1. Zero mean: $\langle u(i) \rangle = 0$
2. Equal variance: $\langle \mathbf{u}(i)^2 \rangle = \langle (\mathbf{x}(i+1) - \mathbf{x}(i))^2 \rangle = l^2$

We have for the end-to-end distance between the starting and the end point

$$\mathbf{R} = \sum_i \mathbf{u}(i) \tag{12.15}$$

so that our preceding conclusion applies. $\mathbf{R}$ is the sum of independent random variables with a given mean and variance, so that $\mathbf{R}$ is normally distributed.

We have

$$\langle \mathbf{R}^2 \rangle = Nl^2 \tag{12.16}$$

For $d = 1$

$$P(N,R) = \left(2\pi R_0^2\right)^{-1/2} \exp\left\{\left[-\frac{R^2}{2R_0^2}\right]\right\} \tag{12.17}$$

For $d = 3$, one can do the same calculation as before. The calculation is similar. What happens in the x , y or z directions are independent and things are symmetric in the x, y, z directions. We have (note the factor 3):

1. $\langle x \rangle = \langle y \rangle = \langle z \rangle = 0$;
2. $\langle x^2 \rangle = \langle y^2 \rangle = \langle z^2 \rangle = l^2/3$;

so that

$$\langle x^2 \rangle + \langle y^2 \rangle + \langle z^2 \rangle = l^2 \tag{12.18}$$

After N steps, one finds

$$\langle \mathbf{R}^2 \rangle = Nl^2 \tag{12.19}$$

and the distribution is

$$P(N,\mathbf{R}) = \left(\frac{2\pi R_0^2}{3}\right)^{-3/2} \exp\left\{\left[-\frac{3R^2}{2R_0^2}\right]\right\} \tag{12.20}$$

12.4 The random walk results are universal

One can ask if the results of the random walk model will survive in more realistic situations. The answer is yes. They will survive and they are model independent as long as we don't make drastic changes. This property is called universality. There are things which matter and things which do not.

For an ideal random walk (a self-avoiding random walk is not ideal), one always finds that the typical size of the region that the random walk inspects is proportional to $t^{1/2}$

$$\sqrt{<\mathbf{R^2}>} \propto t^{\nu} \quad \nu = 1/2 \text{ Ideal Random Walk} \tag{12.21}$$

or to $N^{1/2}$ where N is the number of steps. The mathematical sign $\propto$ means proportional to. When we coin the term "universal", we mean that ν does not change, but that the prefactor can. In general, ν will not depend on the geometry of the network. If we take a square or a triangular lattice, the exponent ν will not change. If the length of the step is not more fixed but if it is drawn from a probability distribution, ν will not change either (if this probability distribution is not pathological). For an ideal random walk, the exponent ν does not depend on the dimension of space. For a self-avoiding random-walk, it does as long as the dimension of space is less than 4.

Remark 4 *Let $p(d)$ be the probability that a random walk on d-dimensional lattice return to the origin (after an infinite number of steps). In 1921, Pólya proved that*

$$p(1) = p(2) = 1 \textit{ but } p(d) < 1 \textit{ for } d > 2 \tag{12.22}$$

Another way to say that is: "All roads lead to Rome except the cosmic paths ! "

This can be seen as follows. Consider a random walk of N steps on a lattice. The region inspected by the random walk has size $\sqrt{N}$. This corresponds to $N^{d/2}$ different sites if the sites are DISTINCT*, i.e. counted once. The density of visited sites is therefore $\propto N/N^{d/2} = 1/N^{d/2-1}$ which growths with N if $d < 2$. The random will start at some point to visit the same site many times. One says that the walk is recurrent. For $d \geqslant 3$, the density decreases meaning that the random walk has a chance to escape. The random walk is transient. The case $d = 2$ is more problematic, but the random walk has a probability 1 to return to the origin.*

12.5 Thermodynamic functions

We assume that all conformations with a given end-to-end distance are of equal energy. Absorbing all constants into the reference entropy:

$$S(\mathbf{R}, N) = k_b \ln P(N, \mathbf{R}) \tag{12.23}$$

which gives

$$S - S_0 - \frac{3k\mathbf{R}^2}{2Nl^2} \tag{12.24}$$

The free energy is then

$$F = E - TS = F_0 + \frac{3k\mathbf{R}^2}{2Nl^2} \tag{12.25}$$

We see that the free energy is related quadratically to the end-to-end vector, as if the chain is an entropic spring.

12.6 The Gaussian Chain

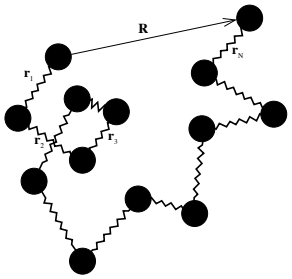


Figure 12.3:

This is a second alternative model kown as the Gaussian chain. A gaussian chain is a collection of beads connected by springs playing the role of harmonic oscillators. The potential exerted on two successive beads is

$$U_0(\mathbf{r_i}) = \frac{3}{2l^2} k_B T \mathbf{r}_i^2 \tag{12.26}$$

where $\mathbf{r}_i$ is the vector between them. The spring constant is similar to the spring constant of the freely joined chain.

Exercice 12.2 *The probability distribution for a single segment is given by the Bolzmann weight*

$$p(\mathbf{r_i}) = C \exp\left\{\left(-\frac{U_0}{k_B T}\right)\right\} \tag{12.27}$$

where C is a normalization constant

$$C \int d\mathbf{r_i} p(\mathbf{r_i}) = 1 \tag{12.28}$$

Show (using polar coordinates):

$$C = \left(\frac{3}{2\pi l^2}\right)^{3/2} \tag{12.29}$$

A more lengthy calculation gives that the end-to-end distribution is again Gaussian

$$P(N, R) = \left(\frac{2\pi R_0^2}{3}\right)^{-3/2} \exp\left\{\left[-\frac{3R^2}{2R_0^2}\right]\right\} \tag{12.30}$$

We note now that since each segment of the Gaussian chain is independent of the others, a chain of length N may be constructed by stringing two chains of length N_1 and N_2 together with $N_1 + N_2 = N$. Noting this, we can trivially find the distribution function of the vector connecting any two arbitrary segments m and n in a Gaussian chain. In particular, the average distance between monomers n and m is

$$\langle (\mathbf{R}_m - \mathbf{R}_n)^2 \rangle = |m - n| l^2 \tag{12.31}$$

Exercice 12.3 *The purpose of this problem is to compute the radius of gyration of a Gaussian chain. We define the coordinates of the center of gravity as*

$$\mathbf{R}_G = \frac{1}{N} \sum_{m=1}^{m=N} \mathbf{R}_m \tag{12.32}$$

The radius of gyration is

$$R_g^2 = \frac{1}{N} \sum_i \langle (\mathbf{R}_i - \mathbf{R}_G)^2 \rangle \tag{12.33}$$

1. *Show that the following two equations are correct*

$$\begin{aligned} R_g^2 &= \langle \frac{1}{N}\sum_i \mathbf{R}_i^2 - \frac{1}{N^2}\sum_i\sum_m \mathbf{R}_i.\mathbf{R}_m \rangle \\ &= \frac{1}{2N^2}\sum_i\sum_m \langle (\mathbf{R}_i - \mathbf{R}_m)^2 \rangle \end{aligned} \tag{12.34}$$

2. *Using (**??**), show*

$$R_g^2 = \frac{1}{2N^2}\sum_{m=1}^{N}\sum_{n=1}^{N} |n-m| l^2 \tag{12.35}$$

3. *The last expression can be transformed into an integral as*

$$\begin{aligned} R_g^2 &\approx \frac{l^2}{2N^2}\int_0^N dn \int_0^N dm |n-m| \\ &= \frac{l^2}{N^2}\int_0^N dn \int_0^n dm\, (n-m) \end{aligned} \tag{12.36}$$

Performing the last integral, show

$$R_g^2 = \frac{1}{6}\langle \mathbf{R} \rangle^2 \tag{12.37}$$

12.7 The freely rotating chain

This is a model where the angle θ between two consecutive segments is fixed, but each segment can rotate freely in the ϕ direction. This model is also called the Kratky-Porod wormlike chain. This model has some kind of "memory" but the end-to-end distance still scales with $\sqrt{N}$.

When $N \gg 1$:

$$\bar{R} = \sqrt{\mathbf{R}^2} = l\sqrt{N\left(\frac{1+\cos\theta}{(1-\cos\theta)}\right)} \tag{12.38}$$

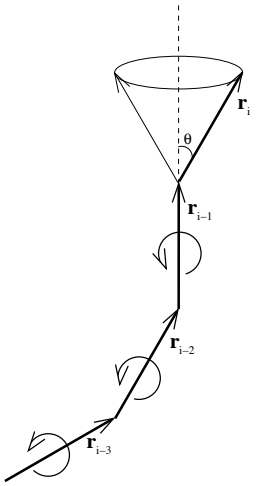


Figure 12.4: . The freely rotating chain. The angle θ is fixed but segments can rotate and draw a cone whose apex is a vertex.

Exercice 12.4 *An ideal chain trapped in a tube: Consider a chain in a cylindrical tube of diameter $D \ll R_0$, see Fig. **??**. We have $D \gg l$, so that the chain retains some lateral wiggling. What is the length of tube $R_\parallel$ occupied by the chain ?*

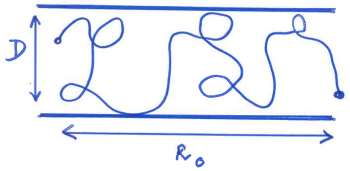


Figure 12.5: A chain of N mers within a tube of diameter D. The length occupied by chain is $R_\parallel$.

Exercice 12.5 *Consider a particle that hops at discrete times between neighboring sites on a onedimensional lattice with unit spacing. At each step, the random walker moves a unit distance to the right with probability p or to left with probability $q = 1 - p$. Let $P(N, r)$ denote the probability that the particle is at site r at the Nth time step.*

1. *Show*

$$P(N,r) = pP(N-1,r-1) + qP(N-1,r+1) \tag{12.39}$$

2. *Introduce the generating function*

$$G(N,k) = \sum_{r=-\infty,+\infty} e^{ikr} P(N,r) \quad k \in [-\pi, +\pi] \tag{12.40}$$

Show

$$\left(-i\frac{d}{dk}\right)^m G(N,k)\Big|_{k=0} =< r^m > \tag{12.41}$$

3. *Show*

$$G(N,k) = \left(pe^{ik} + qe^{-ik}\right) G(N-1,k) \tag{12.42}$$

4. *Assume that the particle starts at the origin*

$$P(0,r) = \delta_{0,r} \tag{12.43}$$

Show

$$G(N,k) = \left(pe^{ik} + qe^{-ik}\right)^N \tag{12.44}$$

5. *Deduce that $P(N,r)$ is the binomial distribution*

$$P(N,r) = \frac{N!}{\left(\frac{N+r}{2}\right)!\left(\frac{N-r}{2}\right)!} p^{(N+r)/2} q^{(N-r)/2} \tag{12.45}$$

6. *Use Stirling approximation and show*

$$P_N(x) \to \frac{1}{\sqrt{2\pi Npq}} e^{-[x-N(p-q)]^2/2Npq} \tag{12.46}$$

7. *What is $< x >$. Take $p = q = 1/2$ and recover the result given in the lecture.*

Exercice 12.6 *Consider a random walk on a finite interval of length N. The two boundary sites are absorbing, i.e. the random walker immediately disappears upon reaching these sites. Suppose that the starting position of the random walk is n, with $0 \leqslant n \leqslant N$. What is F_n, the probability that the walker first reaches the boundary at site N, i.e. without touching site number 0, first? We will write a simple recursion relation for F_n. Consider the probability F_n.*

1. *What is F_0 and F_N ?*

2. *With probability $1/2$, the walk steps to site $n-1$ at which the probability to escape at site $n-1$ is F_{n-1}. Similarly, the walk steps at site $n+1$ with probability $1/2$. Show:*

$$F_n = \frac{1}{2}\left(F_{n-1} + F_{n+1}\right) \tag{12.47}$$

3. *Show $F_n = n/N$. In a fair coin-toss game, the probability that a gambler ruins the casino equals the wealth of the gambler divided by the combined wealth of the gambler and the casino. Is gambling a good idea ?*

4. *Introduce the step size a. Write*

$$F_{n+1} = F(x = na + a) = F(x) + aF'(x) + a^2/2F''(x) \tag{12.48}$$

Show that $F(x)$ solves the Laplace equation

$$\Delta F = 0 \tag{12.49}$$

so that "exit problems" ara analogous to electrostatic problems.

13
Entropic elasticity of polymer chains, self-avoidance, and persistence

13.1 Force-extension curve

As a first trivial example, consider a spring with rigidity k. Let x_0 its extension at rest. We apply a force F to the spring. The equivalent of the Gibbs energy is

$$G(F) = \frac{1}{2}k(x - x_0)^2 - Fx \tag{13.1}$$

where we work in an ensemble where we control F (which plays an equivalent role as the pressure P for a gas). The state of the state minimizes G at a given force F. Taking the derivative with respect to x to find the minimum gives

$$k(x - x_0) - F = 0 \quad \text{or} \quad x = c_0 + \frac{F}{k} \tag{13.2}$$

In this simple example, $U = 1/2k(x - x_0)^2$ and $S = 0$ (no entropy for macroscopic spring).

Macromolecules and biopolymers are elastic and single molecule experiments probe their elasticity. We illustrate this in the case of an ideal polymer.

This an example where we minimize the Gibbs free energy to find the equation of state of a polymer. We consider a simple polymer model composed of sequences of N rigid segments of length l and able to point in any direction independently of each other. We attach the polymer at one end on a surface and apply a force at the other end: see Fig. **??**. What is the relation between the extension R and the force F ?

n We pose this problem to illustrate two points:

1. Elasticity can be entropic.
2. The conformational state of the chain results from the minimization of G. By minimizing G we realize our ambition to equilibrate energy with entropy.

As a starting point, we consider the instantaneous end-to-end vector **R**. Because of the rules for addition of vectors, **R** is the sum

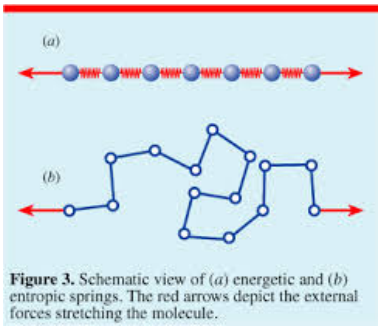


Figure 3. Schematic view of (*a*) energetic and (*b*) entropic springs. The red arrows depict the external forces stretching the molecule.

Figure 13.1:

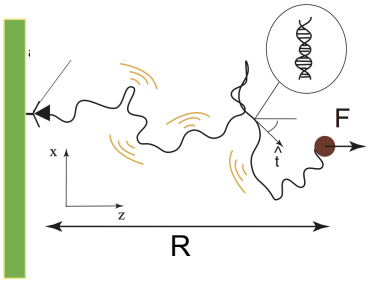


Figure 13.2: A single molecule experiment using a bead trapped in an optical trap.

of the bond vectors $\mathbf{u_i} = \mathbf{x_{i+1}} - \mathbf{x_i}$ with

$$\mathbf{R} = \sum_{\mathbf{i}} [\mathbf{u_i} = \mathbf{x_{i+1}} - \mathbf{x_i}] \tag{13.3}$$

where $\mathbf{x_{i+1}} - \mathbf{x_i}$ is the bond vector for one single mer. We assume that we have N mers.

Since the bond vectors are random variables, the end-to-end vector vector is also a random variable and is Gaussian. It follows that probability distribution of $\mathbf{R}$ has the form

$$P(N,R) = \left(\frac{2\pi R_0^2}{3}\right)^{-3/2} \exp\left\{\left[-\frac{3R^2}{2R_0^2}\right]\right\} \tag{13.4}$$

where $R_0^2 = Nl^2$.

There is no energy associated with a given macroscopic extension $\mathbf{R}$, since the bond vectors can take any direction they want. Therefore, $U = 0$. To calculate $G = U - TS$, we need to compute the entropy. We have seen in the sucrose diffusion experiment that entropy is connected to the number of configurations that the chain can adopt given a configure $\mathbf{R}$. The more configurations we have for a given end to end distance R, the largest the probability to observe a given end to end distance . So we find the entropy

$$S = k \ln W = k \ln P(N,R) = \frac{3}{2} k \frac{R^2}{R_0^2} \tag{13.5}$$

Assume

$$U - TS = +kT \ln P(N,R) \approx +\frac{3}{2} kT \frac{R^2}{R_0^2} + \text{constant} \tag{13.6}$$

and check that the entropy decreases when $\mathbf{R}$ increases: why ?

Since we work at constant force, that is to say constant pressure in the preceding language, the system minimises $G = U - TS - FR$, where FR is the equivalent of PV:

$$G(T,F) = \frac{3}{2} kT \frac{R^2}{R_0^2} - FR \tag{13.7}$$

This is exactly what we had before: The only variable left is R and R will spontaneously choose the value which minimizes $G(T,F)$: see plot of Fig. **??**. Therefore,

$$F = 3kT \frac{R}{R_0^2} \quad \text{or} \quad R = \frac{Nl^2}{3kT} F \tag{13.8}$$

From the classical spring example $F = kx$, we see that the polymer possesses a "spring rigidity k " inversely proportional to T, why ?

Exercice 13.1 *Consider an ideal chain carrying charges $\pm e$ at both ends. What will be its relative elongation in a field of $E = 30\,10^3 V/m$ ($l = 2$, $N = 10^4$). Remember $k_B T = 1/40eV$.*

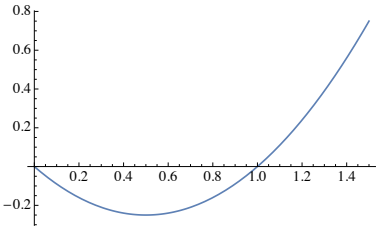


Figure 13.3: Plot of $x^2 - x$. Note the minimum.

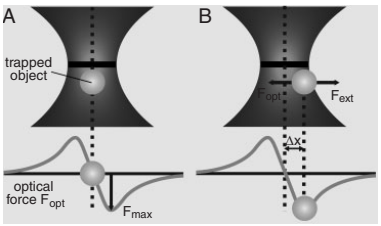


Figure 13.4: Principle of the external force measurement using an optical trap. The particle is made of a dielectric material, meaning that the particle is trapped at the place where the intensity of the electric field is maximum (A) When no external force is applied, trapped particle is resting at its equilibrium position in the trap with no net optical force F_{opt} acting on it. (B) External force F_{ext} causes displacement Δx of the trapped particle from its equilibrium position; consequently, optical force F_{opt} starts acting on the particle that is equal in size and opposite in direction to F_{ext}. For small displacements from the equilibrium, relationship F_{opt} =??$k\Delta x$ holds where k is the optical trap stiffness. Maximal external force that can be measured is F_{max}[**?**] .

13.2 *Flory theory for self-avoiding walks or polymers*

What is missing up to now for the calculating the shape of polymers is the effect of STERIC INTERACTIONS. An argument due to Flory takes these interactions into account.

Suppose that we have a chain with N monomers with radius R. Then the average density of monomers is

$$c = \frac{N}{R^d} \tag{13.9}$$

where d is the dimension of space. Assuming short-ranged interactions, we add a term to the free energy which counts the number of self-interactions. On average the probability to find a monomer in a unit volume is c. Then the probability to find two monomers at the same place within the volume R^d is

$$c \times c \tag{13.10}$$

So the energy per unit volume for self-intersection is proportional to

$$u(T) \times c \times c \tag{13.11}$$

The total energy is this energy integrated over the whole volume R^d

$$u(T)\frac{c}{R^d}\frac{c}{R^d}R^d \tag{13.12}$$

which much positive, since increasing the density increases the number of contacts. The scale of this penalty energy is proportional to some function $u(T)$ in good solvents (we distinguish good solvents where the polymer "loves" the contacts with the solvent molecules from the poor solvent case where the polymer forms a globule to protect himself from the solvent)

Adding the entropic spring energy gives for the total free energy

$$G = \frac{d}{2}kT\frac{R^2}{R_0^2} + u(T)\frac{c}{R^d}\frac{c}{R^d}R^d \tag{13.13}$$

where $R_0 = Nl^2$.

This free energy is minimized when the radius R is such that

$$\frac{\partial G}{\partial R} = 0 \tag{13.14}$$

or

$$R(N) = \left(\frac{u(T)l^2}{kT}\right)^{1/(d+2)} N^{3/(d+2)} \propto N^{\nu} \tag{13.15}$$

with

$$\nu = \frac{3}{d+2} \quad \text{for} \quad d \leqslant 4 \quad \text{and } \nu = 1/2 \quad \text{above} \tag{13.16}$$

When $d = 1$, $\nu = 1$. As anticipated, self-avoidance in $d = 1$ makes the chain straight ! In $d = 2$, $\nu = 3/4$ which is exact. In $d = 3$, $\nu = 3/5$ which is extremely closed to exact (numerical) value 0.5880.

13.3 *Persistence length of a polymer*

Let us start with a continuous model for the chain. Each point on the polymer chain is perfectly defined if we know the distance of this point to the origin along the chain. This distance should not be confused with the flying distance to the origin

$$\mathbf{r} = \mathbf{OM}(s) \tag{13.17}$$

where s is the arclength. The tangent vector at some point is defined as

$$\mathbf{t} = \frac{d\mathbf{OM}(s)}{ds} \tag{13.18}$$

where we take the derivative for each component $(x(s), y(s), z(s))$. Integrating the tangent gives back the end-to-end distance

$$\mathbf{OM}(s) = \int_0^L \frac{d\mathbf{OM}(s)}{ds} ds \tag{13.19}$$

For a discrete chain, the tangent $\mathbf{t}_i$ at node i is simply the vector between node i and $i+1$. Depending on the context, one can use either a continuous or a discrete approach.

To evaluate the correlation between two tangents separated by a distance s along the chain, we shall make use of the following property

$$< \cos\theta_{s_1,s_3} >=< \cos\theta_{s_1,s_2} >< \cos\theta_{s_2,s_3} > \tag{13.20}$$

where s_2 is any point between s_1 and s_3.

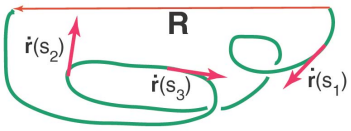


Figure 13.5: The persistence length sets the scale of the correlation between the tangent at different points of the chain. If we change the angle of the tangent at some point s_1, what is the probability that the tangent at a distant point s_3 will see this change ? Because of the exponential dependence of (**??**), the persistence length sets the domain of influence of a perturbation. If this length is large, the polymer is rigid. If this length os small, the polymer is easily deformed.

Exercice 13.2 *To prove this, separate into perpendicular and parallel components as (we do the calculation is $d = 2$ for simplicity: For any vector, the perpendicular vector is well defined)*

$$\dot{\mathbf{r}}_1 = (\dot{\mathbf{r}}_1 \cdot \dot{\mathbf{r}}_2)\dot{\mathbf{r}}_2 + (\dot{\mathbf{r}}_1 \cdot \dot{\mathbf{r}}_2^\perp)\dot{\mathbf{r}}_2^\perp \tag{13.21}$$

$$\dot{\mathbf{r}}_3 = (\dot{\mathbf{r}}_3 \cdot \dot{\mathbf{r}}_2)\dot{\mathbf{r}}_2 + (\dot{\mathbf{r}}_3 \cdot \dot{\mathbf{r}}_2^\perp)\dot{\mathbf{r}}_2^\perp \tag{13.22}$$

with $|\dot{\mathbf{r}}_2^\perp|^2 = |\dot{\mathbf{r}}_2| = l^2$.

$$\dot{\mathbf{r}}_1 \cdot \dot{\mathbf{r}}_2 = |\dot{\mathbf{r}}_1||\dot{\mathbf{r}}_2|\cos\theta_{1,2} \tag{13.23}$$

$$\dot{\mathbf{r}}_1 \cdot \dot{\mathbf{r}}_2^\perp = |\dot{\mathbf{r}}_1||\dot{\mathbf{r}}_2^\perp|\cos(\pi/2 - \theta_{1,2}) \tag{13.24}$$

$$= |\dot{\mathbf{r}}_1||\dot{\mathbf{r}}_2^\perp|\sin\theta_{1,2} \tag{13.25}$$

We have

$$\dot{\mathbf{r}}_1 \cdot \dot{\mathbf{r}}_3 = l^2(\dot{\mathbf{r}}_1 \cdot \dot{\mathbf{r}}_2)(\dot{\mathbf{r}}_3 \cdot \dot{\mathbf{r}}_2) + l^2(\dot{\mathbf{r}}_1 \cdot \dot{\mathbf{r}}_2^\perp)(\dot{\mathbf{r}}_3 \cdot \dot{\mathbf{r}}_2^\perp) \tag{13.26}$$

so that

$$\cos\theta_{1,3} = \cos\theta_{1,2}\cos\theta_{2,3} + \sin\theta_{1,2}\sin\theta_{2,3} \tag{13.27}$$

From Fig. **??**, *we see that each time we have one configuration with $\theta_{1,2}$, we have a symmetric configuration with $-\theta_{1,2}$. Using* $\sin(-\theta) = -\sin\theta$, *we get that the average of the* sin *are equal to zero*

$$< \sin\theta_{12}\sin\theta_{23} >= 0 \tag{13.28}$$

so that $\forall s_2 \in [s_1, s_3]$

$$< \cos\theta_{s_1,s_3} >=< \cos\theta_{s_1,s_2} >< \cos\theta_{s_2,s_3} > \tag{13.29}$$

The only function with this property is the exponential, so that we can write

$$\cos(\theta(s-t)) = \exp\{[-|s-t|/l]\} \tag{13.30}$$

Recall that a correlation function can be interpreted as a probability. If we rotate the tangent at a given point, what is the probability that a node located at a distance s of this point will feel our perturbation ? Formula (**??**) shows that the domain of influence of our perturbation is actually small and not larger than l. Because of the exponential, nodes at distance s marger than l will not feel the perturbation and will fluctuate indepedently.

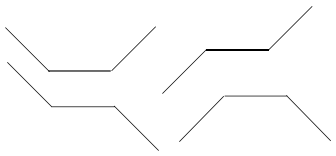


Figure 13.6: 4 configurations to illustrate the symmetry $\theta_{1,2} \rightarrow -\theta_{1,2}$, $\theta_{2,3} \rightarrow -\theta_{2,3}$.

CONCLUSION : Our problem is to connect l to the rigidity of the polymer. For ideal chains with no internal energy, l is very small. For more rigid polymers which resists bending, l is much larger (see table **??**).

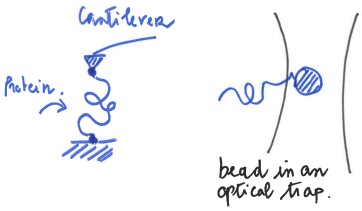
Actin	$15\,\mu m$
Microtubules	$1-6\,mm$
ADN	$50\,nm$
Dextran	$0.5\,nm$
P.E.G.	$0.7\,nm$

Table 13.1: Persistence length of some polymers.

14
Single-Molecule Mechanics

14.1 Optical tweezers

A single laser beam focused by a high numerical aperture microscope objective is able to trap dielectric particles, usually microspheres, near the lens focus. Such an arrangement is called optical tweezers and has a wide range of applications in physics and biology.



14.2 Atomic force microscopy

Atomic Force Microscopy (AFM) appears as a very natural tool to work in the single molecule domain. This apparatus was originally designed to visualize surfaces with atomic scale resolution. Its working principle is to scan the surface of a sample with a very sensitive position detector and to record the modulation of the topological signal. The AFM relies on a very thin cantilever as a detector. Somewhat similar to the needle of a dj's record player, this micro-fabricated beam is typically 100 microns long, 10 microns wide and a fraction of a micron thick. It has an extremely sharp tip at its end (radius of curvature in the tens of nanometers). The position of this cantilever is measured by reflecting a collimated laser beam onto its surface and imaging the light spot on a two- or four- quadrant diode detector. The sample is scanned horizontally by a XY piezo stage, providing atomic resolution.

As we have stated, the AFM is primarly a visualization tool and its use as a single molecule micro-manipulation device is a secondary feature. The very sensitive cantilever has motivated researchers to use this device to measure the force required to stretch a biopolymer or to break a molecular bond. To achieve this goal, the operator stops the horizontal sample-scanning process and gently moves the cantilever vertically above the sample while recording its deflection. The AFM provides some natural features :

1. The position of the cantilever can be adjusted with sub-nanometer resolution and the vertical scanning speed can be high.

2. The deflection of the cantilever is also read with sub-nanometer resolution, and the response time is in the milli-seconde range.

3. The AFM may be used to visualize the sample.

4. Strong forces in the nanoNewton range may be applied to the sample.

The force sensitivity of the AFM is related to the cantilever size and stiffness. Different cantilevers provide a range of stiffness from 1 N/m to $10^{-3}N/m$(or $1pN$ to $1nN$ per nanometer) of cantilever deflection. A very common error consists in saying that the best sensor is the one with the smallest stiffness. We shall see that the best sensor (in term of signal to noise) in in fact the smallest device. Since the cantilever size is typically 100 microns they are not the best sensors in terms of noise. A strong effort is under way to reduce the size of the cantilever to improve their signal to noise. Typically the minimum force measured with the AFM is 5 pN.

Exercice 14.1 *In order to measure forces accurately with an AFM, it is important to measure the cantilever spring constant. Experimentally, the basic idea is to look at the fluctuations of the tip of the cantilever (see Fig.* **??***).*

The force exerted on the cantilever can be deduced from Hooke's law $F = -kx$.

1. *Assume* $F = 0$. *Show that the fluctuations see in Fig.* **??** *are the ones of an abstract particle in a potential well* $1/2kx^2$.

2. *From this, you should deduce an expression for* $< x^2 >$.

3. *Do the integral (they have been done somewhere during the lecture) and show*
$$\frac{1}{2}k < x^2 >= \frac{1}{2}k_B T \tag{14.1}$$

4. *We want now to measure an applied force. Assume* $F \neq 0$. *Show that the fluctuations* $< \delta d^2 >$ *of the tip around the new position d obey a relation similar to (***??***).*

5. *Deduce that the incertitude on the force measured by looking at the mean deflection point is*
$$< \delta F^2 >= (kk_B T)^{1/2} \tag{14.2}$$

6. *Do you prefer to choose a rigid or a soft cantilever to measure the force ?*

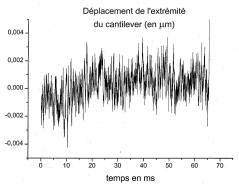


Figure 5: Enregistrement du mouvement brownien, dans un liquide, de la pointe d'un microscope à force atomique. (Enregistrement fourni gracieusement par Pascal Silberzan, Institut Curie.)

Figure 14.1: Position of the cantilever tip as a function of time. Due to thermal fluctuations, the tip experiences strong random displacements.

15
How to convert chemical energy into work

15.1 The detailed balance principle

This principle reads as follows: In the state of equilibrium, every elementary transformation is balanced by its exact opposite or reverse, see Fig. **??**. This is equivalent to say: At equilibrium, the number of processes destroying situation A and creating situation B will be equal to the number of processes producing A and destroying B. If you know the probability of a transition from a state A to the other state B of a physical system (in some appropriate time unit), and you also know the probability of the reverse reaction, then you automatically know what is equilibrium condition for N molecules distributed in the two states:

$$N_A P(A \to B) = N_B P(B \to A) \tag{15.1}$$

where $N = N_A + N_B$ and where N_A and N_B are the "occupation number" (i.e. the number of molecules in state A or B) and this condition only applies to equilibrium systems.

This property is useful to distinguish equilibrium from non-equilibrium systems and is synonymous of a symmetry. When detailed balance is broken, time-reversal symmetry is also broken. In case (b) of the companion figure, the cycle runs clockwise and not anti-clockwise. As a result, there is a macroscopic flux $A \to B \to C \to A$ of matter (or of information). This is not possible is the system at equilibrium, since there is not flux for an equilibrium system (the absence of flux is the essence of equilibrium systems).

In particular, living cells are out-equilibrium system, and detailed balance is always broken. The reason for this is that cell uses chemical energy to perform work. Therefore, energy (ATP consumption) is fed into the system into and cells are open systems to energy fluxes. This is evident if we drive an energy flux into a reaction, the reverse reaction will provide energy. This point is particularly well illustrated in the case of the F_1-ATPase rotary motor. This rotary motor is able to synthesis ATP (from ADP) with a proton flux (through change of conformations of the molecule). The synthase is fully reversible in that hydrolysis of ATP drives the REVERSE flux of protons (in the reverse direction).

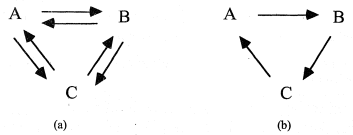


Figure 15.1: The principle of detailed balance. (a) The equilibrium between three interconverting compounds A, Band C is a result of "detailed balance" between each pair of compounds. (b) Although a conversion from one compound to another can also produce concentrations that remain constant in time, this is not the equilibrium state, since the cycle runs only way and detailed balance is broken between the two ways of running the cycle.

Thus, the principle of detailed balance has a more general validity.

Detailed balance implies that rates constant and equilibrium ratios are not independent. Rate constant for chemical reaction are equivalent to the transition probabilities $P(A \rightarrow B)$ we have seen before. As an example, consider the reaction

$$X + Y \rightleftharpoons 2Z \tag{15.2}$$

The forward and reverse reaction rates are

$$R_f = k_f a_X a_Y \text{ and } R_r = k_r a_Z^2 \tag{15.3}$$

where the $a's$ are the activities (i.e. concentrations). At equilibrium, there is an exact balance between the forward and the reverse rates, meaning that the fluxes equal each other

$$k_f a_X a_Y = k_r a_Z^2 \tag{15.4}$$

so that we get the equilibrium condition between the concentrations (the activities) and the chemical rates

$$K(T) = \frac{k_f}{k_r} = \frac{a_Z^2}{a_X a_Y} \tag{15.5}$$

In other words, there is a relationship between the equilibrium constants and the reaction rates.

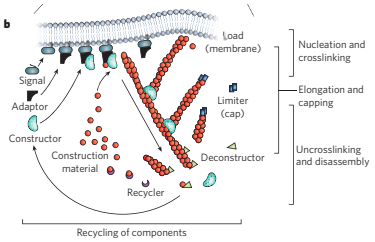


Figure 15.2: There are three basic steps involved in the assembly of protrusive, branched actin-filament networks: filament elongation; nucleation and cross-linking of new filaments from filaments close to the membrane; and capping of filaments. Disassembly of the network involves a separate set of proteins that severs the filaments and recycles the subunits.

Exercice 15.1 *If you are a biologist: Actin is a biopolymer which polymerizes in the immediate vicinity of the membrane. When it polymerizes, the membrane is pushed forwards. Consider Fig.* **??**. *Can you tell why the cycle represented in this figure run only anti-clockwise ? To answer to this question, you have to guess where energy is added to the system and released from the system and you have discuss the process with the help of an energy diagram.*

Exercice 15.2 *One may ask if the principle of detailed balance depends on the details of the chemical mechanism. To see this, assume that the preceding reaction consists of two steps (a) and (b) as follows:*

$$\begin{cases} X + X & \underset{k_{ra}}{\overset{k_{fa}}{\rightleftharpoons}} W \\ W + Y & \underset{k_{rb}}{\overset{k_{fb}}{\rightleftharpoons}} 2Z + X \end{cases} \tag{15.6}$$

which ultimately achieves

$$X + Y \rightleftharpoons 2Z \tag{15.7}$$

What are the ratios

$$\frac{k_{fa}}{k_{ra}} \text{ and } \frac{k_{fb}}{k_{rb}} \tag{15.8}$$

as a function of the activities $a's$? Show that the equilibrium concentrations of X, Y and Z obey a relationship independent of the concentration of W

15.2 *Standard Free-energy changes: How to convert chemical energy into work*

Energy is the ability to do work: How do we convert chemical energy into mechanical work ? The trick is to couple a reaction to a mechanical process (rotation, translation, diffusion etc.).

Consider the hydrolysis of ATP

$$\mathrm{ATP} + \mathrm{H_2O} \rightleftharpoons \mathrm{ADP} + \mathrm{P}_i + \mathrm{H_2O} \tag{15.9}$$

where P_i represents the phosphate ion. In order to determine whether the reaction will proceed spontaneously from left to right, we need to determine the sign of the total change in energy ΔG

$$\begin{aligned}\Delta G = \int_{\text{reactants}}^{\text{products}} dG &= G(\text{products}) - G(\text{reactants}) \\ &= G(\mathrm{ADP} + \mathrm{P}_i) - G(\mathrm{ATP} + \mathrm{H_2O})\end{aligned} \tag{15.10}$$

Since the free energy of a molecule changes with temperature, pressure, and wether it is pure or in mixture, one needs to know the conditions for which a free energy change is reported. The free energy change is usually reported for the standard state (molar free energy, i.e. for one mole) and for ATP hydrolysis is

$$\Delta G = -28\mathrm{kJ.mol}^{-1}$$

So the reaction will proceed spontaneously to the right, because the free energy of ATP in water is higher than the free energy of ADP and P_i. However, the energy barrier along the reaction coordinate is so high that this reaction cannot happen spontaneously. We need a catalyser, i.e. a molecule which lowers the energy barrier as seen below.

The way to transform free energy into work is to couple the ATP hydrolysis to an other chemical or mechanical reaction. Then the maximum chemical or mechanical work which can be extracted is bounded from above by the free energy change is ATP hydrolysis.

Consider, for example, the maltose transporter with the reaction

$$\begin{aligned}&\mathrm{H_2O} + \mathrm{ATP}(\mathrm{in}) + \mathrm{Maltose}(\mathrm{out}) \\ &\longrightarrow \mathrm{ADP} + \mathrm{P}_i + \mathrm{Maltose}(\mathrm{in})\end{aligned} \tag{15.11}$$

where the maltose is transported from the outside of the cell to the inside by an enzyme which uses ATP hydrolysis[1], see Fig. **??**. The cycle proceeds into 4 steps:

1. ATP binds to the inner face of the membrane and maltose binds to the outer face. This is a high energy conformation of the transporter.
2. The transporter relaxes this high energy conformation by moving the maltose inside the barrel.
3. Then, ATP can be hydrolysed resulting in the formation of ADP. This is why the maltose transporter is an enzyme which catalyse this reaction.

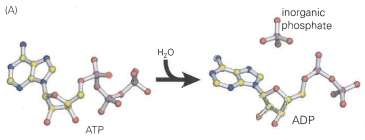


Figure 15.3: ATP loses its terminal phosphate group upon hydrolysis. This reaction occurs rapidly in the forward direction when CATALYZED.

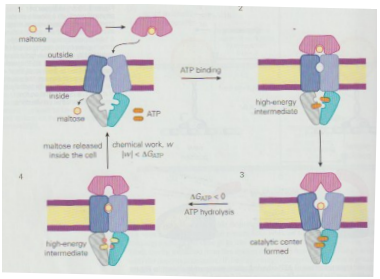


Figure 15.4: The maltose transporter which couples transport of maltose molecules across the membrane with ATP hydrolysis.

[1] Maltose = 2 glucose molecules together

4. This conformation is unstable and relaxes by releasing the maltose molecule in the inside of the cell (with ADP + P_i).

In short, the gain in (chemical) energy due the hydrolysis of ATP is used to drive a conformational change in the transporter. This is this conformational change which allows the maltose molecule to be transported through the barrel. Since energy is provided by ATP hydrolysis, the system maltose molecule + transporter is open to an energy flux. As in the detailed balance section, the cycle can run only one way if energy is provided by ATP hydrolysis.

15.3 The F-1ATPase motor

The next question is far from trivial: can we increase the concentration of maltose inside the cell so that the cycle will run the other way around. In that case, the energy provided would be the increase of entropy due to the maltose molecules flowing outside the cell (remember $F = U - TS$). By the same token, this would provide a way to synthesize ATP from ADP. The problem is that we cannot increase the concentration of maltose to infinity without reaching the sedimentation limit. The F-1ATPase motor protein uses this strategy to synthesize ATP. This protein is molecular turbine machine using protons flux. If the flux is driven one way, the machine synthesize ATP and the machine can use ATP to drive the flux of protons the other way.

15.4 Free energy and work

We have seen that the change of Gibbs free energy is the amount of energy which can be converted into work during a process. What kind of work do we refer to ? As summarized in Table **??**, expansion work, meaning varying the volume of the system, is not the only kind of work which can be done on the system. Chemical work involves changes in the number of molecules of a certain species, such as in chemical reaction or transport across a concentration gradient.

Consider what happens to the free energy when a small number of molecules moves from outside to the inside of the cell. Let us say that the number of moles inside changes as $n \to n + dn$. For a mechanical displacement with a force F and a displacement dr, we have

$$\Delta G = \int F dr \tag{15.12}$$

What is the equivalent of the mechanical work (**??**) for our CHEMICAL WORK which consists in transferring molecules ? If $\Delta\mu$ is the change in chemical potential between the outside and the inside, the equivalent of (**??**) is

$$\Delta G = \int \Delta\mu \, dn \tag{15.13}$$

Table 15.1: Different types of work that can be done by a system.

Type of work	Intensive variable	Extensive variable	Work
Mechanical	Force, F	Change in distance, dr	$W = \int F dr$
Expansion	Pressure, P	Change in Volume, V	$W = \int P dV$
Electrical	Voltage Difference, ΔV	Change in charge , dq	$W \int \Delta V q$
Surface	Surface tension, γ	Change in surface area, dA	$W = \int \gamma dA$
Chemical	Chemical potential difference, $\Delta\mu$	Change in the number of molecules, dn	$W = \int \Delta\mu \, dn$

Note that there is a close relationship between the change in free energy and the amount of work done on the system. Actually, the change in free energy in a process equal the maximum amount of work that can done or extracted in a process.

The coupling of ATP hydrolysis discussed in the preceding section to work underlies many processes in biology. It is also an example where a chemical work can be transferred into mechanical work, i.e. a change of a protein conformation. Consider a kinesin motor protein. This motor is able to transport vesicles along microtubule tracks, see Fig. **??**. The work DONE by the kinesin is equal to the resistive force F due to friction and viscosity times the displacement dr. This is formula (**??**) with the appropriate sign. The movement of the kinesin is powered the hydrolysis of ATP within the motor domains with a change in free ΔG given by (**??**). The amount of work delivered by the kinesin is limited by ΔG given by (**??**).

The synthesis of ATP is coupled to the movement of ions across the membrane, down a concentration gradient.

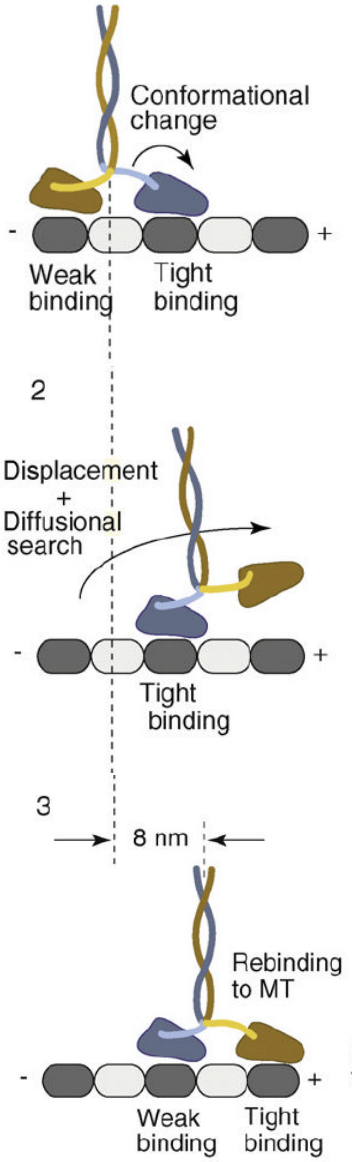


Figure 15.5: Kinesins are motor proteins which "walk" along microtubule tracks in "hand-over-hand" manner with each head taking 16 nm steps. In solution both ends are bound to ADP. The binding of one head to a microtubule causes the release of ADP which is rapidly replaced by ATP. The binding of ATP forces the second head to diffuse forward and brings it to the next binding site. While the trailing head hydrolyses ATP into ADP, the leading head releases ADP and get bound to ATP. As the result, the process starts again. The motion is directional, because the microtubule tracks break symmetry so that diffusion is more effective from the left to

15.5 *Feynman's ratchets*

Diffusion is an isotropic process which can not generate directed motion. However, e.g. for biological systems directed motion is essential, e.g. in intracellular transport. This is what we have seen for the maltose transporter. Is it possible to build a rectifier for diffusion which leads to a directed transport? The answer to this question is the so-called ratchet or Brownian ratchet. Before we discuss ratchets for diffusion in more detail we have a brief look at the famous Feynman ratchet and pawl.

The Feynman-Smoluchowski ratchet is a simple machine which consists of a paddle wheel and a ratchet. The ratchet has asymmetric paddles so that the pawl only allows its motion in one direction.

The full Feynman-Smoluchowski ratchet is shown in **??**. The ratchet is kept in a heat bath of temperature T_2 and coupled to a paddle wheel in a different heat bath with temperature T_1. It appears as it is possible to use this machine to extract useful work from heat at thermal equilibrium and lift the weight m. This would be a violation of Second Law of Thermodynamics.

The idea behind this is the following. The molecules in the heat baths undergo random Brownian motion with a mean kinetic energy determined by its temperature. Assuming that the device is small enough so that the even single collisions with molecules can turn the paddle. These collisions tend to turn the paddle in both directions with the same probability. However, the ratchet prevents the motion in one direction. Effectively this appears to lead to a turning of the system in one direction, lifting the weight in the process.

Feynman's analysis shows that this is not true and so the Second Law is not violated. One also has to consider collisions of the molecules with the pawl. These will lift the pawl from time to time allowing motion in the "forbidden" direction. Effectively no net rotation arises if the heat baths are at the same temperature $T_1 = T_2$.

Note that chemists have been able to construct molecular ratchets and address some of the conceptual issues that pertain[**?**], see fig. **??**.

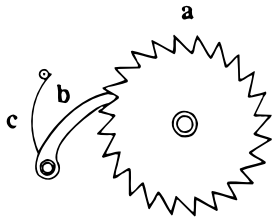


Figure 15.7: A ratchet consists of (a) a wheel with asymmetric paddles. The pawl (2) allows its motion only in one direction. A string that holds the pawl against the wheel(c) Here clockwise motion is not possible.

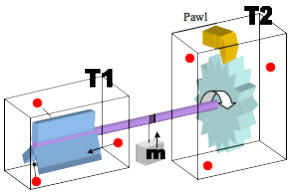


Figure 15.8: The Feynman-Smoluchowski ratchet consists of a paddle wheel (in heat bath of temperature T_1) and a ratchet (in heat bath of temperature T_2). At first sight it appears that this system can extract useful work (lifting the weight m) from heat (random fluctuations) in a system in thermal equilibrium. This would imply a violation of the Second Law of Thermodynamics.

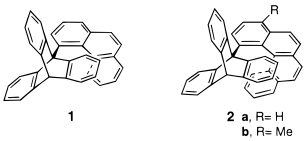


Figure 15.9: Two molecules candidate for (1) the wheel and (2) the pawl and string.

15.6 *Rectifying Brownian motion*

How can we get directional motion ? This is a problem known as rectification of diffusion. Many experiments have been proposed and we follow reference [**?**]. In order to get a directional motion, the particle is subjected to a potential which is periodically switched on and off. A ratchet potential $U(x)$ is periodic, time-dependent and not reflexion symmetric. The last point is crucial.

If the potential is switched on the particles are driven by the force $F = -U'(x)$ towards the minima of the potential. If now the potential is switched off, the particles start to diffuse isotropically . Next the potential is switched on again after some time. Again

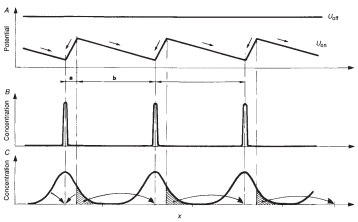


Figure 15.10: Schematic illustration of an asymmetric pumping. When the potential is switched on, particles move to minima of the $U(x)$; After the potential is switched off ($U(x,t) = 0$) the particles start diffusing symmetrically; If the potential is switched on again the particles are captured in the minima again; due to the asymmetry of $U(x)$ more a captured in the minimum to the left than that to the right of the original position.

the particles are driven by the force to the minima of the potential. However due to the lack of reflection symmetry more particles will be captured in the minimum to the left than in the minimum to the right of the original position. Repeating this switching will then generate an effective current to the left (in general: in the direction of the maximum which is closer to the original position).

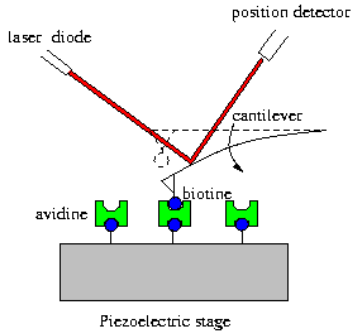


Figure 15.11: An Atomic Force Microscop setup.

15.7 *Equilibrium constants and chemical potential*

In studying chemical reactions, one is interested in the number of molecules of various type as a function of time. Chemical reaction changes one type of molecules into another. For example,

$$3\,H_2 + N_2 \underset{k_b}{\overset{k_f}{\rightleftharpoons}} 2\,NH_3 \tag{15.14}$$

In chemical equilibrium, the concentrations [X] of various molecules satisfy the law of mass action

$$K_e(T) = \frac{[NH_3]^2}{[N_2][H_2]^3} \tag{15.15}$$

More generally, we can write (ν_i can be either positive or negative)

$$\varnothing \rightleftharpoons \sum_i {}^\circ{}_i\, A_i \tag{15.16}$$

with

$$K_{eq} = K_d^{-1} = \prod_i [A_i]^{\nu_i} \tag{15.17}$$

The law of mass action can be motivated as follows. For homogenous system, i.e. small systems with large diffusion constants, the probability to find a N_2 molecule in an arbitrary subvolume is proportional to the concentration. by the same token, the probability to find 3 H_2 molecules is proportional to $[H_2]^3$? Thus, the joint probability to have one N_2 molecules together with 3 H_2 is proportional to the product $[N_2]\,[H_2]^3$ and the forward reaction rate per unit volume is $k_f[N_2]\,[H_2]^3$. The backward reaction rate is similarly proportional to $k_b[NH_3]^2$ and the equilibrium takes place when both flux are equal.

$$k_b[NH_3]^2 = k_f[N_2]\,[H_2]^3 \tag{15.18}$$

or for the dissociation constant

$$K_d = k_f/k_b \tag{15.19}$$

When the reaction takes place, it changes the number of molecules and the energy $G(T, P, N)$

$$\begin{aligned}\Delta G &= \frac{\partial G}{\partial N_{NH_3}}\Delta N_{NH_3} + \frac{\partial G}{\partial N_{N_2}}\Delta N_{N_2} + \frac{\partial G}{\partial N_{H_2}}\Delta N_{H_2} \\ &= 2\mu_{NH_3} - \mu_{N_2} - 3\mu_{H_2}\end{aligned} \tag{15.20}$$

Using the chemical potential for ideal solution $\mu = kT \ln X + \mu_0$, the minimum energy condition $\Delta G = 0$ for equilibrium gives

$$2\ln[NH_3] - \ln[N_2] - 3\ln[H_2] = -2\mu_{0,NH_3} + \mu_{0,N_2} + 3\mu_{0,NH_3} = \Delta G_0 \tag{15.21}$$

and we find that the equilibrium constant depends exponentially on the net internal free energy difference ΔG_0 between the reactants and the product

$$K_{eq} = K_0 \exp\{[-\Delta G_0/kT]\} \tag{15.22}$$

with K_0 being a prefactor (here equal to 1 but $\propto 1/T^3$).

Remark 5 *The exponential dependence of the equilibrium constant should not be confused with the Arhenius factor.*

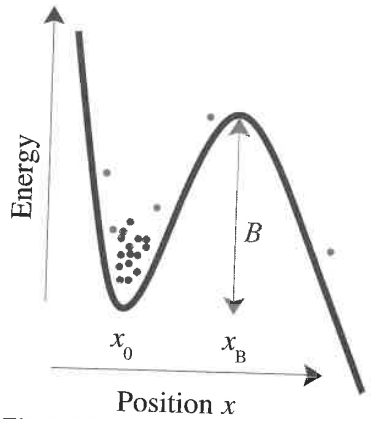


Figure 15.12: Barrier-crossing potential, see [**?**]. Energy E as a function of some reaction coordinate x for a chemical reaction. The dots schematically represent how many molecules are at each position. The reactants (left) are separated from the products (right) by an energy barrier B. The rate of reaction is the the number of molecules crossing the top of the energy barrier.

15.8 Problems

1. There are three properties of enthalpy to keep in mind. The first is that the change in enthalpy is the heat supplied at constant pressure. The second is that H is a state function. The third is that the slope $C_p = \Delta H/\Delta T$ is the heat capacity at constant pressure.

   (a) Ethanol is is brought to the boil at 1 atm. When an electric current of 0.682 A from a 12.0 supply is passed for 500 s through a heating coil immersed in the liquid, the temperature is found constant but 4.33 g of ethanol is vaporized. What is the molar enthalpy of vaporization of ethanol ($M = 46.07$ g.mol^{-1}) ? answ: 4.35×10^4 $J.mol^{-1}$.

   (b) Assuming that enthalpy is a state function, what is the relation between the enthalpy change for a forward process and the reverse process (i.e. vaporization and condensation) ?

   (c) Consider an arbitrary chemical reaction with stoichiometric coefficients ν_i. What is the enthalpy change associated with this reaction in terms of the molar enthalpy of the reactants and products ?

2. Consider a perfect gas undergoing isothermal expansion at temperature T between volume V_i and V_f. For a reversible process the amount of work done on the system is

$$w = -\int_{V_i}^{V_f} p dV \tag{15.23}$$

   (a) What the amount of heat q_{rev} supplied to the system ? hint: first law of thermodynamics.

   (b) Use the thermodynamic relationship

$$\Delta S = \frac{q_{\text{rev}}}{T} \tag{15.24}$$

   and compute the change in entropy for the gas.

(c) The entropy is state function. Use the entropy of mixing to evaluate the change of entropy and compare your result with the preceding question.

(d) Assume that the heat capacity is contant over the range of temperature of interest. Using (**??**), show that

$$\Delta S = C_p \ln \frac{T_f}{T_i} \tag{15.25}$$

(e) Discuss why $\Delta S > 0$ if $T_f > T_i$.

(f) Can you guess why the temperature appears in the denominator of (**??**) ?

3. Suppose that we had a tiny system of 4 molecules A, B, C, D that could occupy threee equally spaced levels of energy 0, ϵ, and 2ϵ. We know that the total energy of the system is 4ϵ.

(a) Make explicit with an energy diagram some of the 19 possible combinaisons.

(b) What is the entropy of this system ?

(c) Assume that the total energy is proportional to the temperature T. What happens if we increase the temparature ? What happens if $T = 0$?

(d) Residual entropy: For some substances, the entropy is greater than zero at $T = 0$. Calculate the residual entropy for a gas of N molecules which can occupy two positions.

15.9 Langmuir-Hill function: Ligand recognition

As a biological case with very broad applicability, we start by considering binding problems in which several different molecular species can exist either separately or in complexes. The simplest receptor-binding system can exist in one of the two microstates: bound and unbound, see Fig. **??**.

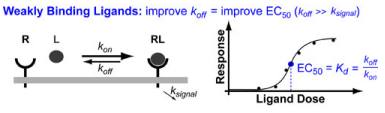


Figure 15.13:

To calculate the probability p for a receptor of being bound to a ligand, we observe that the fraction ϕ is nothing but this probability per unit area At equilibrium, the generalized force to transfert molecules from one state to the other one $\mu_0 - \mu$ is equal to zero:

$$\mu = \mu_0 \tag{15.26}$$

which means

$$-\epsilon + kT \ln \frac{\phi}{1-\phi} = \mu_0 \tag{15.27}$$

$$p = \frac{e^{(\mu_0 - \epsilon)/kT}}{1 + e^{(\mu_0 - \epsilon)/kT}} \tag{15.28}$$

Since the chemical potential which serve as a reference is equal to the chemical potential of the ligands in solution $\mu_0 = kT \ln l$, where l is the volume fraction of ligands in solution. Because l is proportional to the concentration of ligands L, the probability for

a receptor of being occupied depend on the concentration of free ligands as

$$p(l) = \frac{le^{-\epsilon/kT}}{1 + le^{-\epsilon/kT}} \tag{15.29}$$

or

$$p(l) = \frac{l/K_d}{1 + l/K_d} \tag{15.30}$$

where K_d is the equilibrium dissociation constant at which the receptor has a probability of being occupied of 1/2.

16
Surface Thermodynamics

Previous : particular case of a most general problem, i.e. adsorption on a surface. Now: How surface tension varies with particle/molecule adsorption ?

A colloidal system represents a multiphase (heterogeneous) system, in which at least one of the phases exists in the form of very small particles: typically smaller than 1 mm but still much larger than the molecules. Such particles are related to phenomena like Brownian motion, diffusion, and osmosis. The terms micro-heterogeneous system and disperse system (dispersion) are more general because they include also bicontinuous systems (in which none of the phases is split into separate particles) and systems containing larger, non-Brownian, particles. The term dispersion is often used as a synonym of colloidal system. Examples for gas-in-liquid dispersions are the foams or the boiling liquids. Gas-in-solid dispersions are the various porous media like filtration membranes, sorbents, catalysts and isolation materials.

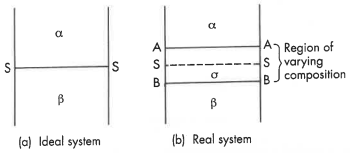


Figure 16.1: Representation of an interface between bulk phase α and β.

As a rule the fluid dispersions (emulsions, foams) are stabilized by adsorption layers of amphiphile molecules. These can be ionic and nonionic surfactants, lipids, proteins, etc. All of them have the property to lower the value of the surface (or interfacial) tension, σ, in accordance with the Gibbs adsorption equation

$$d\sigma = -\sum_i \Gamma_i d\mu_i \tag{16.1}$$

where

1. Γ_i is the surface concentration (adsorption) of the ith component.
2. μ_i is it chemical potential.

Note that if a species absorbs to a surface $\Gamma_i > 0$ and the surface tension decreases as the chemical potential of that species is increased.

Consider solute

$$\mu_2 = \mu_2^\theta + RT \ln c_2 \tag{16.2}$$

$$\Gamma_2 = -\frac{1}{RT} \frac{d\sigma}{d \ln c_2} \tag{16.3}$$

which means generally a strong decrease in the surface tension if we increase the bulk concentration.

16.1 Thermal fluctuations of interfaces: Fourier methods

Fourier methods are based on representing arbitrary signals as weighted sums of complex sinusoids. They are intuitive, apply to a large class of interesting signal processing systems and physical effects, and numerical Fourier analysis can be performed very efficiently. Here we want to characterize the thermal fluctuations of interfaces in terms of Fourier components.

Remind that an interface separates two phases, e.g. liquid-gas and has a width. This width is typically of molecular size. We are interested in phenomena which occur in a typical length scale much larger than the typical width of the interface. For example, the shape of the interface may experience sinusoidal variations due to thermal fluctuations with a wave length much larger than this width. In this limit the interface may be seen as infinitely thin. The interface is, therefore, seen as a mathematical surface with a free energy proportional to its area.

$$F = \sigma \times \text{Area} \tag{16.4}$$

where σ is the surface tension. To represent the surface, we use the following representation for the position vector

$$\text{Position vector} = (x, y, h(x, y)) \tag{16.5}$$

where the height $h(x, y)$ is the coordinate of a point along the z direction. $h(x, y)$ is a function of the other coordinates. For a finite interface along the x and y directions

$$0 \leqslant x \leqslant L \quad \text{and} \quad 0 \leqslant y \leqslant L \tag{16.6}$$

Without loss of generality, we will assume that the surface is clamped along a frame.

The area of the surface is given by

$$\begin{aligned} A &= \iint_{0 \leqslant x,y \leqslant L} dxdy \sqrt{1 + (\partial_x h)^2 + (\partial_y h)^2} \\ &= L^2 + \frac{1}{2} \iint_{0 \leqslant x,y \leqslant L} \left[(\partial_x h)^2 + (\partial_y h)^2 \right] \end{aligned} \tag{16.7}$$

where we have assumed that the height $h(x, y)$ and the derivates are small. The interface fluctuates if $h(x, y)$ is not a constant. In this case, there is an excess in free energy equal to

$$\Delta F = \frac{\sigma}{2} \iint_{0 \leqslant x,y \leqslant L} dxdy \left[(\partial_x h)^2 + (\partial_y h)^2 \right] \tag{16.8}$$

We want to calculate the average of $< \Delta F >$ when the interface is subjected to thermal fluctuations which make $h(x, y)$ random

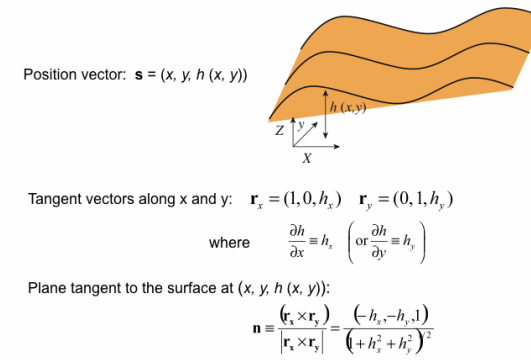


Figure 16.2: Monge representation of a surface.

variables. In particular, we want to calculate the mean-squared fluctuation

$$< h(x,y)^2 > \tag{16.9}$$

Forget for the moment about the y direction. Then $h(x)$ is only a function of the x coordinate. In Fourier coordinates we define

$$h(x) = \frac{1}{\sqrt{L}} \sum_q e^{iqx} \tilde{h}_q \quad q = 2\pi n/L \quad n = 0, 2, \ldots, L-1 \tag{16.10}$$

Exercice 16.1 *1. Show*

$$\tilde{h}_l = \frac{1}{\sqrt{L}} \int_0^L dx\, h(x) e^{-ilx} \tag{16.11}$$

2. Show

$$\Delta F = \frac{\sigma}{2} \sum_q q^2 |\tilde{h}(q)|^2 \tag{16.12}$$

3. By analogy with a spring, show that

$$|\tilde{h}(q)|^2 = \frac{kT}{\sigma q^2} \tag{16.13}$$

In two dimensions, q in the Fourier transform is a vector

$$\mathbf{q} = q_x \hat{u}_x + q_y \hat{u}_y \tag{16.14}$$

where $\hat{u}_x$ and $\hat{u}_y$ are unit vectors along the x and y direction. The definition of the Fourier transform is

$$h(x,y) = \frac{1}{\sqrt{L^2}} \sum_q e^{i\mathbf{q}\cdot\mathbf{r}} \tilde{h}_q \quad \mathbf{r} = x\hat{u}_x + y\hat{u}_y \tag{16.15}$$

and the same result as in Eq. (**??**) holds.

Exercice 16.2 *Show*

$$\begin{aligned} \Delta F &= \frac{kT}{2\sigma} \sum_q < |\tilde{h}(q)|^2 > \\ &= \frac{kT}{2\pi\sigma} \int_{2\pi/L}^{2\pi/a} \frac{dq}{q} \\ &= \frac{kT}{2\pi\sigma} \ln(L/a) \end{aligned} \tag{16.16}$$

This result shows that the mean square fluctuations diverge with the system size.

Exercice 16.3 *For typical values ($\sigma = 100 dyne/cm^2$ with $1 dyne = 10^{-5} N$, $a = 3$ and $L = 1 cm$) what is the value of the"divergence". Gravity acting in the z-direction, explain why we can introduce a gravitational energy per unit area $\rho g h^2$ and show that this divergence disappears.*

16.2 Ratchets

17
The geometry of curvature: A quick reminder

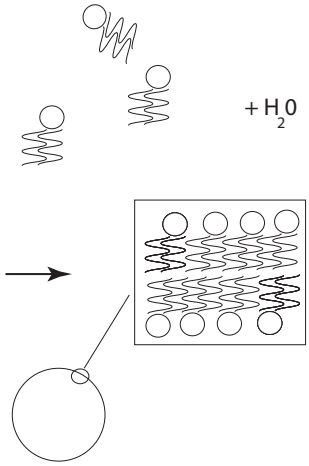


Figure 17.1:

In this chapter, we introduce what we mean by curvature. Curvature is one of the most important concept in differential geometry and we shall use this language to characterize both vesicle shapes and membrane fluctuations.

Differential geometry is a field of mathematics which describes surface embedded in a 3 or more dimensional space, i.e; varieties. One may wonder why this language is adapted to colloidal structures. One answer is that membrane are characterized by two very different length scales. On the one side, the bilayer is only 50 Åthick. On the other side, a typical vesicle has a radius of 20 μm. This huge separation of length scales allows us to see a bilayer as a thin sheet. Surfaces are, therefore, an abstract concept well adapted for our modeling.

The concept of curvature is useful if we want to understand the concept of bending energy. When small vesicles change their shape, there is a gain or a cost in bending energy. The bending energy is very different from surface energy of surfactant monolayers interface which proportional to the area of the interface. As we will see shortly, we can have highly bend surfaces without cost of energy.

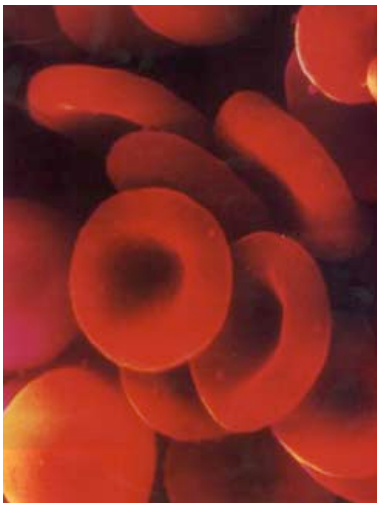


Figure 17.2: Healphy red blood cells have a biconcave shape that is explained by curvature energy

Example 17.1 *Assume for the moment that the bending energy of a sphere with a radius R is proportional to $1/R^2$. Then its total bending energy is integrated over the total area*

$$E_{bend} = \frac{1}{2}\kappa \times 4\pi R^2 \times \frac{1}{R^2} = 2\pi\kappa \tag{17.1}$$

where the factor $1/2$ is a numerical convention and where κ is a constant which is material dependent. We will explain why the bending energy per unit of area is the square of the inverse of the radius of the sphere. We see that the cost of bending is scale invariant. A small or a large sphere have the same energy.

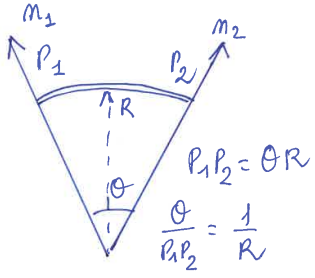


Figure 17.3:

17.1 The geometry of a plane curve

We proceed by introducing the curvature. Let t_1 and t_1 be the tangents, n_1 and n_2 the normals, at two neighboring points P_1 and P_2. Let he intersection of the normals be at M. Clearly, the angle

between the tangent is equal to the angle between the normal

$$\angle(t_1, t_2) = \angle(n_1, n_2) \tag{17.2}$$

Let P_2 approaches P_1 along the curve. In general, the ratio

$$\lim_{P_1P_2 \to 0} \frac{\angle n_1 n_2}{P_1 P_2} = \frac{1}{R} \tag{17.3}$$

approaches a limit. The ratio $1/R$ is called the curvature and the the factor R which has the dimension of a length is called the radius of curvature. This quantity is also defined in another way as follows. We consider the point P_1 and two neighboring points on the curve. These three points define a circle whose radius is R when the two neighboring pints approaches P_1.

At some exceptional points, the radius of curvature may be infinite. At these points, the circle of curvature degenerates into a straight line and is thus identical with the tangent. At such point the tangent crosses the curve, so that the point is a point of inflection.

A curve has two natural or intrinsic coordinates. The first is the arc length which measures the distance along the curve starting at one arbitrary point. The second is the curvature. The only line of constant curvature is the circle.

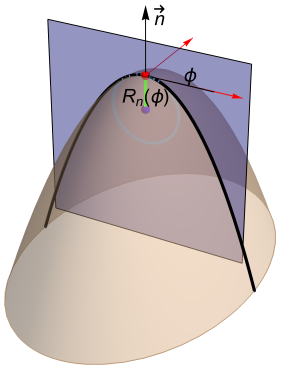


Figure 17.4:

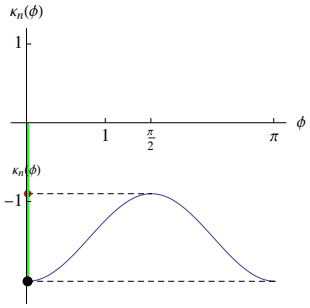


Figure 17.5:

17.2 *The geometry of a 2d-surface embedded in 3d*

At each point P, we can elevate a normal vector $\mathbf{n}$. Any plane which contain the normal vector intersects the surface along a curve $\mathcal{C}$. Since this curve is planar, we know how to calculate the radius of circle tangent to $\mathcal{C}$ at P. Call R the radius of curvature. If we now rotate the plane by an angle ϕ around the normal $\mathbf{n}$, the radius $R(\phi)$ becomes a function of ϕ. For different ϕ values, it has a maximum and a minimum, since it is a periodic function of ϕ with the symmetry $\phi \to -\phi$.

The general formula whose derivation we will omit here for the curvature of the normal section is the the follwing formula found by Euler:

$$\frac{1}{R} = \frac{\sin^2\phi}{R_1} + \frac{\cos^2\phi}{R_2} \tag{17.4}$$

where R_1 anf R_2 are the radius of curvature when $\phi = 0, \pi/2$ (principal axes).

Let us call H the mean curvature :

$$\begin{aligned} H = & \frac{1}{2}\left(\frac{1}{R_{max}} + \frac{1}{R_{min}}\right) \\ = & \frac{1}{2}\left(\frac{1}{R_1} + \frac{1}{R_2}\right) \end{aligned} \tag{17.5}$$

for any directions 1, 2 perpendicular to each other. Eq. (**??**) has two important features :

- There are two radii of curvature for a surface instead of one for a line: There are two possible directions in the tangent plane.
- Radii of curvature have sign and it is possible to construct minimal surfaces where $H = 0$ everywhere. Both radii of curvature are small but they have opposite sign so that the mean curvature is zero (see Fig. **??**)

How do we determine the value and the sign of the two radii of curvature ? We need to parametrize the surface and our energy must be independent on our parametrization (the energy must be the same if we use polar and rectangular coordinates) and independent on what we call the exterior and the interior. For a sphere, the volume enclosed by the envelop is usually called the interior. But this definition is arbitrary and if exchange the role of exterior and the interior, then the radii of curvature changes sign. Our energy must however be independent of this convention.

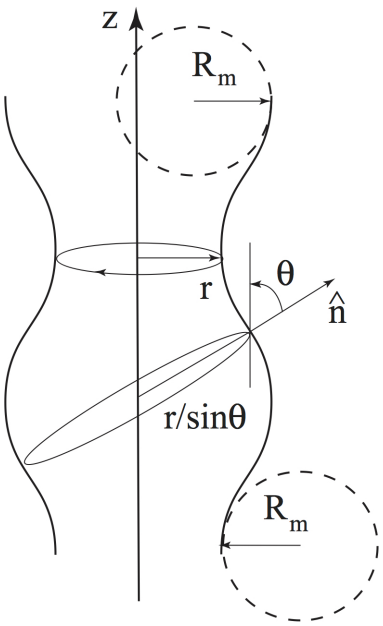


Figure 17.6: Example a constant curvature surface with symmetry of revolution. Revolving a curve around the z-axis gives a surface where each point has coordinate (r, z). The circles with radius R_m correspond to the curvature along a meridian. Note that the center of these circles can be on both sides of the surface (so that the mean curvature changes sign). The curvature along a parallel is shown by the inner circle of radius $r/\sin\theta$ with a center lying on the z-axis. This example is the only non-trivial constant mean curvature (i.e. $H = cst. > 0$) surface of symmetry of revolution (Delaunay surfaces).

17.3 *Application of the concept of curvature to the elasticity of surfactant layers*

From what we have previously discussed, the interesting concept is the mean curvature:

$$H = \frac{1}{R_1} + \frac{1}{R_2} \tag{17.6}$$

which is a quantity which varies as one moves along the surface. The sign of this H is a matter of pure convention. For a vesicle, what we call inside and outside is arbitrary. However, if we change convention, the sign of H changes. But the energy cannot change. It is the same to say that if we bend a surface upwards or downwards, the energy cost will be the same. Therefore the bending energy of a vesicle depends on the square of the mean curvature and we will write

$$E_{bending} = \frac{1}{2}\kappa \iint dS\ (2H)^2 \tag{17.7}$$

where κ is the bending constant which is phospholipid dependent. The following exercice helps to understand why the dimension (1D, a wire, or 2D, a surface) is crucial for the bending energy as a function of the scale of the object.

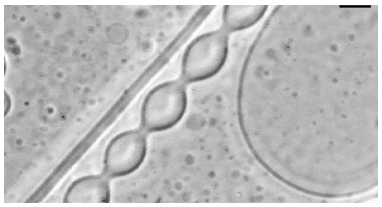


Figure 17.7: Confocal image of an artificial vesicle made of phospholipids. Note that the resemblance between these Myelin shapes and the Delaunay surface is striking.

Exercice 17.1 *1. Consider a rope of length $2\pi R$ bend into a circle with radius of curvature R. What is the bending energy ?*

2. Consider a spherical vesicle. What is the bending energy of this vesicle ? How does it scale with R ? Compare with te first question and discuss the effect of dimensionality.

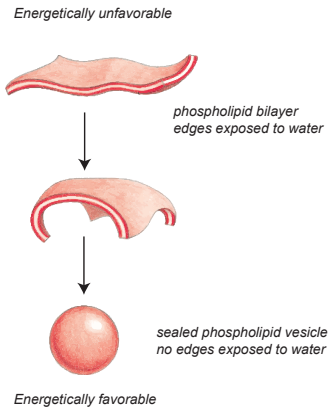


Figure 17.8:

The following explains why curvature is important for thin shell elasticity.

One the most fundamental application of the concept of curvature is the variation of an elementary area as one moves along the normal at one point on a reference surface.

Let us consider such a point P on an arbitrary surface with normal n. A neighborhood of P has a surface element dA. If ϵ is a small number, we can construct a new surface element as follows. To each point in the neighborhood of P, let us move by a distance ϵ along the normal. This application maps the all points in the neighborhood of P to only one point in the neighborhood of P' image of P. The new neighborhood has an area dA'.

To simplify the notations, we define $c_1 = 1/R_1$ and $c_2 = 1/R_2$. We have

$$dA' = dA\left(1 + \epsilon(c_1 + c_2) + \epsilon^2 c_1 c_2\right) + O(\epsilon^3) \tag{17.8}$$

where the $O(\epsilon^3)$ means that all other therms are negligible.

Exercice 17.2 *Demonstrate this formula in the case where the surface is a sphere*

Eq. (**??**) is at the heart of all elastic theories of surfactant monolayers and bilayers[1]. For a monoloyer of thickness l, the free energy PER MOLECULE is the sum of three contributions

[1] See I. Szleifer et al, J. Chem Phys, 92, 6800, 1990

$$f = \underbrace{f_{tail}}_{\text{Entropic tail}} - \underbrace{\int_0^l \pi(x)a(x)dx}_{\text{Lateral compressibility}} + \underbrace{f_{head}}_{\text{Head}-\text{head interaction}} \tag{17.9}$$

where the integral extends NORMAL to the interface. The second term include the work done to change the area per lipid at some distance x from a reference surface via the lateral pressure $\pi(x)$. The third is the contribution due the interaction between the head groups.

Using for the area per lipid at a distance x along the normal

$$a(x) = a(0)(1 + x(c_1 + c_2) + x^2 c_1 c_2) \tag{17.10}$$

gives a bending energy as a sum of two contribution integrated over the lateral surface of the whole monolayer.

$$\frac{1}{2}\kappa \iint dS(c_1 + c_2)^2 + \bar{\kappa} \iint dS c_1 c_2 \tag{17.11}$$

The elastic constant entering into (**??**) are function of the tensile stress along the normal. The bending modulus κ and the Gaussian modulus $\bar{\kappa}$ are macroscopic constants depending on different moments of the tensile stress

$$\kappa = 2a(0)\int_0^l x\pi(x)\,dx \tag{17.12}$$

$$\bar{\kappa} = a(0)\int_0^l x^2\pi(x)\,dx \tag{17.13}$$

This model assumes that the head group interaction gives no contribution to the bending modulus. Experiments show that this indeed the case. Only varying the length of the hydrophobic tails changes the bending modulus.

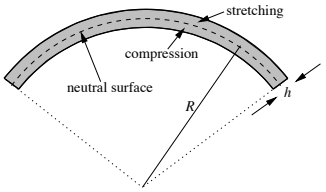


Figure 17.9: Figure 2: When a piece of material is bent, the outer side is stretched, while the inner side is compressed. Using our knowledge of the elastic behavior, we can thus predict its resistance to bending.

17.4 A toy model for the curvature energy

Let us assume that the energy per lipid molecule has the simple form of a Hook's energy

$$f = \frac{1}{2} k_s \left(l - l_s\right)^2 \tag{17.14}$$

The incompressibility of the chains implies that the volume v_0 occupied by the layer is constant. When the layer is flat, the volume is simply $a_0 l_s$. When the layer is bent, the volume occupied by a chain depends on curvature. To lowest order in l

$$v_0 = a_0 l \left(1 + \frac{l}{2}(c_1 + c_2)\right) \tag{17.15}$$

Exercice 17.3 *Demonstrate this formula using Eq.(**??**)*

Thus, the incompressibility condition relates the volume v_0 to the chain length l. When the curvature changes, the length l adjusts itself to keep the same volume v_0 per lipid.

Solving for $l(v_0)$, we get

$$l = l_s \left(1 - \frac{l_s}{2}(c_1 + c_2)\right) \tag{17.16}$$

We get the curvature energy per lipid.

$$f = \frac{k_s l_0^4}{8} \left(c_1 + c_2\right)^2 \tag{17.17}$$

To get the total energy of the monolayer, we can sum over the lipid

$$\sum f_i \tag{17.18}$$

or, more conveniently, introduce a surface density of lipids $\rho = \text{cst}$.

$$E = \frac{1}{2}\kappa \iint dS \left(c_1 + c_2\right)^2 \tag{17.19}$$

where the bending modulus κ is an elastic constant.

$$\kappa = \frac{1}{4} k_s l_0^4 \rho \tag{17.20}$$

Sometimes, it is useful to define the mean curvature at a point P of a surface

$$H = \frac{1}{2}\left(c_1 + c_2\right) \tag{17.21}$$

A crucial theorem states that the mean curvature does not depend on the way the surface is parametrized, i.e. on the way axes are labeled. We can use many different ways to parametrize the surface and we will always get the same result. Therefore, the curvature energy in **??** is a well defined quantity which does not care on the way we parametrize the problem.

17.5 A note on units

As other things, quantities have dimension : length, second or energy. For a surface, the bending constant appearing in (**??**) has the dimension of an energy, since the mean curvature has the dimension of 1 over length, the bending modulus has the dimension of an energy. Typically, the value of κ is about $30\,k_BT$.

Units depend on where you are coming from (chemist, biologists or physicists) but also on the problem at hand. We use the most convenient ones. A key idea in physics is to specify the units of things. Lengths are expressed in meters, times in seconds and Forces in Newton (N). These units are perfectly adapted to the macroscopic world. Using them to describe the microscopic world is very clumsy. In general, lengths are expressed in $\mu.m$ or $n.m$. Forces at the scale of the cell are in the range of the pico-Newton ($10^{-12}N$) to the nano-Newton ($10^{-9}N$) range.

By definition, the work done by a force is

$$W = force \times distance \tag{17.22}$$

Here is the table of conversion between the different units which seem appropriate at the scale of a cell :

$$12\,\text{kCal/mol} = 810^{-20}\text{J/molecule} = 0.5\,eV = 20\,k_BT \tag{17.23}$$

where k_BT is the standard unit used to describe thermal forces (T is the temperateure and k_B is the Bolzmann constant). We have

$$1\,k_BT = 4.1\text{pN.nm} \tag{17.24}$$

and k_BT is thus an appropriate unit, since forces are in the pico-Newton range and distances are in nanometer range.

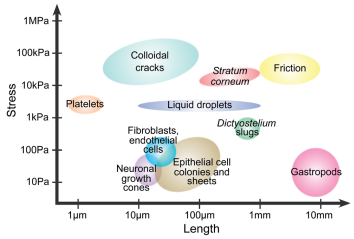


Figure 17.10: From R.W. Style et al., Soft Matter, 4047, 2014

17.6 The spontaneous curvature

For geometric raisons, we have seen that some amphiphilic molecules prefer to bend the interface. The curvature energy (**??**) is not appropriate. Because $(c_1 + c_2)^2$ is always positive, the minimum energy state is the one for which

$$c_1 + c_2 = 0 \tag{17.25}$$

This equation defines what people call a minimal surface , i.e. the shape of a soap film. The only minimal surfaces with symmetry of revolution are the planes and the catenoid.

If the surface is naturally bent, we will change our definition and will define the an energy as

$$E = \frac{1}{2}\kappa \iint dS\,(c_1 + c_2 - c_0)^2 \tag{17.26}$$

where c_0 is called the spontaneous curvature.

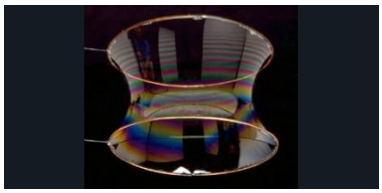


Figure 17.11: This surface is called the catenoid. See http://infima.ba/2012/02/05/the-geometry-of-soap-films-and-soap-bubbles/.

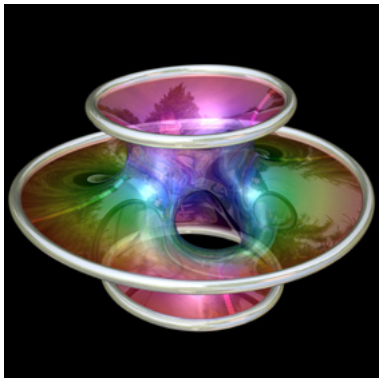


Figure 17.12: Costa minimal surface : see http://bugman123.com/MinimalSurfaces/index.html

17.7 *The Gaussian curvature*

We have seen that the mean curvature H, cf. (**??**) is invariant under reparametrization of the surface. there is also an other quantity independent on the way we decide to describe the surface. This quantity is the Gauss curvature, i.e. the product of the two inverses of the radii of curvature $c_1 c_2$.

For a CLOSED surface, it took Gauss to understand and to demonstrate that this quantity when integrated over the surface is a constant

$$\oint dS\, c_1 c_2 = 4\pi(1-g) \tag{17.27}$$

What do we mean by that ? Take a sphere, an ellipsoid or any surface with no hole, you will get always te same result. The integrated Gauss curvature depends only on the genius of the surface. For the torus torus pictured aside, the result will differ from the sphere. The torus has a hole, but the result will not differ if we displace the hole out of center. For this reason, the Gaussian curvature is not an appropriate way to gauge energy changes. This is however a way to characterize changes in topologies.

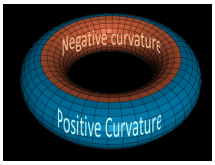


Figure 17.13: A torus.

18
Bilayer elasticity : The example of vesicles

18.1 The different meanings of surface tension

There are different meanings for what we call "surface tension". We read the following in Wikipedia : "At liquid-air interfaces, surface tension results from the greater attraction of liquid molecules to each other (due to cohesion) than to the molecules in the air (due to adhesion). The net effect is an inward force at its surface that causes the liquid to behave as if its surface were covered with a stretched elastic membrane. Thus, the surface becomes under tension from the imbalanced forces, which is probably where the term "surface tension" came from."

This description is perfectly correct for an air-liquid interface where molecules diffuse continuously between the bulk and the interface. It can non only have an elastic origin, but it is also entropic per nature. The surface tension at the liquid-air interface will depend on the temperature.

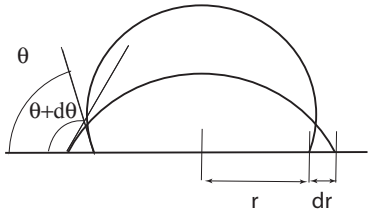


Figure 18.1: The surface tension fixes the angle of contact between a drop and a substrate.

The situation we have in mind for vesicles is rather different. There is no exchange between the bilayers and the surrounding medium. On the time scales of experiments, the number of phospholipids on the vesicle surface is therefore constant. The only way to change the area is to stretch tangentially the bilayer, i.e. to change the area per lipid headgroup. This stretching energy has the form

$$f_{\text{stretch}} = \frac{1}{2}\sigma\left(\frac{a}{a_0} - 1\right)^2 \tag{18.1}$$

and the constant σ is a surface tension like term. For vesicle stretching is very dangerous. The bilayer lyses quite easily and the variations of area per lipid headgroup are small if the vesicle keeps its integrity. The total area of a vesicle is thus constant.

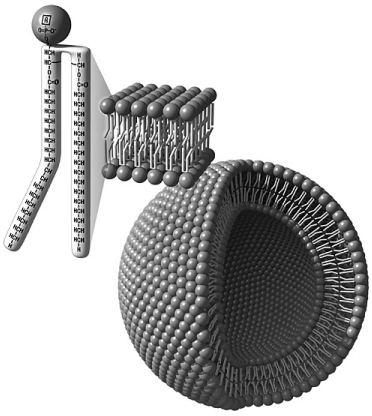


Figure 18.2: Cartoon of a giant vesicle whose size is about 20 μm. The thickness of the bilayer is very small compared to the size of the vesicle. There is no exchange of lipids between the solution and the bilayer. Flip-flop of molecules between the two leaflets is also rare. Vesicles adopt a shape optimizing a curvature energy with the constraint of constant surface and volume.

18.2 Mechanisms for bending

There are two main approaches. If a lipid bilayer consists of two identical monolayers, it tends to remain flat; because its structure is symmetrical with respect to the mid-plane, there are no physical reasons for it to bend in any direction. So, a straightforward way to

cause membrane bending is to create bilayer asymmetry. The second approach is to impose physical constraints on the membrane, such as frames or scaffolds that enforce bilayer curva- ture. Both lipids and proteins can be used to implement each of these two strategies [1]

Bilayer asymmetry can be achieved by generating a difference in the lipid compositions of the two monolayers. Lipid molecules of different kinds can be seen as the elements of a mosaic, with various shapes similar to cylinders, cones or inverted cones. If, for example, there are more inverted cone-like molecules in the outer monolayer than in the inner monolayer, the bilayer will tend to adopt a concave shape . Alternatively, asymmetry can be created by introducing more lipid molecules into one monolayer than in the other. The membrane will then bulge in the direction of the monolayer that has the larger number of molecules. Proteins can generate membrane asymmetry by inserting their hydrophobic domains into the lipid bilayer matrix on one side of a membrane, causing the membrane to bulge towards the affected monolayer. Most membrane-bound proteins have the potential to do this, because they already have hydro- phobic domains inserted into membranes to anchor themselves. A theoretical analysis6 of this hydrophobic insertion mechanism has revealed that the largest membrane curvatures are generated by shallow insertions that penetrate the external membrane monolayer only to about a third of its thickness. Common protein domains, such as amphipathic α-helices (which contain both hydrophobic and hydrophilic parts) and short hydrophobic loops, induce membrane curvature in this way, and are predicted to be much more effective than lipids in doing so.

[1] Michael Kozlov. Nature, 463, 439, 2010.

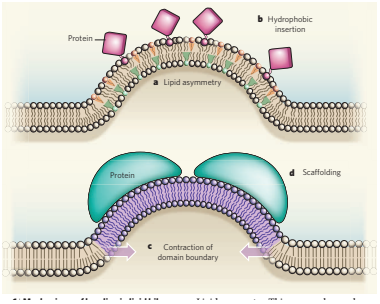


Figure 18.3: Lipid asymmetry. (a) This occurs when each monolayer is enriched with lipid molecules of different shapes (such as the orange and green molecules shown) and/or when one monolayer contains more lipid molecules than the other. (b)Proteins cause membrane asymmetry by inserting their hydrophobic domains into one side of the bilayer. (c) When bilayer matrices contain domains consisting of different lipid phases (such as the ordered (brown) and disordered (purple) regions shown), the boundaries between the domains tend to contract, causing the intervening region to bend. (d), Finally, proteins bound to the bilayer can act as scaffolds that force curvature on the membrane.

18.3 Curvature energy and constraints

Since the membrane is permeable to water, one might expect that the volume of the enclosed fluid can adjust freely. However, if additional molecules are present in the aqueous solution such as ions or impurities, which cannot move through the membrane, any net transfer of water will lead to an osmotic pressure. Typically, such a pressure is huge on the scale of the bending energy. A small variation of volume will led to a large osmotic stress that the vesicle cannot sustain. The only way to keep its closed shape is to allow only tiny changes in volume. Consequently, the enclosed volume is essentially fixed by the number of enclosed, osmotically active molecules and by the concentration of these molecules in the exterior fluid through the requirement that the osmotic pressure is essentially zero.

In summary, the shape of a vesicle minimizes a curvature energy

$$\frac{1}{2}\kappa \iint dS\ (c_1 + c_2 - c_0)^2 \tag{18.2}$$

with the two constraints :

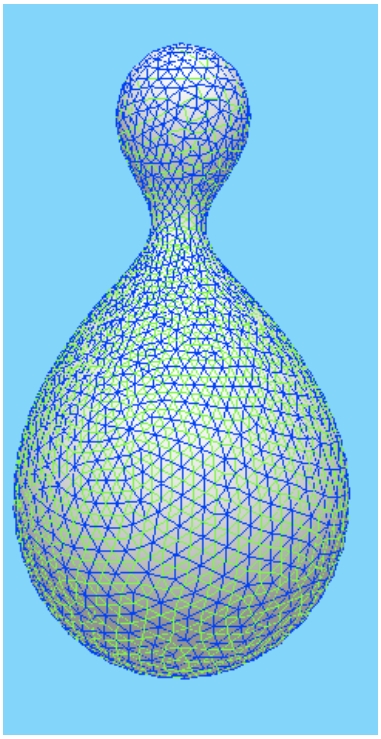


Figure 18.4: A numerical shape of a vesicle showing a bud

1. Given volume.
2. Given total area.

Exercice 18.1 *The volume of a sphere is $4\pi R^3/3$and its area is $4\pi R^2$. Consider a vesicle with an arbitrary shape and we define the radius of the equivalent area sphere, i.e. $A = 4\pi R_0^2$. Define the parameter*

$$v = V/[4\pi R_0^3/3] \tag{18.3}$$

1. *What is the shape of vesicle if $v = 1$. In general, do we have $4\pi R_0^3/3 > V$ (why ?) or $v < 1$.*
2. *Assume a large enough spontaneous curvature. Imagine an experimental setup where you can increase the area while keeping the volume constant. What could happen ? See Fig.* **??**.

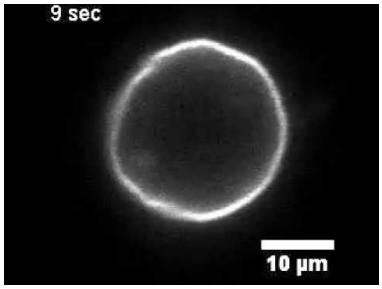


Figure 18.5: Effect of thermal fluctuations on vesicle shapes

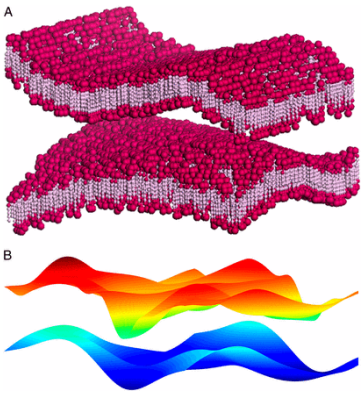


Figure 18.6: Two fluctuating bilayers with their abstract representation. The two membrane bump onto each other and this creates a repulsive force between the two membranes. The strength of this repulsive interaction can be of the same order of magnitude than the Van der Waals forces which is an attractive force.

18.4 A note on thermal fluctuations

For typical vesicles, the bending modulus is of the order of $\kappa \approx 25\, k_B T$. This does not mean that the shapes do not experience any random undulations due to thermal fluctuations, see figure on the side. Thermal fluctuations are very difficult to analyse in spherical geometries. For almost plane membranes, it is much more easy to analyse. We will discuss two effects during the lecture.

1. Entropic forces and entropic pressure for a membrane bumping into a wall.
2. Entropic surface tension effects for a fluctuating membrane.

18.5 Micropipette experiments

We study the mechanical properties of living cells in order to understand their response to stress in the circulation and the tissues. For example, by characterizing the response of white cells to an applied pressure we learn how these cells flow through the smallest vessels of the body and migrate within tissue to sites of infection. In addition, by measuring the response of cells to applied forces and stresses, we learn about the underlying structure of a cell. Does it behave like a liquid or a solid? What molecular structure is responsible for its behavior? How do mechanical and chemical stimuli alter its behavior? How do we study and measure the mechanical properties of the cell ?

The cell must be deformed in some way by a known force or stress and its deformation must be measured.

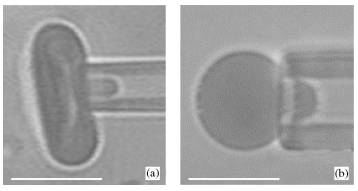


Fig. 6. Aspiration of a flaccid (a) and swollen (b) red cell into a pipette. The diameter of the flaccid red cell is approximately 8 µm and that of the swollen cell is about 6 µm. The scale bars indicate 5 µm.

Figure 18.7:

19
Diffusion: Macroscopic theory

A useful reference for this chapter is the book of H. Berg.

19.1 Einstein Diffusion equation

We start with Fick's law in d-dimensions

$$\frac{\partial c}{\partial t} = D\Delta c \tag{19.1}$$

where $c(\mathbf{x})$ is a concentration and D is the diffusion constant with the dimension length^2/time. The Laplacian is an operator with

$$\Delta c = \sum_{i=1,d} \frac{\partial^2 c}{\partial x_i^2} \tag{19.2}$$

This equation results from a conservation law and is derived in two steps. First, we define a current $\mathbf{j}$ with

$$\frac{\partial c}{\partial t} + \nabla \cdot \mathbf{j} = 0 \tag{19.3}$$

and we assume that the current is proportional to the gradient of c

$$\mathbf{j} = -D\nabla c \tag{19.4}$$

where the minus sign tells us the current will flow down the gradient. Fick's law is valid for concentrations which have been averaged over many realizations. In other words, it is valid for situations where we can neglect fluctuations. Here, we want more. We want an equation for the probability itself.

To derive such an equation we go back to the random walk problem. For typographic reasons we will consider the $1d$ case where sites are labeled by integer x_i. Remember that the walker steps with equal probability $1/2$ to right or to the left at each time step. He (or she !) never stays at rest. A realization (a sample) of the r.w. is the series $\{x_1, x_2, \ldots, x_{N-1}\}$ for the positions at successive times. Let $P(x_N, t_N)$ be the probability that the position x equal x_N after N steps, knowing that the r.w. started at the origin. Since he (or she) never stops walking, this means that $x = x_N \pm a$ at time t_{N-1}, where a is the step size. Or,

$$\begin{aligned} &P(x_N, t_N) = \\ &\frac{1}{2}\left[P(x_N - a, t_{N-1}) + P(x_N + a, t_{N-1})\right] \end{aligned} \tag{19.5}$$

This equation is a recurrence equation for the probability and is known as a Master equation. We solve this equation by subtracting $P(x_N, t_{N-1})$ on both sides and dividing by Δt (the time interval between successive steps)

$$\frac{P(x_N,t_N)-P(x_N,t_{N-1})}{\Delta t} = \frac{1}{\Delta t}[P(x_N-a,t_{N-1})+P(x_N+a,t_{N-1}) - 2P(x_N,t_{N-1})] \tag{19.6}$$

We will take the "hydrodynamic" limit where

1. a is much smaller than all macroscopic lengths we will be interested in.
2. Δt is also much smaller than all macroscopic times but larger than microscopic times (random forces are correlated at microscopic times).

In other words, we will separate the fast and the slow variables. In this regime, the variable x_i become a continuous variable and

$$\frac{P(x_N,t_N)-P(x_N,t_{N-1})}{\Delta t} = \frac{\partial P}{\partial t} \tag{19.7}$$

with

$$P(x-a) = P(x) - a\frac{\partial P}{\partial x} + \frac{a^2}{2}\frac{\partial^2 P}{\partial x^2} \tag{19.8}$$

$$P(x+a) = P(x) + a\frac{\partial P}{\partial x} + \frac{a^2}{2}\frac{\partial^2 P}{\partial x^2} \tag{19.9}$$

so that the discrete master equation is correctly approximated in the hydrodynamic limit by a continuous process obeying a diffusion equation

$$\frac{\partial P}{\partial t} = \frac{a^2}{2\Delta t}\frac{\partial^2 P}{\partial x^2} \tag{19.10}$$

where $D = a^2/2\Delta t$ is a finite constant. This equation can be generalised to arbitrary d dimensions and must be supplemented by appropriate boundary conditions. We conclude that the conditional probability $P(x, t|x = 0, t = 0)$ obeys a diffusion equation.

Exercice 19.1 *Gaussian solutions:*

1. *Show that $D = a^2/(2d\Delta t)$ in d dimensions.*
2. *Show directly that*

$$P(x) = \frac{1}{\sqrt{2\pi\sigma^2}}\exp\left\{\left[-x^2/(2\sigma^2)\right]\right\} \tag{19.11}$$

with $\sigma = 2Dt$ is solution of the diffusion equation in 1 dimension.

3. *Show*

$$P(x) = \frac{1}{(4\pi Dt)^{d/2}}\exp\left\{\left[-x^2/(4Dt)\right]\right\} \tag{19.12}$$

in arbitrary d dimensions.

Exercice 19.2 *Scaling. Scaling arguments are very helpful to get the solutions of problems without solving differential equations. Here is an example. You have been asked to cook the dammed chicken. It takes* $1h\,15\,mn$ *to cook a* $1.2\ kg$ *chicken. Yours weights* $2\ kg$*. What is the cooking time in your case ? (hint : Scale the diffusion equation to have the same temperature profile for both chickens. You can assume that the chicken has spherical symmetry.)*

It is common to work in different coordinate systems. In polar coordinates, we have:

$$\begin{aligned}\Delta f = &\quad \frac{1}{r}\frac{\partial}{\partial r}\left(r\frac{\partial f}{\partial r}\right) + \frac{1}{r^2}\frac{\partial^2}{\partial \theta^2} \quad \text{2-d}\\ \Delta f = &\quad \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial f}{\partial r}\right) + \frac{1}{r^2\sin\theta}\frac{\partial}{\partial \theta}\left(\sin\theta\frac{\partial f}{\partial \theta}\right)\\ &\quad + \frac{1}{r^2}\frac{\partial^2}{\partial \phi^2} \quad \text{3-d}\end{aligned} \tag{19.13}$$

19.1.1 FRAP experiments

FRAP was developed in the 1970s as a technique to study protein mobility in living cells by measuring the rate of fluorescence recovery at a bleached site. The FRAP technique originally found success as a method to measure diffusion in cellular membranes [42,43]; however, the recent advent and availability of both fluorescent protein technology and confocal microscopy have led to a marked increase in the use of FRAP for studying protein mobility in the cell interior. The scope of these studies has expanded not only to address diffusion rates, but also to assess protein dynamics and interactions with other cellular components . FRAP has now been adopted as a common technique for studying almost all aspects of cell biology, including chromatin structure, transcription, mRNA mobility, protein recycling, signal transduction, cytoskeletal dynamics, vesicle transport, cell adhesion and mitosis.

Commonly, FRAP results are analyzed qualitatively to determine whether protein mobility is rapid or slow, whether binding interactions are present, whether an immobile fraction exists, or how a particular treatment (such as ATP depletion or a mutation in the protein of interest) affects these properties. Several mathematical models have been also developed to understand better the underlying processes, to ensure the accuracy of a qualitative interpretation, and to extract quantitative parameters from a FRAP curve.

Exercice 19.3 *In a typical Frap experiment, one bleaches a spot of size R. Use dimensional analysis to guess the characteristic time scale of typical Frap recovery curve.*

Two limit cases will be discussed during the lecture:

1. Diffusion-limited.
2. Reaction-limited where the recovery depends on the off rate of a reaction (diffusion is assumed to be very fast)

Figure 19.1:

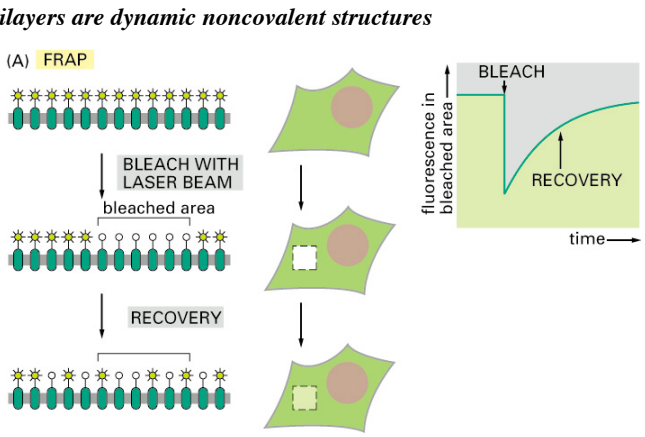


Figure 10–40 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

Exercice 19.4 *We consider a Frap experiment for a single binding reaction*

$$F + S \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} C \tag{19.14}$$

where F *represents free proteins,* S *represents vacant binding sites,* C *bound* [FS] *complexes.*

1. *What are the equations describing the binding reactions (including reaction) ?*
2. *What is the concentration F_{eq} ?*
3. *Assume that diffusion is very fast and that vacant sites are in excess. How do you simplify these equations ?*
4. *We define* k_{on}* *Show that these equations reduce to*

$$\frac{dc}{dt} = k^*_{on} F_{eq} - k_{off} c(t) \tag{19.15}$$

5. *The frap recovery data is the sum of the bound and free fluorescence. Conclude that the intensity recovers as*

$$I(t) = 1 - \exp\left\{\left[-k_{off} t\right]\right\} \tag{19.16}$$

19.2 *Boundary conditions for the diffusion equation*

Eq. (**??**) is a partial differential equation and it makes no sense to find a solution without specifying the boundary conditions. Assume that we are interested in solving (**??**) on a domain $\Omega = [0, L]^d$. These are as follows:

1. One must specify the initial conditions at $t = 0$ over the domain of interest.
2. One must specify "something" (the value of c or the current) at the boundary of this domain.

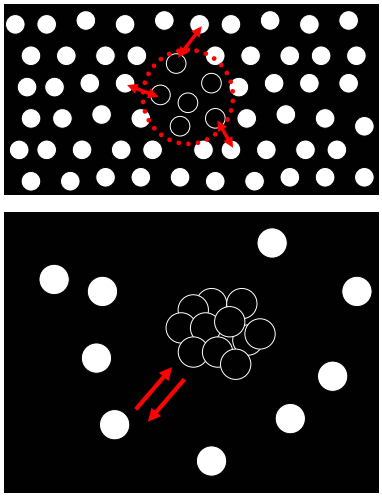


Figure 19.2: (a) Frap can occur without specific interaction. Simply the diffusion drives the exchange of molecules between the bleached and the non-bleached area. (b) Cluster of molecules. There is a contnuous exchange between the bound and the un-bound molecules. If we bleach the cluster, the molecules inside the cluster loose fluorescence.

Changing one of these conditions completely alters the solution and the physical consequences ! Here are some of the most popular boundary conditions for stationary solutions:

1. We fix the values of $c(\mathbf{x})$ on the boundaries of Ω (i.e. $c(0) = c(L)$ are given). If $c = 0$, the boundary are absorbing. All the walkers crossing the boundaries disappear (think of a random walk on a roof: if you hit the border, you get out of the system !)

2. We fix the outward current $dc/d\hat{\mathbf{n}}$[1]. If $dc/d\hat{\mathbf{n}} = 0$, there is no current. The boundaries are perfectly reflecting walls.

[1] $\hat{\mathbf{n}}$ is the outward normal at the boundary of Ω and $dc/d\hat{\mathbf{n}} = \hat{\mathbf{n}} \cdot \nabla c$.

19.3 An example of first passage probability: The gambler ruin problem

Consider a random walk on a finite interval of length N. The two boundary sites are absorbing, i.e. the random walker immediately disappears upon reaching these sites. Suppose that the starting position of the random walk is n, with $0 \leqslant n \leqslant N$. What is F_n, the probability that the walker first reaches the boundary at site N, i.e. without touching site number 0, first? We will write a simple recursion relation for F_n.

Exercice 19.5 *Consider the probability F_n.*

1. *What is F_0 and F_N ?*$(0, 1)$

2. *With probability $1/2$, the walk steps to site $n-1$ at which the probability to escape at site $n-1$ is F_{n-1}. Similarly, the walk steps at site $n+1$ with probability $1/2$. Show:*

$$F_n = \frac{1}{2}\left(F_{n-1} + F_{n+1}\right) \tag{19.17}$$

3. *Show $F_n = n/N$.*

This exit probability also represents the solution of the gambler ruin problem. In a casino, you continue to bet as long as you have money. Let n represent your wealth which that changes by a small amount ± 1 with equal probability by a single beat with the casino. You lose if your wealth hits zero and you break the casino is your wealth hits N (the total sum of your wealth and the one of the casino). This calculation shows that the probability to break the casino is n/N. Conclusion: Owning the casino is a good idea, gambling in the casino is a bad idea.

19.4 Diffusion limited chemical reactions

Exercice 19.6 *Consider a perfect adsorbing sphere of radius a[**?**]. A molecule is initially located at a distance r_0 of the center of the sphere. In this problem, we will ask this simple question: What is the probability*

$p(a, r_0)$ for the molecule to be adsorbed ? It will turn our the answer is simple. It is

$$p(a, r_0) = \frac{a}{r_0} \tag{19.18}$$

and not as a^2/r^2 as if the movement where ballistic (in that case, the result would be proportional to the cross-section). To answer to this problem, consider a sphere of radius $r_0 > a$ where the concentration is maintained at $c = c_m$. Assume that there is a second sphere of radius $b > r_0$ where the concentration is maintained at $c = 0$ (adsorbing conditions).

1. *Solve the stationary diffusion equation in the two regions with the appropriate boundary conditions. To solve this equation, pose $u(r, t) = rc(r, t)$ in the diffusion equation where r is the radial coordinate. What is the equation for $u(r, t)$?*
2. *Compute the current at $r = a$ and $r = b$.*
3. *Compute the total flux of particles through the spheres a and b.*
4. *What is the probability that a random walk starting at r_0 bump into a ? Same question for b.*
5. *Let $b \to \infty$ and recover (**??**).*

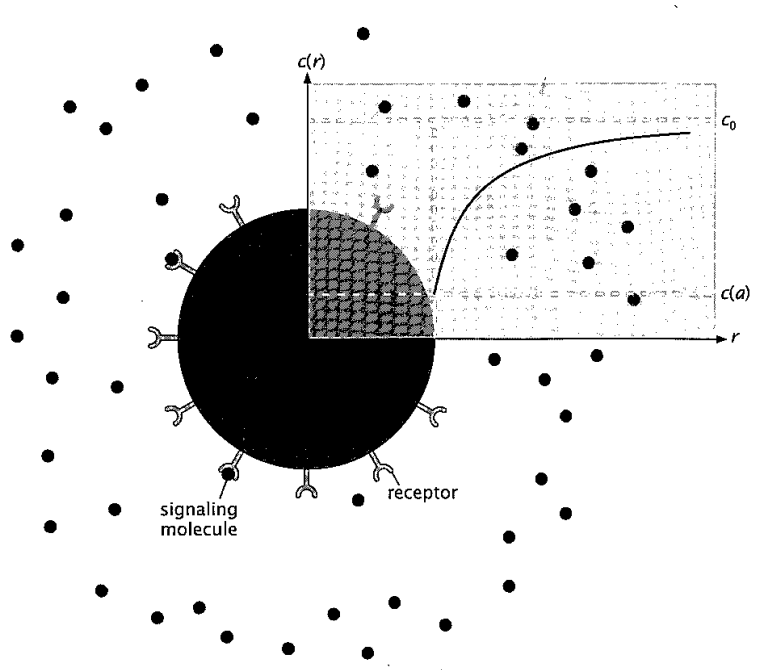


Figure 19.3: An absorbing sphere for a solute diffusing in the bulk. The concentration of solute decreases in the vicinity of the sphere. This depletion zone is characteristic of problem controlled by diffusion.

Exercice 19.7 *Consider the situation schematized in Fig. **??**. Assume that the concentration at $r \to \infty$ is maintained at c_0. The sphere of radius a is covered by sensors with surface density σ. The rate of uptake of solute molecules per unit surface is given by*

$$\frac{dn}{dt} = \sigma k_{on} c(a) \tag{19.19}$$

This equation defines k_{on} as the usual kinetic rate in chemical reaction.

1. *If M is the total number of receptors, give M as a function of σ.*
2. *Show that solution of the 3-d diffusion equation with symmetry of revolution is given by $c(r) = \beta + \alpha/r$.*
3. *Using mass conservation, show*
$$-4\pi r^2 J(r) = Mk_{on}c(a) \tag{19.20}$$
4. *Use the last equation to compute the concentration as*
$$c(r) - c(a) = \frac{Mk_{on}c(a)}{4\pi D}\left(\frac{1}{a} - \frac{1}{r}\right) \tag{19.21}$$
5. *Show*
$$c(a) = \frac{c_0}{1 + Mk_{on}/(4\pi Da)} \tag{19.22}$$
6. *Plot $c(r)$.*
7. *Deduce that the net adsorption rate is*
$$k = \frac{4\pi DaMk_{on}}{4\pi Da + Mk_{on}} \tag{19.23}$$
8. *Investigate the two limits of a perfect adsorber, $k_{on} \to \infty$, and of a bad adsorber, $k_{on} \to 0$. Conclude that the net adsorption rate can be written as*
$$\frac{1}{k} = \frac{1}{k_{on}} + \frac{1}{k_D} \tag{19.24}$$
where $1/k_D$ is a diffusion time which depends on the diffusion constant. Thus, our boundary condition together with the diffusion equations set two characteristic time scales. This is in contrast with the usual condition of perfect adsorption with only one time scale.

Remark 6 *The diffusion-limited rate constant $4\pi Da$ is the maximum rate constant which can be observed (unit is is $m^3.molecules^{-1}.s^{-1}$. In Molar unit, $[k_a] = M^{-1}$, this result reads as $4000\pi DaN$, where N is the Avogadro number and where all lengths are in dm.*

Exercice 19.8 *We consider the bimolecular reaction*
$$\mathrm{A} + \mathrm{B} \longrightarrow \mathrm{AB} \tag{19.25}$$
for which the concentrations usually evolve according to the law of mass action
$$\frac{d[\mathrm{AB}]}{dt} = k[\mathrm{A}][\mathrm{B}] \tag{19.26}$$
Usually, the on-rate k is independent of t. This will not be case here. We assume that an A *molecule and a* B *molecule react immediately to form a complex* AB *when they encounter each other within a reaction radius, so that the speed of reaction is limited by their encounter rate via diffusion. We consider the case of spherical target* A *of radius a ($d = 3$). One way to formulate the problem is an idealized first passage process, in which the A molecule is fixed while the B molecule diffuse around. Let $c(r, t)$ be the concentration of B molecules.*

The initial conditions and the boundary conditions are as follows

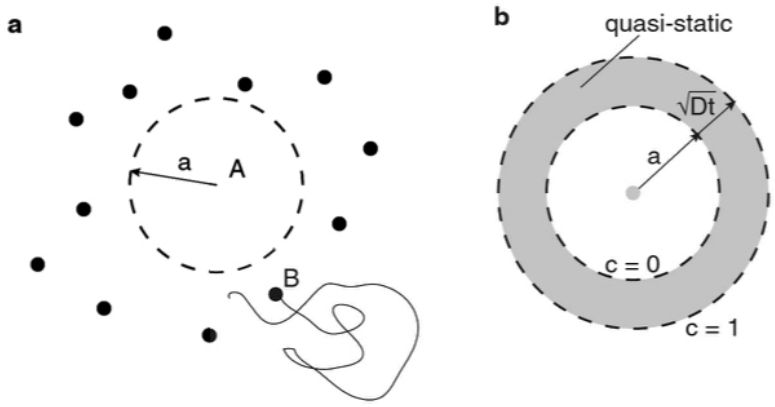


Figure 19.4: Diffusion limited reaction rate. (a) Diffusing molecules B in a neighborhood of a fixed target molecule A with reaction radius a. In (b) Quasi-static approximation for calculating time-dependent reaction rate.

(i) $c(r, t = 0) = c_0$ *for* $r > a$.

(ii) $c(r = a, t) = 0$, *since there is an uptake of* B *molecules at* $r = a$.

(iii) $c(r \to \infty) = c_0$ *for a continuous supply of* B *molecules at infinity to counterbalance the rate of uptake of* B *at* $r = a$.

1. *Define* $u(r, t) = ru(r, t)$. *What is the equivalent-diffusion equation for* $u(r, t)$?

2. *To solve this equation with the appropriate boundary conditions for* $u(r, t)$, *introduce the Laplace transform of* $u(r, t)$

$$\tilde{u}(r, s) = \int_0^\infty dt\, u(r, t) \exp\{[-st]\} \tag{19.27}$$

Show

$$s\tilde{u}(r, s) - rc_0 = D\tilde{u}''(r, s) \tag{19.28}$$

3. *Show*

$$\tilde{u}(r, s) = \frac{c_0}{s}\left[r - a\exp\left\{\left[-(r-a)\sqrt{s/D}\right]\right\}\right] \tag{19.29}$$

4. *We assume that the inverse Laplace transform of*

$$s^{-1}\left[1 - \exp\left\{\left[-r\sqrt{s/D}\right]\right\}\right]$$

is

$$\mathrm{erf}(r\sqrt{4Dt})$$

where

$$\mathrm{erf}(z) = \frac{2}{\sqrt{\pi}}\int_0^z e^{-r^2} dr \tag{19.30}$$

where rmerf *is the error function, see Fig.* **??**. *Show:*

$$c(r, t) = c_0\left(1 - \frac{a}{r}\right) + \frac{ac_0}{r}\mathrm{erf}\left[\frac{r-a}{\sqrt{Dt}}\right] \tag{19.31}$$

5. *Show that the time-dependent flux is*

$$\phi = 4\pi a^2 D c_0\left(1 + \frac{a}{\sqrt{\pi Dt}}\right) \tag{19.32}$$

6. *Make the $t \to \infty$ limit. Show $k = 4\pi a^2 D$. Remark that the rate k depends on the diffusion constant D.*

Exercice 19.9 *The time-dependent reaction rate can be calculated using the quasi-static approximation. Because of it simplicity and general applicability, we detail the calculation in arbitrary dimension d.*

We divide the region exterior to the adsorbing sphere into two zones. The "near" and the complementary "far" zone.

1. *In the near zone, $a < r \leqslant a + \sqrt{Dt}$, it is assumed that diffusing particles have sufficient time to explore the domain before being adsorbed by the target. The concentration is almost quasi static. What changes with time is the locus of the boundary which increases as $\sqrt{Dt}$.*

2. *In the complementary far zone, it is assumed that the probability of being adsorbed is negligible, since the particles are unlikely to diffuse more than $\sqrt{Dt}$ in a time t. Thus, $c(r) \approx c_0$ in the far zone.*

1. *Show that the static solution in $2d$ is $c(r) = A + B \ln r$.*

2. *Match the solution to the boundary condition $c(a) = 0$ and $c(a + \sqrt{Dt}) = c_0$ and show*

$$c(r,t) \approx \frac{c_0 \ln(r/a)}{\ln(\sqrt{Dt}/a)} \quad t >> 1 \tag{19.33}$$

3. *Compute the time-dependent flux*

$$J(t) = 4\pi a^2 D \frac{\partial c}{\partial r}\Big|_{r=a} \tag{19.34}$$

4. *How J depends on the size of the adsorbing sphere ? Conclude.*

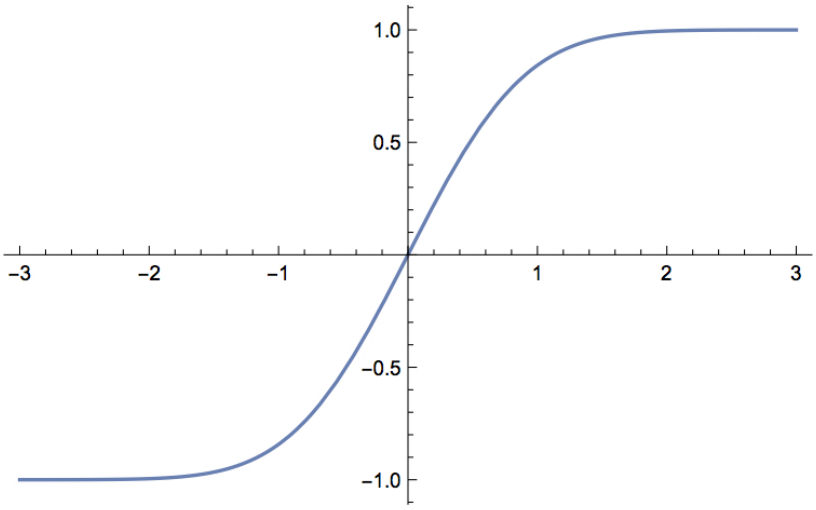


Figure 19.5: Plot of the function erf(z).

19.5 The Peclet number

The Peclet number is a dimensionless ratio. It is the ratio of two rates. The first rate is the rate at which a particle moves some distance λ due to being carried along by the flow of the liquid. The second rate is the rate at which it diffuses the same distance λ. Here λ is whatever distance we are interested in. So, the Peclet number is defined to be

$$\text{Pe} = \frac{R_1}{R_2} \tag{19.35}$$

where

1. R_1 = Rate at which flow carries molecules a distance λ.
2. Rate at which diffusion carries molecules a distance λ.

If the flow speed is u, the time taken to transport a molecule over a distance λ is λ/u. The rate is therefore u/λ. In contrast, the time to diffuse a distance λ is λ^2/D. As a result, the rate is D/λ^2. Thus,

$$\text{Pe} = \frac{u\lambda}{D} \tag{19.36}$$

which depends on the length scale λ. On small scales, diffusion is faster than flow. On macroscopic scale, flow is faster. For E. Coli looking for nutriments, $D \approx 10^{-5} cm^2/s$ (for phosphate molecules), $u = 30\mu m/s$ (speed of E. coli), $\lambda = 2\mu m$ (size), Pe = 0.02.

19.6 Diffusion in a force field

We have considered so far a free brownian particle. What happens if the particle is subjected to an external force F ? If this force derive from a potential $\phi(x)$, the current is the sum of the usual drift term and a mobility term

$$J = -\mu P(x)\nabla\phi - D\nabla P \tag{19.37}$$

where the mobility μ is yet undetermined.

Conservation of probability requires

$$\frac{\partial P}{\partial t} = \nabla \cdot J \tag{19.38}$$

and translates into

$$\frac{\partial P}{\partial t} = \frac{\partial}{\partial x}\left[-\mu P(x)\nabla\phi - D\nabla P\right] \tag{19.39}$$

Assuming stationarity

$$\begin{aligned} -\mu P(x)\nabla\phi - D\nabla P &= 0 \\ \text{or } \frac{dP}{dx} &= -\frac{\mu}{D}\frac{d\phi}{dx}P(x) \end{aligned} \tag{19.40}$$

whose solution is given by

$$P(x) = \frac{1}{Z}e^{-\frac{\mu}{D}\phi(x)} \tag{19.41}$$

where Z is some normalization constant. Remark that we have made no statement concerning equilibrium and we have only hypothetized that the process is stationary. If the process at equilibrium, we recover the Bolzmann's distribution if the Einstein relation holds

$$\frac{\mu}{D} = \frac{1}{kT} \tag{19.42}$$

Although this derivation is general, it is interesting to state clearly the hypotheses tacitly made to get (**??**). Since the probability $P(x,t)$ does depend only on the position and not on the speed, we have tacitly assumed that the speed relaxes very fast to some local equilibrium. Actually, (**??**) is only valid in the strong friction limit.

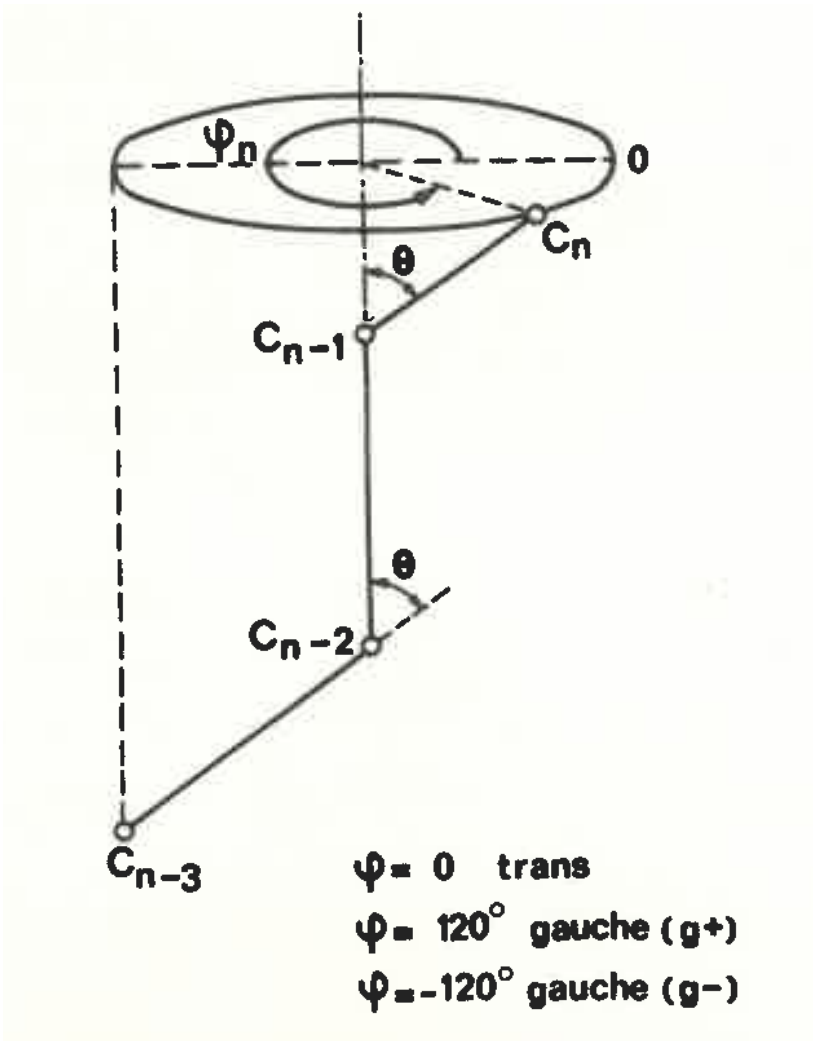


Figure 19.6: Three successive monomers of a flexible polymer chain. The angle θ is fixed, but the upper monomer can rotate by an angle ϕ. The three segments are coplanar when $\phi = 0$ (trans-configuration) and this configuration corresponds to the true minimum energy configuration (see Fig. **??**). The two gauche configurations are obtained when $\phi = \pm 120\circ$.

Remark 7 *In classical mechanics particles at rest occupy minimum energy states. Here, due to thermal fluctuations, the particle has a finite probability $p(U_i)$ to be in a state of energy U_i above the minimum energy state. Assuming thermal equilibrium, the probability $p(U_i)$ is*

$$p(U_i) = \frac{1}{Z} e^{[-U_i/kT]} \tag{19.43}$$

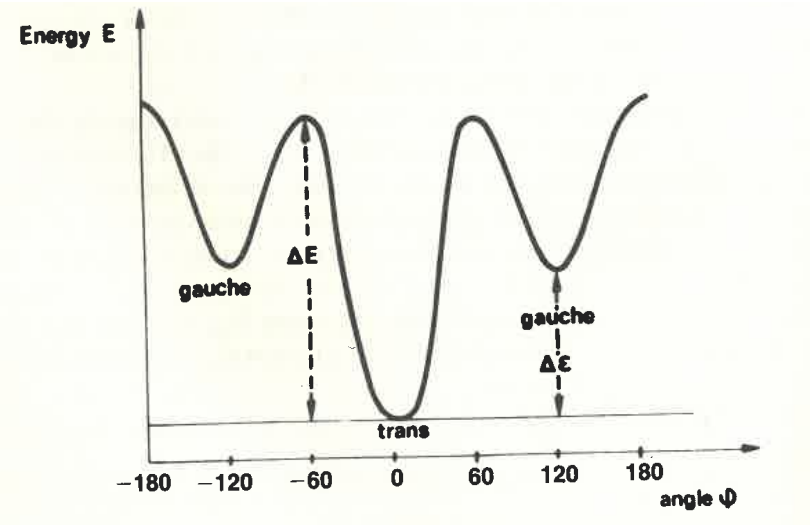


Figure 19.7: Potential profile as a function of the angle ϕ defined in Figure **??**. The potential barriers are small with respect to the thermal energy kT, so that the polymer adopts the three configuration with almost equal probability

where $Z = \sum_i \exp\{-U_i/kT\}$ *so that* $\sum_i p_i = 1$.

Consider a molecule with two conformational states with reaction coordinate x. *The probability to be state* 1 *is* $p_1 = 1/Z \exp\{\{-U_1/kT\}\}$ *(*$1 \rightleftarrows 2$*). We have*

$$\frac{p_1}{p_2} = \exp\{[-(U_1 - U_2)/kT]\} \tag{19.44}$$

At very low temperature, $p_1/p_2 \gg 1$ *so that the only observable state is actually the minimum energy state. At finite temperature, however, state* 2 *is observable with a finite probability. This property is crucial for flexible polymer chains. The energy between successive groups is a function of one angle* ϕ. *The potential barrier* $\Delta\epsilon$ *between the two cis and the trans configuration is small, so that the chain is a flexible coil.*

Exercice 19.10 *Application : The Debye-Hückel theory. Interactions that occur between electrical charges fixed at surface and those which are free in solution play an important role in colloidal systems.*

We consider negatively charged wall that is infinite in the x *and* y *direction. The distance from the charged surface is* z. *The charge density on the wall is* σ. *Let* $\Phi(z)$ *be the electrical potential. Because of Gauss's law*

$$\frac{d\Phi}{dz} = -\frac{\sigma}{\epsilon_0 \epsilon_r} \tag{19.45}$$

The adjacent solution contains positively charged and negatively charged ions in equal quantity with homogeneous density c_0 *when* $\phi(z) = 0$. *We assume that the ions bare a charge* $\pm Ze$.

1. *Calculate* $c_\pm(z)$ *as a function of* $\Phi(z)$.

2. *Write Gauss's theorem in the solution*

$$\Delta\Phi(z) = -\frac{\rho(x)}{\epsilon_0 \epsilon_r} \tag{19.46}$$

and show

$$\Delta\Psi(z) = -\frac{2eZc_0}{\epsilon_0 \epsilon_r} \sinh\left[\frac{Ze\Psi(z)}{kT}\right] \tag{19.47}$$

3. *Without solving this equation, show that there exists a characteristic length scale l_p which enters into the problem.*

4. *Assume*

$$\sinh\left[\frac{Ze\Psi(z)}{kT}\right] \approx \frac{Ze\Psi(z)}{kT} \tag{19.48}$$

and solve the differential equation. What is the physical interpretation of l_p ?

5. *Assume that the ions come from the dissociation of* NaCl *(0.1 M). What is the order of magnitude of l_p ?*

19.7 *A First-passage problem: The escape over a potential barrier*

We consider a brownian particle in a field of force. The force is the derivative of a potential $V(x)$ and to want the calculate the probability to escape from a metastable state. We will assume that the barrier is sufficiently large with respect to kT so that the particule will neither come back after having passed over the barrier. This problem is a first passage problem.

The x coordinate is a reaction coordinate. For a chemical reaction, x corresponds to the relative distance between two molecules A and B When the relative distance between the two molecules is small, the two molecules form a chemical complex. The translocation of the particle over the barrier is, therefore, equivalent to the dissociation of the complex A−B.

If we assume first order kinetics, we describe the reaction as

$$\frac{\mathrm{d[A{-}B]}}{\mathrm{dt}} = -\mathrm{k_{off}}\,[\mathrm{A{-}B}] \tag{19.49}$$

where $\mathrm{k_{off}}$ has the dimension of 1/time. This is the characteristic time one has to wait before the chemical bond break spontaneously because of thermal fluctuations. In the Kramers problem, this time is the first passage time over the barrier.

$$\frac{\partial P}{\partial t} + \frac{\partial J}{\partial x} = 0 \tag{19.50}$$

where

$$J = -\frac{1}{\mu}P(x)\frac{dV}{dx} - D\frac{dP}{dx} \tag{19.51}$$

In what follows, we assume that the barrier is large with respect to kT

$$V_M - V_A \gg kT \tag{19.52}$$

and we compute the off-rate from the current of particle escaping from A

$$\mathrm{k}_{off} = \frac{J}{n_A} \tag{19.53}$$

where n_A is the number of particles in A. The current is small, so n_A does not vary. k_{off} has the right dimension, since $\mathrm{k_{off}} = 1/\mathrm{time}$.

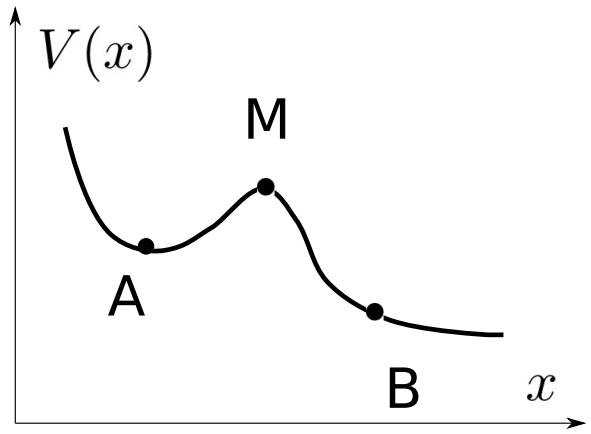


Figure 19.8: Potential profile for a brownian particle. The effect of a force applied to the equivalent chemical bond is to lower the potential barrier.

In a stationary regime, the current is constant

$$J = \text{constant} \tag{19.54}$$

independent of the reaction coordinate x, since all particle which escape neither come back. Using (**??**) we obtain:

$$\frac{\partial V}{\partial x} P(x) + kT \frac{\partial P}{\partial x} = -\mu J \tag{19.55}$$

The general solution of this equation is

$$\begin{aligned} P(x) &= a(x) e^{-V(x)/kT} \\ a(x) &= \frac{J\mu}{kT} \int_x^{x_0} dx'\, e^{+V(x')/kT} \end{aligned} \tag{19.56}$$

where x_0 is a constant of integration to determined by the boundary conditions.

These are as follows:

1. n_A is known because the number of particle near A is given by the Bolzman's distribution (there is only a small number of particles which can escape)

$$\begin{aligned} n_A = \int dx\, P(x) = \int dx\, a(x) e^{-V(x)/kT} \\ \propto a(x_A) e^{-V_A/kT} \end{aligned} \tag{19.57}$$

   where $V(x) = V_A + \ldots$ in the domain where the integrand is not small (see Comment **??**).

2. We define an arbitrary point B at the right of the barrier. The exact locus of B will not matter. We take $P(x = x_B) = 0$ at B as the equivalent condition for the particle neither to come back. We have, therefore, $x_0 = x_B$, so that $P(x_B) = 0$.

From (**??**) we get the current

$$J = \frac{kT}{\mu} \frac{a(x)}{\int_x^{x_B} e^{V(y)/kT}\, dy} \tag{19.58}$$

in particular for $x = x_A$

$$J = \frac{kT}{\mu} \frac{a(x_A)}{\int_{x_A}^{x_B} e^{V(y)/kT}\, dy} \tag{19.59}$$

But

$$\int_{x_A}^{x_B} e^{V(y)/kT}\, dy \propto e^{V_M/kT} \tag{19.60}$$

since $V_M \gg V_A$ and $V_M \gg V_B$. Taking the ratio, we get the well-known Arrhenius factor (Kramers, 1940)

$$\mathrm{k}_{off} = \frac{J}{n_A} \propto e^{-(V_M - V_A)/kT} \tag{19.61}$$

Remark 8 *We want to evaluate the integral*

$$I = \int_{-\infty}^{+\infty} dx\, g(x) e^{\lambda f(x)} \tag{19.62}$$

where $\lambda \gg 1$ and where the function $f(x)$ has a maximum. A useful approximation is the saddle-point method. Since $f(x)$ possesses a maximum at some point x_0, the dominant contribution to the integral comes from a domain centred around x_0. We Taylor expand $f(x)$ to second order

$$f(x) = f(x_0) + \frac{1}{2}(x - x_0)^2 f''(x_0) + \dots \tag{19.63}$$

and

$$\begin{aligned} I =& g(x_0) e^{\lambda f(x_0)} \int_{-\infty}^{+\infty} dx\, e^{\frac{1}{2}(x-x_0)^2 f''(x_0)} \\ =& \sqrt{\frac{2\pi}{|f''(x_0)|}} g(x_0) e^{\lambda f(x_0)} \quad \lambda \gg 1 \end{aligned} \tag{19.64}$$

If $f(x)$ possesses a minimum, take $\lambda < 0$

$$I \approx \sqrt{\frac{2\pi}{|f''(x_0)|}} g(x_0) e^{\lambda f(x_0)} \quad |\lambda| \gg 1 \tag{19.65}$$

Exercice 19.11 *Use this approximation for the integral representation of $n!$*

$$(n+1)! = \int_0^{\infty} dt\, t^{n-1} e^{-t} \tag{19.66}$$

Exercice 19.12 *Path integral method. The Langevin equation can be written as*

$$f(t) = \mu \frac{dx}{dt} + \frac{dV}{dx} \tag{19.67}$$

We know that the random force $f(t)$ is drawn from a Gaussian distribution

$$P[f(t)] \propto \exp\left\{ \left[-\frac{1}{4\mu kT} \int dt\, f(t)^2 \right] \right\} \tag{19.68}$$

1. *Why Eq. (**??**) is valid ?*
2. *Explain formula (**??**).*
3. *Show that the probability to observe a trajectory is*

$$P[x(t)] = \mathcal{J} \exp\left\{ \left[-\frac{1}{4\mu kT} \int dt \left(\mu \frac{dx}{dt} + \frac{dV}{dx} \right) \right]^2 \right\} \tag{19.69}$$

where $\mathcal{J}$ is independent of T (don't try to calculate $\mathcal{J}$). At low temperature, the exponential will dominate and we will drily ignore thereafter $\mathcal{J}$

20
Introduction to stochastic processes

In a world of objects as small as living cells, $R \approx 10\mu m$, transport of molecules is effected by diffusion, rather than bulk flow, movement is rested by viscosity and not by inertia[**?**]. To illustrate this statement, it is interesting to compute characteristic orders of magnitude[1] . The average density ρ of a protein is about 1.2 times the one of water. The size of a cell is about $10\mu m$. The mass of cell is therefore $M \approx 5\,10^{-12}$kg. When a small object of the size of a cell cruises into water, it experiences a drag flow in the direction opposite to its velocity.

At small Reynolds numbers (see later for a definition), the drag force is $6\pi\eta R \times$ velocity, where η is the viscosity of water $\eta = 10^{-3} kg\, m^{-1}\, s^{-1}$. The ratio

$$\tau = \frac{\text{Mass}}{6\pi\eta R} = \text{Characteristic time} \tag{20.1}$$

has the dimension of a time. For objects of the same size as cells, we find $\tau = 210^{-5} s$. If the object cruises at a speed of $10\mu\, s^{-1}$, the distance traveled after the "operator" shut down the propellers is about $2\,10^{-4}\mu\, m$. This is of the order of Å and this is much less than the size of the object ! To compare with our macroscopic world, we can think about a tanker. The size of a tanker is about 380m, its weight is about $400\,10^6$kg. If we assume that the same formula holds true for the drag coefficient of the tanker - this assumption is silly - we find $\tau = 5.610^4$s. If the speed of the tanker is initially 15nm/h $= 15 \times 1.6$km/h, the distance cruised before its stops, is about 223km. Obviously, there is something wrong - the Stokes formula does not apply to a tanker - but the difference between the cell and the tanker (viscosity versus inertia) is striking !

The idea that we can go down the scale of sizes while enjoying the peaceful life also silly. In a 1966 well-known Hollywood movie directed by Richard Fleischer, a scientist is nearly assassinated. In order to save him, a submarine is shrunken to microscopic size and injected into his blood stream with a small crew. Problems arise almost as soon as they enter the bloodstream. This was foreseen ... The thermal energy of thermal motion kT is enough to perturb drastically small object movements. The passengers of the submarine imagined by Fleischer actually experience a very hectic life due

[1] Applying Newton's law, the equation of motion of a particle immersed into a medium of viscosity η is

$$M\frac{d^2\mathbf{x}}{dt^2} + 6\pi\eta R\frac{d\mathbf{x}}{dt} = 0$$

This known as the Stokes law, where the drag coefficient $6\pi\eta R$ is proportional to the size of the object. Rigorously speaking, for this law to be valid, the object is assumed to be spherical. If not, small logarithmic corrections enter into this formula without dramatic consequences.

Figure 20.1: The fantastic voyage directed by Richard Fleischer.

to incessant impacts of molecules bumping onto the submarine. It would be very hard for them to survive to such blitz ! Obviously fluctuations matter in the small world.

These lectures are about the biophysical constraints with the focus on noise and diffusion imposed by the smallness of the objects "cruising" in the micro and nano-world. Such biophysical constraints matter as soon as we try to detect and count molecules. The principles at work at the scale of nano-micro objects are very different in nature from what we know from our every day experiences and they matter in the design of experimental setups.

20.1 *A short review of probability theory*

20.2 *Introduction*

Figure 20.2: 'Un coup de dés jamais n'abolira le hasard. Poême de S. Mallarmé, 1897.

Random or "unsure" variables are essential in physics: They play a fundamental role in quantum theory, statistical mechanics, and kinetic theory. They are also crucially involved in the analysis of uncertainty in experimental data. We review here the concepts of random variable theory that will be needed later [**?**].

20.3 Cumulative distribution and probability density function

Let us consider a random variable and ask what is the probability for x to be less than some value, say a. This random variable x is regarded as specified if one knows the cumulative distribution function

$$F(a) = P_c(x \leqslant a) \quad a \in]-\infty, +\infty[\tag{20.2}$$

where $P_c(\ldots)$ is the probability of occurrence of the event $x \leqslant a$. The cumulative distribution $F(x)$ has the following properties

1. $F(0) = 0$, $F(1) = 1$.

2. If $x_1 < x_2$ then $F(x_1) \leqslant F(x_2)$.

3. $F(x + 0) = F(x)$ (continuity from the right).

The probability density function is introduced by taking the derivative (if it exists)

$$p(x) = \frac{dF}{dx} \tag{20.3}$$

20.4 Continuous probability distribution versus discrete variables

20.4.1 Discrete random variables - I

Let us start with a random variable with possible values x_n, $n = 1, \ldots, K$. Since the outcome spans a discrete set of values, it is called a discrete random variable. If $x = x_n$ with probability p_n

$$\sum_{n=1}^{K} p_n = 1 \tag{20.4}$$

The expectation of x is

$$< X >= \sum_{n=1}^{K} p_n x_n \tag{20.5}$$

and the variance of x is

$$< x^2 > - < x >^2 = \sum_{n=1}^{K} p_n x_n^2 - \left(\sum_{n=1}^{K} p_n x_n \right)^2 \geqslant 0 \tag{20.6}$$

20.4.2 *Continuous random variables*

In this case, $p(x)$ does not exist only at a 'few' discrete points (countable set). We have $p(x) \geqslant 0$, $\forall x$ and

$$\int_{-\infty}^{+\infty} dx\, p(x) = 1$$

The probability to find x in the interval $x \in [x_1, x_2]$ is simply equal to the integral

$$P(x_1 \leqslant x \leqslant x_2) = \int_{x_1}^{x_2} dx\, p(x) \tag{20.7}$$

To determine the probability density function $p(a)$ for a given a, we perform the experiment n times and count the number of trials $\Delta n(a)$ such that the result is $a \leqslant x \leqslant a + \Delta a$

$$p(a)\Delta a = \frac{\Delta n(a)}{n} \tag{20.8}$$

20.4.3 *Discrete random variables - II*

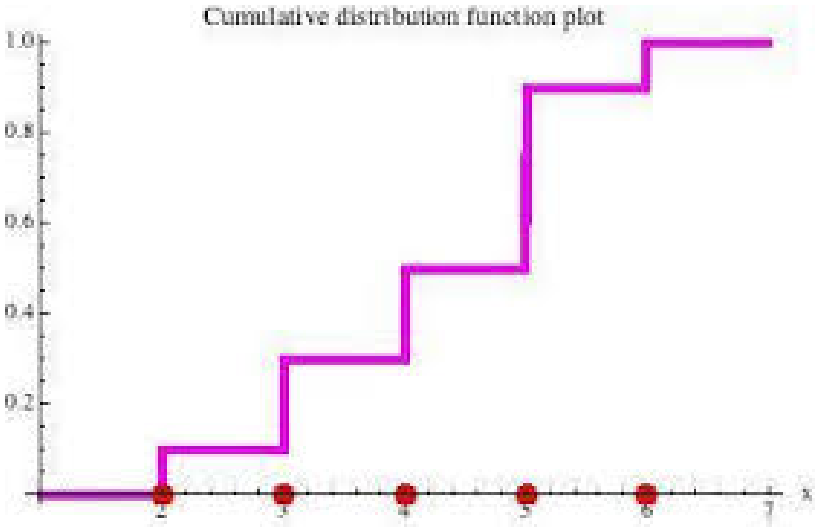


Figure 20.3: Cumulative distribution function for a discrete random variable.

This section introduces the δ functions. The meaning is the same as in subsection 1. In the case of a discrete random vraiable, the cumulative distribution function resembles a staircase. We introduce the Dirac δ-distribution specified by the integral property

$$\int_{-\infty}^{+\infty} dx\, \phi(x)\delta(x - x_0) = \phi(x_0) \tag{20.9}$$

where ϕ is an arbitrary test continuous function. In the case of discrete random variable, the cumulative probability distribution is discontinuous at x_0 and

$$\left.\frac{dF}{dx}\right|_{x=x_0} = k\delta(x - x_0) \tag{20.10}$$

where $k = F(x_0+) - F(x_0-)$ is the step height.

In particular, if $F(x)$ is the Heaviside function defines as

$$F(x) = \theta(x) = \begin{cases} 1 & x \geqslant 0 \\ 0 & \text{otherwise} \end{cases} \tag{20.11}$$

Then

$$\frac{d\theta}{dx} = \delta(x) \tag{20.12}$$

As a result, the probability density for a discrete random variable (assuming that the random variable takes the value x_n with probability p_n is

$$f(x) = \sum_n p_n \delta(x - x_n) \tag{20.13}$$

We have for any function of the random variable x, $\phi(x)$

$$\phi(x) = \int dx\, \phi(x) = \sum_n p_n \phi(x_n) \tag{20.14}$$

20.5 Change of variable

Given a random variable with density distribution $p(x)$, and a new random variable y defined by the transformation

$$y = g(x) \tag{20.15}$$

the probability density $q(y)$ of this new variable is given by

$$q(y) = \int_{-\infty}^{+\infty} p(x)\delta(y - g(x))dx \tag{20.16}$$

This is equivalent to say

$$q(y)\Delta y = p(x)\Delta x \tag{20.17}$$

for all intervals Δy image of Δx by the application $g(x)$. Taking the limit $\Delta x \to 0$, we get the formula

$$q(y) = p(x)\left[\left|\frac{dg}{dx}\right|\right]^{-1} \tag{20.18}$$

Remark that we take the absolute value and that we have assumed that $g(x)$ is one-to-one.

Exercice 20.1 *A random variable x is uniformly distributed in the interval* $[0, 1]$. *Find the probability density of the random variable* $y = -\ln x$.

20.6 Moments and cumulants

The expectation value $< x >$ of a random variable is taken as

$$< x >= \begin{cases} \int_{-\infty}^{+\infty} dx\, xp(x) & \text{Continuous} \\ \sum_n xp(x_n) & \text{Discrete} \end{cases} \tag{20.19}$$

Higher moments are defined in the same way, k is not necessarily an integer

$$< x^k >= \begin{cases} \int_{-\infty}^{+\infty} dx\, x^k p(x) & \text{Continuous} \\ \sum_n x^k p(x_n) & \text{Discrete} \end{cases} \tag{20.20}$$

For $k = 2$, we define the variance (σ is called the standard deviation)

$$< \sigma^2 >=< x^2 > - < x >^2 \tag{20.21}$$

with the important result

$$\sigma^2 \geqslant 0 \text{ since } < x^2 > \geqslant < x >^2 \tag{20.22}$$

A central point in physics is to characterize the correlations between random variables. Let x and y be these random variables, we define

$$< xy >_c =< xy > - < x >< y > \tag{20.23}$$

If x and y are independent, then $< xy >=< x >< y >$, so that $<< xy >>= 0$. Take now $y = x$ and define the cumulant of order 2 by

$$< x^2 >_c =< x^2 > - < x >^2 \tag{20.24}$$

which is nothing but the variance. Higher cumulants will be defined shortly using the generating function. For the moment, it suffices to say that cumulants probe how far the random variable x is from being deterministic (i.e. with only one possible value). Cumulants are one other way to write the probability density function, since both quantities are related.

We define the characteristic function

$$\phi(\omega) =< e^{i\omega x} >= \int_{-\infty}^{+\infty} dx\, e^{i\omega x} p(x) \tag{20.25}$$

where $\phi(\omega)$ and $p(x)$ contain the same information, since they are Fourier transform of each other. Cumulants are defined from $\ln \phi(\omega)$ by taking the logarithmic derivative

$$\frac{d^n}{d\omega^n} \ln \phi(\omega) \bigg|_{\omega=0} = i^n < x^n >_c \tag{20.26}$$

Or, equivalently, by series expanding

$$< e^{i\omega x} >= \exp\left\{ \left\{ \sum_{n\geqslant 1} i^n \frac{\omega^n}{n!} < x^n >_c \right\} \right\} = \sum_{n\geqslant 0} i^n \frac{\omega^n}{n!} < x^n > \tag{20.27}$$

This formula may seem a little awkward, note the way the cumulants enter into the exponential, but it is of constant use. We can already kill the suspense and state that the only distribution with zero cumulants for $n > 2$ is the Gaussian probability distribution.

Exercice 20.2 *Use*

$$\int_{-\infty}^{+\infty} e^{-ax^2} e^{-ikx} = \sqrt{\frac{\pi}{a}} e^{-k^2/4a^2} \tag{20.28}$$

and demonstrate the preceding statement.

Exercice 20.3 *Physical limit of biochemical signaling[**?**]. We want to count molecules with a sensor of size a. Let $\bar{c}$ the mean concentration of molecules and we expect to count on average $\bar{N} \sim \bar{c}a^3$ molecules. What is the noise associated with this measurement? A volume of size a can be cleared by diffusion is a time $\tau_D \sim a^2/D$. What is the fractional accuracy if we integrate a measure over a time τ ? ($\delta c/\bar{c} \sim 1/\sqrt{Da\bar{c}\tau}$).*

20.7 Examples of distribution

20.7.1 The binomial distribution

This is the probability to get k successes in n trials for an event occuring with probability p. The probability distribution is given by

$$P(x = k) = C_n^k p^k (1-p)^{n-k} \tag{20.29}$$

The probability for no success in N trials is $(1-p)^N$ and the probability for at least one success is $1-(1-p)^N$. The case $p = 1/2$

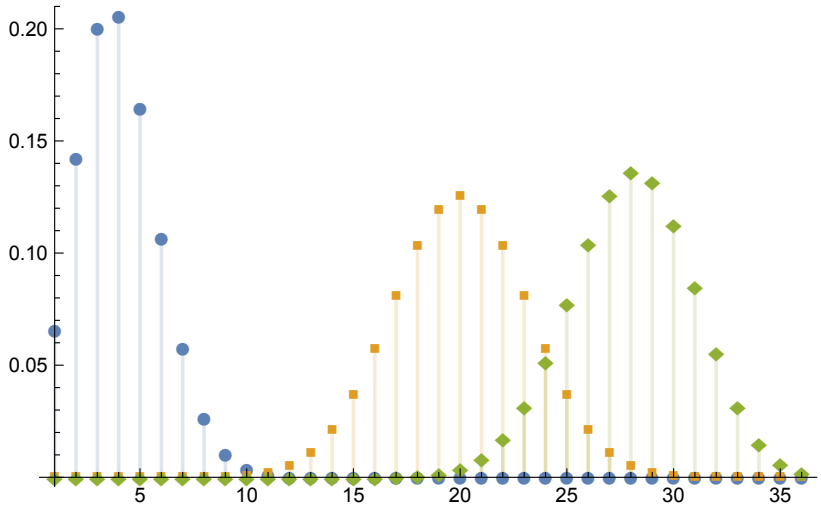


Figure 20.4: Binomial distribution for $p = 0.1, 0.5, 0.7$.

corresponds to flipping a coin.

20.7.2 The normal distribution

The normal random variable has probability distribution

$$f(x) = \frac{1}{\sqrt{2\pi\sigma^2}} \exp\left\{\left[-\frac{(x-\mu)^2}{2\sigma^2}\right]\right\} \tag{20.30}$$

The mean is μ and the variance is σ^2. As $\sigma \to 0$, the random variable is almost sure. With these definitions, (**??**) is normalised to 1,

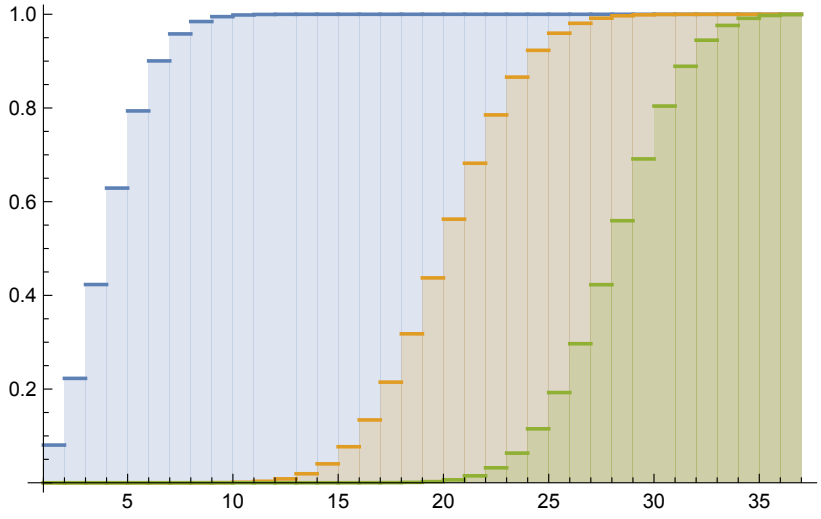


Figure 20.5: Cumulative probability distribution for the binomial distribution.

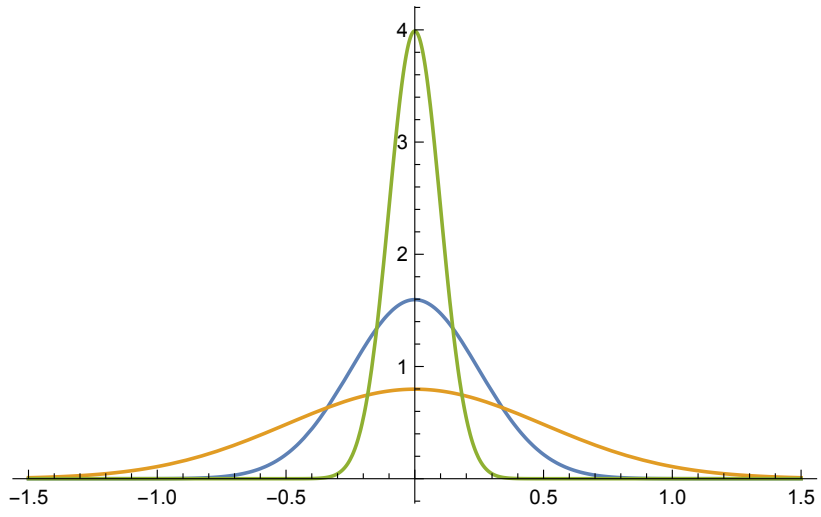


Figure 20.6: The normal distribution tends to a Dirac distribution as $\sigma \to 0$.

so that the $\sigma \to 0$ limit gives the δ-Dirac function. The generalization to multiple variables is

$$P(\mathbf{x}) = P(\{x_i\}) = \frac{1}{\sqrt{(2\pi)^N \det C}} \exp\left\{\left[-\frac{1}{2}\mathbf{x}^T \cdot C^{-1} \cdot x\right]\right\} \tag{20.31}$$

where $\mathbf{x}^T$ is the transpose of the vector $\mathbf{x}$.

Exercice 20.4 *This distribution is correctly normalized as it can be shown when C is diagonal. This will the case here. While you are at it, also show*

$$\ln \det C = \mathrm{tr} \ln C \tag{20.32}$$

Exercice 20.5 *If you have not done before, the following trick is useful. To calculate*

$$\int_{-\infty}^{+\infty} dx \exp\left\{\left[-\alpha x^2\right]\right\}$$

, evaluate first

$$\left[\int_{-\infty}^{+\infty} dx \exp\left\{\left[-\alpha x^2\right]\right\}\right]^2 = \int_{-\infty}^{+\infty} dx \exp\left\{\left[-\alpha x^2\right]\right\} \int_{-\infty}^{+\infty} dy \exp\left\{\left[-\alpha y^2\right]\right\} \tag{20.33}$$

and use polar coordinates. While you are at it, take the derivative with respect to α to calculate $< x^2 >$.

Exercice 20.6 *Use this to show that the Fourier transform is a gaussian. Show that the only probability distribution with culants equal to zero for $n > 2$ is a gaussian probability distribution.*

20.7.3 The Poisson distribution

This distribution is of tremendous importance both in physics and in chemistry. Photons statistics is Poissonian as the distribution of molecules in chemical kinetics. Poisson's statistic follows the limit of rare events for the binomial distribution. We make $p \ll 1$, therefore

$$(1-p)^{N-n} = e^{(N-n)\ln(1-p)} \approx e^{-Np} \tag{20.34}$$

Second[2]

$$\frac{N!}{(N-n)!} \approx N^n \tag{20.35}$$

[2] Use the Stiling's formula $l! \approx (l/e)^l \sqrt{2\pi l}$

and we arrive at:

$$P(N,n) = (Np)^n e^{-Np}/n! \tag{20.36}$$

Often the symbol $\lambda = Np$ is assigned. λ is the number of heads in N tosses. For the Poisson distribution, both the mean and the variance are equal to λ

$$< x >= \lambda \quad \sigma^2 =< x^2 > - < x >^2 = \lambda \tag{20.37}$$

Exercice 20.7 *Consider an assembly if m radioactive atoms. Two characteristics are important in understanding radioactive decay. First, the probability per unit time that an undecayed atom will decay within an infinitesimal time interval Δt is constant*

$$\frac{\textit{Probability of decay in}\Delta t}{\Delta t} \to a \text{ as } \Delta t \to 0 \qquad (20.38)$$

where a is the probability per unit time of observing a decay. Seconds, the atom are independent; the state of one atom does not affect another. What is the probability to observe r decays in each time interval ? answ. Define $\mu = pm$, i.e. the average number of radioactive decays in each time interval.

Exercice 20.8 *Let X have range $\{0, 1, 2, 3, \ldots\}$ and $p_X(j) = e^{\lambda}\lambda^j/j!$ for all j (Poison distribution with mean λ).*

1. *Compute $g(t) =< \exp\{[itj]\} >$, $i^2 = -1$.*
2. *Compute $< X >$, $< X^2 >$ and $< X^2 > - < X2 >$.*

20.7.4 The Bolzmann distribution

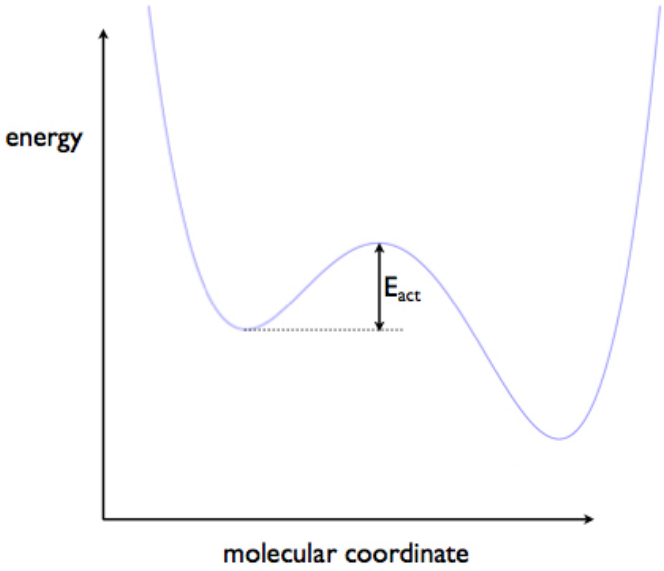


Figure 20.7: The simplest model of a molecule with two conformational states. Along some molecular coordinate x, the potential energy $V'x)$ has two minima separated by a barrier. The height of the barrier is the activation energy E_{act} which will determine the rate of reaction through the Arrhenius law, $k \propto e^{-E_{act}/kT}$.

Consider a two-conformational states molecules with energy $E_{\pm}$. the probability to observe the molecule in the state $+$ is given by

$$p_+ = \frac{e^{-\beta E_+}}{e^{-\beta E_+} + e^{-\beta E_-}} \quad \beta = 1/kT \qquad (20.39)$$

Observe $p_+ + p_- = 1$ as it should be.

As shown in Fig. **??**, these probability are experimentally accessible. Using single molecule devices which mesure the electrical current passing through a ionic canal (patch-clamp), one mesures

the time spent t_{open} in the open conformation. The probability to find the canal in the open conformation at an arbitrary time t is given by

$$p_{\text{open}} = \frac{t_{\text{open}}}{t_{\text{open}} + t_{\text{close}}} \tag{20.40}$$

where $t_{\text{open}} + t_{\text{close}}$ is the time of observation. Remark that we assume that the statistics on an ensemble of many channels at the same time are the same as the statistics on a single channel in the course of time. If true, this property in fundamental and it is called ergodicity: ensemble averages and time average are equivalent.

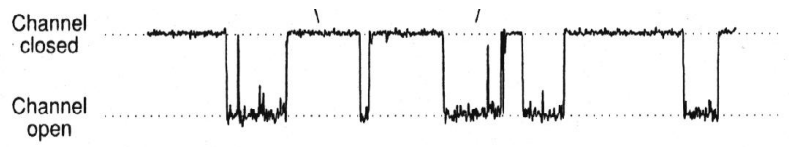


Figure 20.8: The opening of a ionic ion-channel is all-or-none and is a stochastic event. The probability for channel opening is the fractional time passed in the open conformation. Such experimental results are routine using patch-clamp setups.

20.8 Consequence of the binomial coefficient: the mixing entropy

Suppose that there are N_0 solvent molecules and n solute molecules. We assume $n \ll N_0$. For simplicity, let us represent the solution in terms of $N = N_0 + n$ boxes that can be either occupied by a solute or a solvent molecule. The number of different configurations for given n, N is given by the combinatorial factor for distributing n items in N boxes:

$$\Omega(n) = \frac{N!}{n!(N-n)!} \tag{20.41}$$

Recall the definition of the Bolzmann's entropy

$$S(n) = k \ln \Omega \tag{20.42}$$

where k is the Bolzmann's constant. So, we take logs and use the Stirling Formula

$$\ln N! \approx N \ln N - N + \frac{1}{2} \ln(2\pi N) \tag{20.43}$$

and we have the entropy of mixing

$$S(n) = k \left[N \ln N - n \ln n - (N-n) \ln(N-n) \right] \tag{20.44}$$

It is often useful to consider the mixing entropy per unit volume, or, here, per box. The concentration of solute is $\phi = n/N$

$$S(\phi)/N = \phi \ln \phi + (1-\phi) \ln(1-\phi) \tag{20.45}$$

From thermodynamics, the free energy per box is ($U = 0$ for an ideal solution)

$$\begin{aligned} F &= U - TS \\ &= -kT \left[\phi \ln \phi + (1-\phi) \ln(1-\phi) \right] \end{aligned} \tag{20.46}$$

and we recover the usual formula for the chemical potential

$$\mu = kT \ln \frac{\phi}{1-\phi} \approx kT \ln \phi \tag{20.47}$$

20.9 The central limit theorem

In his most restrictive form, the central limit theorem goes as follows:

Theorem 20.1 *Let X_1, X_2, $X_3, \ldots, X_n$ be a sequence of n and identically distributed variables having each finite value of expectation μ and variance σ^2. Form*

$$Y_n = \frac{\sum_{i=1,n} X_i - n\mu}{\sigma\sqrt{n}} \tag{20.48}$$

The distribution for Y_n approaches the standard distribution as $n \to \infty$.

As shown by Lyapounov (1901), this theorem holds even if the independent variables X_i's have non-identical distributions.

Exercice 20.9 *Consider the Cauchy distribution with probability density:*

$$f(x) = \frac{1}{\pi(1+x^2)} \tag{20.49}$$

In this exercice we are going to demonstrate the following property: If X and Y are two independent random variables with Cauchy distribution, then the variable $Z = (X+Y)/2$ is also Cauchy distributed. This property does not contradict the central limit theorem. The reason for this is that the first and the second moments do not exist for a Cauchy distribution, since

$$\begin{aligned} \frac{x}{1+x^2} &\approx 1/x \quad x \gg 1 \\ \frac{x^2}{1+x^2} &\approx 1 \quad x \gg 1 \end{aligned} \tag{20.50}$$

and the integrals diverge,

$$< x^2 >= \int_{-\infty}^{+\infty} dx \, \frac{x^2}{\pi\left(1+x^2\right)} = \infty \tag{20.51}$$

The method of characteristic functions is going to be very useful. Let X and Y be two independent random variables

1. *Show $< e^{it(X+Y)} >=< e^{itX} >< e^{itY} >$ for any t*
2. *Assume the following result*

$$k_X(t) = \int_{-\infty}^{+\infty} e^{itx} \frac{dx}{\pi(1+x^2)} = e^{-|t|} \tag{20.52}$$

Deduce

$$k_{Z=(X+Y)/2}(t) = e^{-|t|} \tag{20.53}$$

which is the characteristic function au a Cauchy distribution. This leads to the conclusion that $Z = (X+Y)/2$ is Cauchy distributed.

20.10 Correlation functions and Conditional probability distribution

Consider a function $x(t)$ that varies in time. We define the Fourier transform with the conventions

$$\tilde{x}(\omega) = \int_{-\infty}^{+\infty} dt e^{+i\omega t} x(t) \tag{20.54}$$

$$x(t) = \int_{-\infty}^{+\infty} \frac{d\omega}{2\pi} e^{-i\omega t} \tilde{x}(\omega) \tag{20.55}$$

In particular, the Dirac-delta distribution has the useful integral representation

$$\delta(t) = \int_{-\infty}^{+\infty} \frac{d\omega}{2\pi} e^{-i\omega t} \tag{20.56}$$

We are interested in situations in which the variations of $x(t)$ are random, drawn out of some distribution. $x(t)$ is said to be stochastic process. A good approximation of the mean is calculated by sampling the signal at times $\{t_i\}_{i=1,N}$

$$< x >= \frac{1}{N} \sum_{i=1,N} x(t_i) \quad N \gg 1 \tag{20.57}$$

We define the following three probabilities

1. The probability $P(x,t)$ that $x(t)$ takes a given value x at time t.
2. The joint probability $P(x_2,t_2;x_1,t_1)$ that $x(t)$ takes the value x_2 at $t = t_2$ AND that it takes another value x_1 at time $t = t_1$.
3. The conditional probability $P(x_2,t_2|x_1,t_1)$ that the random variable takes the value $x = x_2$ at time t_2 GIVEN that $x = x_1 = x(t_1)$ at time t_1 prior to t_2.

The following rule applies

$$P(x_2,t_2;x_1,t1) = P(x_2,t_2|x_1,t_1)P(x_1,t_1) \tag{20.58}$$

Note that the kinetic rate constants introduce above are actually conditional probabilities.

In a STATIONARY process all probability distributions are invariant under time translation $t \to t + \tau$. Therefore:

$$P(x,t) = \quad P(x) \text{ independent of } t \tag{20.59}$$

$$P(x_2,t_2;x_1,t_1) = \quad P(x_2,t_2 - t_1;x_1,0) \tag{20.60}$$

$$P(x_2,t_2|x_1,t_1) = \quad P(x_2,t_2 - t_1|x_1,0) \tag{20.61}$$

We want to know how the signal $x(t)$ is correlated in time. To characterize these correlations we build the correlation function

$$C(t,\tau) =< (x(t) - < x >)(x(t+\tau) - < x >) > \tag{20.62}$$

For stationary processes, time translational invariance implies that $C(t,\tau)$ does depend only on the time interval τ

$$C(t,\tau) = C(\tau) \tag{20.63}$$

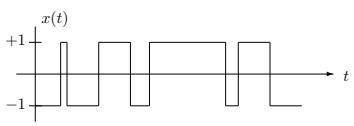


Figure 20.9:

Example 20.1 *A useful example of correlation function is for the random telegraph wave, see fig.* **??** *for a representative sample function. This process can be defined through the following two properties:*

1. $x(t) = \pm 1$ *with probability* 0.5.

2. *$x(t)$ changes polarity at Poisson times, i.e., the probability of k sign changes in a time interval T is*

$$P(k \text{ signs changes in } T) = \frac{(\lambda T)^k e^{-\lambda T}}{k!} \tag{20.64}$$

What is

$$\begin{aligned} &< (x(t_1) - < x >)(x(t_2) - < x >) > \\ &\qquad =< x(t_1)x(t_2) > \ ? \end{aligned} \tag{20.65}$$

Other way to ask the same question. For $t_2 \gg t_1$, the value of $x(t_2)$ is independent of the value of $x(t_1)$ at t_1, because the time interval is so large that there is no correlation. However, when t_2 is almost equal to t_1, what happens at $t = t_2$ is certainly correlated with what happened at $t = t_1$. There is a range for the correlation.

The trick is to compute the probability $p_{e,o}$ of even and odd number of sign change between the time interval $t_2 - t_1$. If we know this probability p_e or p_o, we can compute the correlation function

$$\begin{aligned} < x(t_2)x(t_1) > &= p(x_2 = x_1)p_e \\ &\quad - p(x_2 = -x_1)p_o \end{aligned} \tag{20.66}$$

since the product $< x(t_1)x(t_2) >$ can only take the values ± 1.

We have:

$$\begin{aligned} p_e &= \sum_{k \text{ even}} \frac{(\lambda T)^k e^{-\lambda T}}{k!} \\ &= e^{-\lambda T} \sum_{k \geqslant 0} \frac{1 + (-1)^k}{2} \frac{(\lambda T)^k}{k!} \\ &= e^{-\lambda T} \frac{e^{\lambda T} + e^{-\lambda T}}{2} \\ &= \frac{1}{2}\left(1 + e^{-2\lambda T}\right) \end{aligned} \tag{20.67}$$

Similarly

$$p_o = \frac{1}{2}\left(1 - e^{-2\lambda T}\right) \tag{20.68}$$

so that

$$< x(t_2)x(t_1) >= e^{-2\lambda |t_2 - t_1|} \tag{20.69}$$

The values of x_2 at time t_2 are therefore correlated with the values of x at time t_1, but the correlations decreases exponentially. When $|t_2 - t_1| > 1/(2\lambda)$, the exponential is so small that it is almost 0. Therefore, $1/2\lambda$ sets a characteristic correlation time.

A very general property of the correlation function is that it tends to zero as τ tends to infinity. When the time interval is large enough, what happens at t and at $t + \tau$ is not correlated and the mean of the product tends to product of the means

$$\begin{aligned} &\lim_{\tau \to +\infty} < (x(t) - < x >)(x(t+\tau) - < x >) >= \\ &\lim_{\tau \to \infty} < (x(t) - < x >) >< (x(t+\tau) - < x >) >= 0 \end{aligned} \tag{20.70}$$

What happens between time $t = 0$ and $t = +\infty$ depends on the particular case considered. The function $c(\tau)$ is not necessarily decreasing but it can oscillate. Fig **??** is taken from ref. [**?**]. It shows

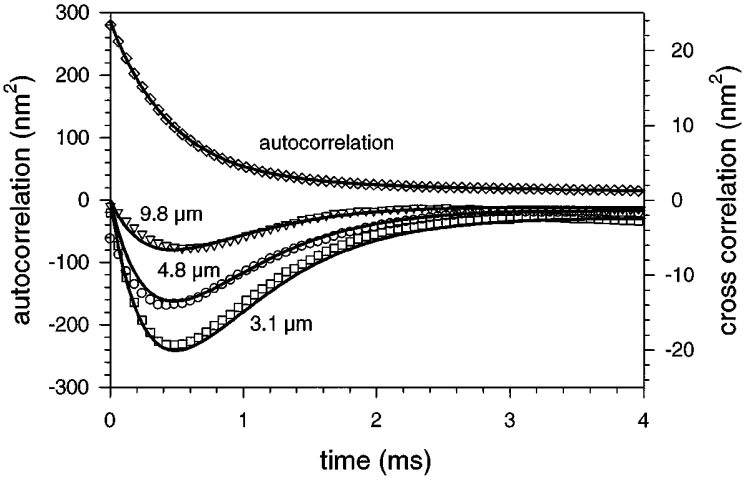


Figure 20.10: Longitudinal correlation functions of the position of the two beads. The upper curve shows the autocorrelation function of a single bead in its trap, together with a double exponential fit. The lower curves show the cross-correlation functions of two beads held at separations of 9.8, 4.8, and 3.1 μm, respectively.

the correlation function of positions of a bead in an optical trap with a double well potential. For a single bead (upper curve), the correlation function decreases gently to zero. When two beads are present in the trap, one in each well, the shape of the correlation function changes considerably because of hydrodynamic interactions between the two beads.

An interesting physical interpretation of the correlation function is also made by forming the ratio

$$\frac{< (x(t)- < x >)(x(t+\tau)- < x >) >}{< (x(t)- < x >)^2 >} \tag{20.71}$$

where the denominator scales the correlation function to 1 at $t = 0$. This quotient is nothing but the probability that the random variable takes the value $x(t+\tau)$ at time $t+\tau$ knowing that $x = x(t)$ at t. This a conditional probability distribution. Quite often we may find the notation

$$< x^2 >_c = << x^2 >> = < (x(t)- < x >)^2 > \tag{20.72}$$

Remark 9 *Note that two random variables are independent if their join probability distribution can be factorized into two independent factors*

$$P(x,y) = P_x(x)P_y(y) \tag{20.73}$$

Two random variables x, y can be such that their cross-correlation vanishes without being statistically independent, see next exercice.

Exercice 20.10 *Uncorrelated does not mean independent. Let x be a Gaussian distributed random variable with $< x >= 0$ and $\sigma^2 = 1$. Let w to take the value ± 1 with equal weight and define $y = wx$.*

1. *Use δ-function to complete the formula:*

$$P(x,y) = \frac{1}{\sqrt{2\pi}} \exp\Big\{\Big[-x^2/2\Big]\Big\} \frac{1}{2} (\ldots) \tag{20.74}$$

2. *Show that:*

$$P_x(x) = \int dy P(x,y) = \frac{1}{\sqrt{2\pi}} \exp\{[-x^2/2]\} \tag{20.75}$$

$$P_y(y) = \int dx P(x,y) = \frac{1}{\sqrt{2\pi}} \exp\{[-y^2/2]\} \tag{20.76}$$

so that $P(x,y) \neq P_x(x)P_y(y)$.

3. *Show that the cross-correlation vanishes*

$$< xy >_c = \iint dxdy\, xyP(x,y) = 0 \tag{20.77}$$

Exercice 20.11 *Consider the following problem in epidemiology. Suppose there is a rare but contagious disease A which occurs in 0.01% of the population. Suppose further that there is a simple test for the disease which is accurate 99.99% of the time (that is, out of every 10,000 tests, the correct answer is returned 9,999 times, and the incorrect answer is returned only once. Now let us administer the test to a large group of people from the general population. Those who test positive are quarantined. What is the probability that someone chosen at random from the quarantined group actually has the disease ?*

Let A be the event that someone picked at random has the disease. We have $P(A) = 0.01$ *and* $P(\Omega\backslash A) = 1 - P(A)$. *Let B denote the event than an individual tests positive. We want to calculate the conditional probability* $P(A|B)$

From Baye's theorem

$$P(A \cup B) = P(A|B)P(B) = P(B|A)P(A) \tag{20.78}$$

Therefore

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)} \tag{20.79}$$

with $P(A) = 0.0001$ *and* $P(B|A) = 0.9999$. *Therefore* $P(B|\Omega\backslash A) = 1 - P(B|A) = 0.0001$ *But*

$$P(B) = P(B|A)P(A) + P(B|\Omega\backslash A)P((\Omega\backslash A) \tag{20.80}$$

We conclude

$$P(A|B) = 1/2 \tag{20.81}$$

Exercice 20.12 *Let us calculate the probability of having n particles in a subvolume V, for a box having total volume KV and total number of particle* $T = KN_0$.

1. *Find the exact formula for this probability: n particles in V, with a total of T particles in KV ? (Hint: What is the probability that the first n particles fall in the subvolume V, and the the remainder* $T - n$ *fall outside in the subvolume* $(K-1)V$. *How many ways are there to pick n particles from T total particles ?)*

2. *The Poisson probability distribution*

$$\rho_n = a^n e^{-a}/n! \tag{20.82}$$

arises whenever there is a large number of possible events T each of which with a small probability a/T. Show

$$\sum_n \rho_n = 1 \tag{20.83}$$

3. *As $K \to +\infty$, show that the probability that n particles fall in the subvolume V has the Poisson distribution (**??**). What is a ?(You will need to use the fact that $e^{-a} = (\exp\{[-1/K]\})^{Ka} \approx (1-1/K)^{Ka}$ as $K \to \infty$ and the fact that $n \ll T$.). Here we do not assume that n is large. The Poisson distribution is valid even if there are only a few events. (answ. you should get $T!/n!(T-n)!(1/K)^n(1-1/K)^{T-n}$. Use $T = KN_0$, where N_0 is the mean number of particles after T trials. The same calculation as in the lectures fives $1/n!(N_0K)^n(1/K)^n e^{-N_0}$. Therefore, $a = N_0$.)*

4. *Show that the variance in the number of particles found in volume V is equal to N_0, the expected number of particles in the volume*

$$< (n - < n >)^2 >= N_0 \tag{20.84}$$

Exercice 20.13 *Consider a particle that hops at discrete times between neighboring sites on a one-dimensional lattice with unit spacing. At each step, the random walker moves a unit distance to the right with probability p or to left with probability $q = 1 - p$. Let $P(N, r)$ denote the probability that the particle is at site r at the Nth time step.*

1. *Show*

$$P(N,r) = pP(N-1, r-1) + qP(N-1, r+1) \tag{20.85}$$

2. *Introduce the generating function*

$$G(N,k) = \sum_{r=-\infty,+\infty} e^{ikr} P(N,r) \quad k \in [-\pi, +\pi] \tag{20.86}$$

Show

$$\left(-i\frac{d}{dk}\right)^m G(N,k)\Big|_{k=0} =< r^m > \tag{20.87}$$

3. *Show*

$$G(N,k) = \left(pe^{ik} + qe^{-ik}\right) G(N-1,k) \tag{20.88}$$

4. *Assume that the particle starts at the origin*

$$P(0,r) = \delta_{0,r} \tag{20.89}$$

Show

$$G(N,k) = \left(pe^{ik} + qe^{-ik}\right)^N \tag{20.90}$$

5. *Deduce that $P(N, r)$ is the binomial distribution*

$$P(N,r) = \frac{N!}{\left(\frac{N+r}{2}\right)!\left(\frac{N-r}{2}\right)!} p^{(N+r)/2} q^{(N-r)/2} \tag{20.91}$$

6. *Use Stirling approximation and show that*

$$P_N(x) \to \frac{1}{\sqrt{2\pi Npq}} e^{-[x-N(p-q)]^2/2Npq} \tag{20.92}$$

7. *Take $p = q = 1/2$ and recover the result given in the lecture.*

Exercice 20.14 *Consider the Cauchy distribution with probability density:*

$$f(x) = \frac{1}{\pi(1+x^2)} \tag{20.93}$$

In this exercice we are going to demonstrate the following property: If X and Y are two independent random variables with Cauchy distribution, then the variable $Z = (X+Y)/2$ is also Cauchy distributed. This property does not contradict the central limit theorem. The reason for this is that the first and the second moments do not exist for a Cauchy distribution, since

$$\begin{aligned} \frac{x}{1+x^2} &\approx 1/x \quad x \gg 1 \\ \frac{x^2}{1+x^2} &\approx 1 \quad x \gg 1 \end{aligned} \tag{20.94}$$

and the integrals diverge,

$$< x^2 >= \int_{-\infty}^{+\infty} dx \, \frac{x^2}{\pi\left(1+x^2\right)} = \infty \tag{20.95}$$

The method of characteristic functions is going to be very useful. Let X and Y be two independent random variables

1. *Show $< e^{it(X+Y)} >=< e^{itX} >< e^{itY} >$ for any t*

2. *Assume the following result*

$$k_X(t) = \int_{-\infty}^{+\infty} e^{itx} \frac{dx}{\pi(1+x^2)} = e^{-|t|} \tag{20.96}$$

Deduce

$$k_{Z=(X+Y)/2}(t) = e^{-|t|} \tag{20.97}$$

which is the characteristic function au a Cauchy distribution. This leads to the conclusion that $Z = (X+Y)/2$ is Cauchy distributed.

Exercice 20.15 *For a symmetric diffusion on a line, the probability density*

$$Prob[\text{ particle } x \in (x, x+dx)] = P(x,t)dx \tag{20.98}$$

satisfies the diffusion equation

$$\frac{\partial P}{\partial t} = D\frac{\partial^2 P}{\partial x^2} \tag{20.99}$$

supplemented by the initial condition $P(x, t=0) = \delta(x)$.

1. *If L denotes the units of length and T denotes the time units, what is the dimension of D ?*

2. *We are interested in the mean square displacement*

$$< x^2 >= \int_{-\infty}^{+\infty} x^2 P(x,t) dx \tag{20.100}$$

*Since $P(x,t)$ solves (**??**), $< x2 >$ should depend on D and t. What is the only combinaison of these parameters with dimension L^2 ? Deduce $< x^2 >$ as a function of t.*

Exercice 20.16 *We consider the integral*

$$\int_{-\infty}^{+\infty} \exp\Big\{\Big[-ak^2 - ikx\Big]\Big\} dk$$

Complete the square ($ak^2 + ikx = a(k + ix/2a)^2 - x^2/4a$) and remember $\int_{-\infty}^{+\infty} \exp\{[-ay^2]\} = \sqrt{\pi/a}$.

21
Exercices

1. Stirling formula The Stirling approximation is useful in a variety of different contexts. The goal of the present problem is to work through some of the maths.

   (a) Begin by showing that

   $$n! = \int_0^\infty x^n e^{-x} dx \tag{21.1}$$

   To demonstrate this, use repeated integration by parts

   (b) Make plot of the integrand $x^n e^{-x}$ for various values of n. What is the value of x at the maximum ?

   (c) Show that the integral can be written as

   $$\int_0^\infty e^{-f(x)} dx \tag{21.2}$$

   and give $f(x)$. Show that $f(x)$ has a maximum.

   (d) Expand the logarithm around the maximum to second order and use our result on gaussian integrals to show

   $$n! \approx n^n e^n \sqrt{2\pi n} \tag{21.3}$$

2. Bayesian Statistics We introduce two additional probabilities:

   (a) The joint probability for sets A and B together $P(A, B)$.

   (b) The conditional probability of B given A.

   We can compute the joint probability $P(A, B) = P(B, A)$ in two ways:

   $$P(A, B) = P(A|B)P(B) = P(B, A)P(A). \tag{21.4}$$

   Thus,

   $$P(A, B) = \frac{P(B, A)P(A)}{P(B)} \tag{21.5}$$

   a result known as Bayes' theorem.

   If the event space Ω is partitioned as $\{A_i\}$, then

   $$P(B) = \sum_i P(B|A_i)P(A_i) \tag{21.6}$$

   so that,

   $$P(A_i|B) = \frac{P(B|A_i}{\sum_i P(B|A_i)P(A_i)} \tag{21.7}$$

3. As an example, consider the following problem in epidemiology. Suppose there is a rare but highly contagious disease A which occurs in 0.01% of the general population. Suppose further that there is a simple test for the disease which is accurate 99.99% of the time. That is, out of every 10,000 tests, the correct answer is returned 9,999 times, and the incorrect answer is returned only once. Now let us administer the test to a large group of people from the general population. Those who test positive are quarantined. Question: what is the probability that someone chosen at random from the quarantine group actually has the disease? We use Bayes' theorem with the binary partition $A, \Omega\backslash A$. Let B denote the event that an individual tests positive. Anyone from the quarantine group has tested positive. Given this datum, we want to know the probability that that person has the disease. That is, we want $P(A|B)$.

   Applying (**??**) with $A_1 = A$ and $A_2 = \Omega\backslash A$, we have

$$P(A) = 0.0001 \quad P(B|A) = 0.9999 \quad P(\Omega\backslash A) = 0.9999 \quad P(B|\Omega\backslash A) = 0.0001 \tag{21.8}$$

   and

$$P(A|B) = \frac{0.9999 \times 0.001}{0.9999 \times 0.0001 + 0.0001 \times 0.9999} = \frac{1}{2}! \tag{21.9}$$

   despite the test being 99.99% accurate. The reason is that, given the rarity of the disease in the general population, the number of false positives is statistically equal to the number of true positives.

4. Two stochastic variables x and y are said to be independent if and only if

$$P(x, y) = P(x)P(y) \tag{21.10}$$

   Examine Fig. **??** and tell if the variables are independent.

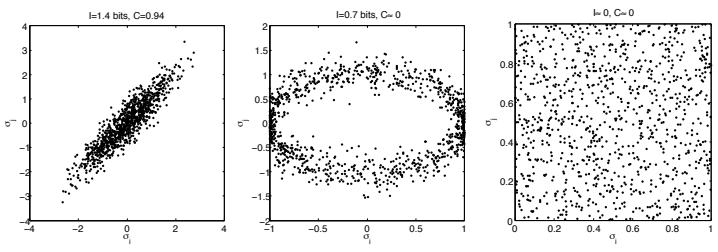


Figure 21.1: Three examples of two variables drawn from three distributions. Shown are the scatter plots of examples drawn. For each example, tell if the variable are correlated and-or if they are independent. After Tkačik et al. [**?**].

22
In preparation

Gibbs-Thomson effect, see [**?**]

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