Effective forces, partly or fully entropic

Simple example of purely entropic force: pressure from ideal gas

N particle number

V box volume

T temperature

p pressure

$$p = \frac{N k_B T}{V}$$

Partition function derivation

non-interacting particles (only E_{kin})

$$p = -\frac{\partial F}{\partial V}$$

$$e^{-F/k_BT} = Z = \int_V d\bar{x}_1 \cdots \int_V d\bar{x}_N \int d\bar{p}_1 \cdots \int d\bar{p}_N \; e^{-(\bar{p}_1^2 + \cdots + \bar{p}_N^2)/2mk_BT}$$

$$= V^N \times \{ V\text{-indep. factor} \}$$ ← here we have separated out the V-dependence

$$\Rightarrow F = \underbrace{-k_B T N \ln V}_{\text{purely entropic - comes from integration over } \bar{x}_i} + \{ V\text{-indep. term} \}$$

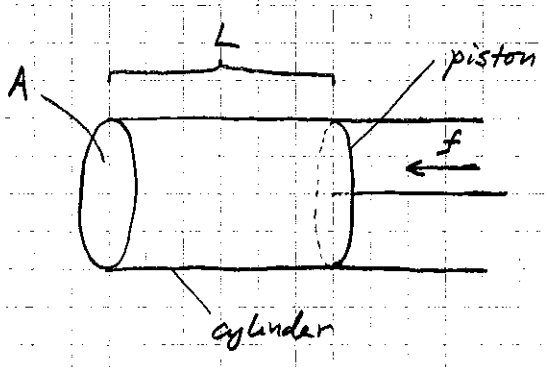
$$p = -\frac{\partial}{\partial V}(-k_B T N \ln V) = \frac{N k_B T}{V} \qquad \text{ok!}$$

Here, we fixed V and found p.

Now, consider the same system but at <u>fixed pressure</u>, and find the <u>equilibrium volume</u>.

Ideal gas law, fixed p

- constant force f and pressure $p = f/A$
- varying volume $V = L \times A$



potential energy fL $(= pV)$

gas has done work against external force f ("stored" potential energy $= fL$)

Partition function

$$Z = \int_L dL \int_V d\bar{x}_1 \cdots \int_V d\bar{x}_N \int d\bar{p}_1 \cdots \int d\bar{p}_N \exp\left\{-\left(\frac{1}{2m}\sum_{i=1}^{N}\bar{p}_i^2 + \frac{1}{2M}\bar{p}_{piston}^2 + fL\right)/k_BT\right\}$$

$$\langle L \rangle = \frac{\int L\, e^{-E/k_BT}}{\int e^{-E/k_BT}} = -k_BT\,\frac{\partial \ln Z}{\partial f}$$ ← try to separate out the f dependence of Z

$$Z = \int_0^\infty dL\; e^{-fL/k_BT} \times L^N \times \{\text{factor indep. of } f \text{ and } L\} = \left\{x \equiv \frac{fL}{k_BT}\right\}$$

$$= \left(\frac{k_BT}{f}\right)^{N+1} \int_0^\infty dL\; e^{-x}\, x^N \times \{\text{factor indep. of } f \text{ and } L\}$$

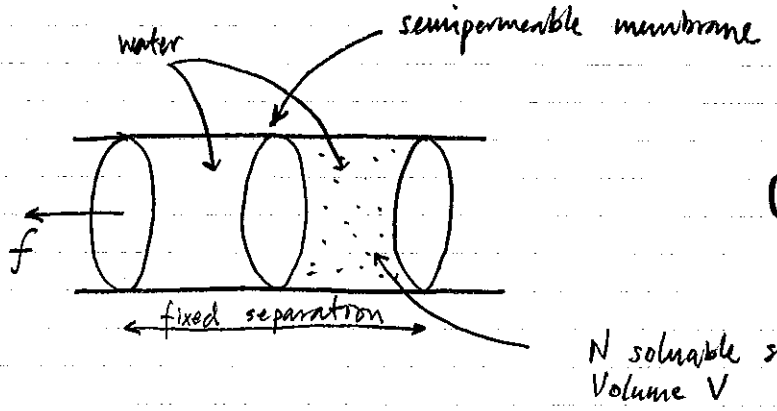
$$= f^{-(N+1)} \times \{f\text{-indep. factor}\}$$

$$\Rightarrow \ln Z = -(N+1)\ln f + \{f\text{-indep. term}\}$$

$$\Rightarrow \langle L \rangle = \frac{(N+1)k_BT}{f} \approx \frac{Nk_BT}{f}$$

$$\langle V \rangle = A\langle L \rangle \approx \frac{Nk_BT}{f/A} = \frac{Nk_BT}{p} \Rightarrow \boxed{p = \frac{Nk_BT}{\langle V \rangle}}$$

Osmotic pressure



(Fig. 1.3, pg. 13)

Assume dilute solution : interaction between sugar molecules negligible

Find Z. Sum over all states : water and sugar molecules, positions $(\vec{r}_i)$ and momenta $(\vec{p}_i)$

$$Z = V^N \times \{ V\text{-indep. factor} \}$$

water molecules give no V-dependence (invisible to membrane)

Z is like an ideal gas

$$P_{equil} = c k_B T \qquad \text{van't Hoff relation}$$

$$c = N/V \qquad \text{number density of sugar molecules}$$

The osmotic pressure from sugar molecules make piston slide to the right.

Force needed for equilibrium : $f = P_{equil} A$ where A is piston area

Interpretation of van't Hoff

- P_{equil} is pressure difference needed to reach equilibrium
- $P_{equil} \propto c \propto T$

Maximum work by osmotic pressure when volume doubles at $T = T_r$ (YT7B)

$$V = xA \qquad 0 \le x \le L$$

Choose force to balance system (just about)

$$f = c k_B T A = N k_B T A \frac{1}{V} = N k_B T \frac{1}{x}$$

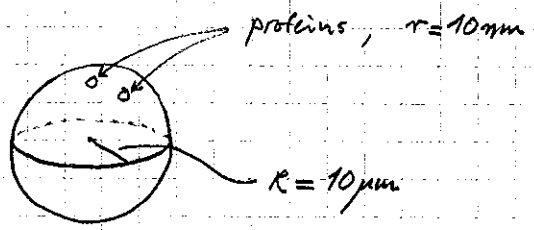
Work done when going from x to $x + dx$: $dW = f\,dx$

$$W_{max} = \int_{x_0}^{2x_0} dx \, \frac{N k_B T_r}{x} = N k_B T_r \left[\ln x \right]_{x_0}^{2x_0} = N k_B T_r \left(\ln 2x_0 - \ln x_0 \right)$$

$$= N k_B T_r \ln 2$$

Is osmotic pressure significant for a cell?

"red blood cell"



Assume a volume fraction of proteins of $\phi = 0.3 = \dfrac{N \times \frac{4}{3}\pi (10^{-8})^3}{V}$

$$\Rightarrow \quad c = \frac{N}{V} \approx 7 \times 10^{22}\ m^{-3}$$

$$= 7 \cdot 10^{22}\ m^{-3} \times \frac{mole}{6 \cdot 10^{23}} \times \frac{10^{-3}\ m^3}{l}$$

$$= 1.2 \cdot 10^{-4}\ M\ (mol/l) \qquad (\text{relatively high})$$

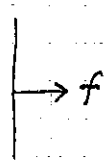
What is the equilibrium pressure (difference)?

$$p_{equil} = c k_B T_r = 7 \cdot 10^{22}\ m^{-3} \times 4.2 \cdot 10^{-21}\ J$$

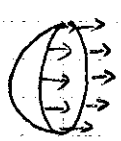
$$\approx 300\ Pa$$

What is the surface tension?

def. surface tension $\sum$ = force per unit length (N/m)



$\sum$ balances the forces from the inside pressure



$$\sum \times 2\pi R = p \times \pi R^2$$

$$\Rightarrow \quad \sum = pR/2 \qquad \text{Laplace formula}$$

$R = 10^{-5}\ m$, $p = 300\ Pa$ $\Big\}$ $\sum = 1.5 \cdot 10^{-3}\ N/m = 1.5 \cdot 10^{-3} \times \dfrac{10^{12}}{10^{9}}\ pN/mm$

$$= 1.5\ pN/mm$$

roughly enough to damage cell membrane

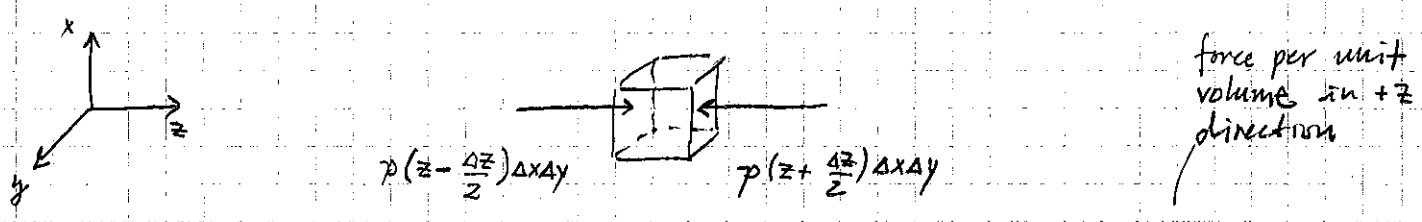
N.B. more serious for small solutes like salt. Lysis = term for when cell bursts.

Osmotic flow

Go back to simple situation with piston. Osmotic pressure makes piston slide to the right. There must be a transfer of momentum to the fluid. How does this occur? What is the mechanism? Ultimately, it must come from the fixed membrane (the only thing fixed relative to piston).

Condition for hydrostatic equilibrium (need to supply a force on the fluid)

Volume element $\Delta x \Delta y \Delta z$ centered at (x, y, z)



External force density in $+z$ direction $\mathcal{F}(z)$

Balance the forces

$$p\left(z+\frac{\Delta z}{2}\right)\Delta x\Delta y - p\left(z+\frac{\Delta z}{2}\right)\Delta x\Delta y = \mathcal{F}(z)\,\Delta x\Delta y\Delta z$$

$$\mathcal{F}(z) = \frac{p\left(z-\frac{\Delta z}{2}\right) - p\left(z+\frac{\Delta z}{2}\right)}{\Delta z} = \frac{dp}{dz} \qquad \Delta z \to 0$$

$$\boxed{\frac{dp}{dz} = \mathcal{F}(z)}$$

if there is a net force ($\mathcal{F}(z) \neq 0$), then the pressure is not a constant.

Let

$c(z)$ = number density of solute particles

$f(z)$ = force acting on each particle

Friction in fluid (viscous drag) means force act indirectly on fluid

$$\frac{dp}{dz} = \mathcal{F}(z) = c(z)f(z)$$

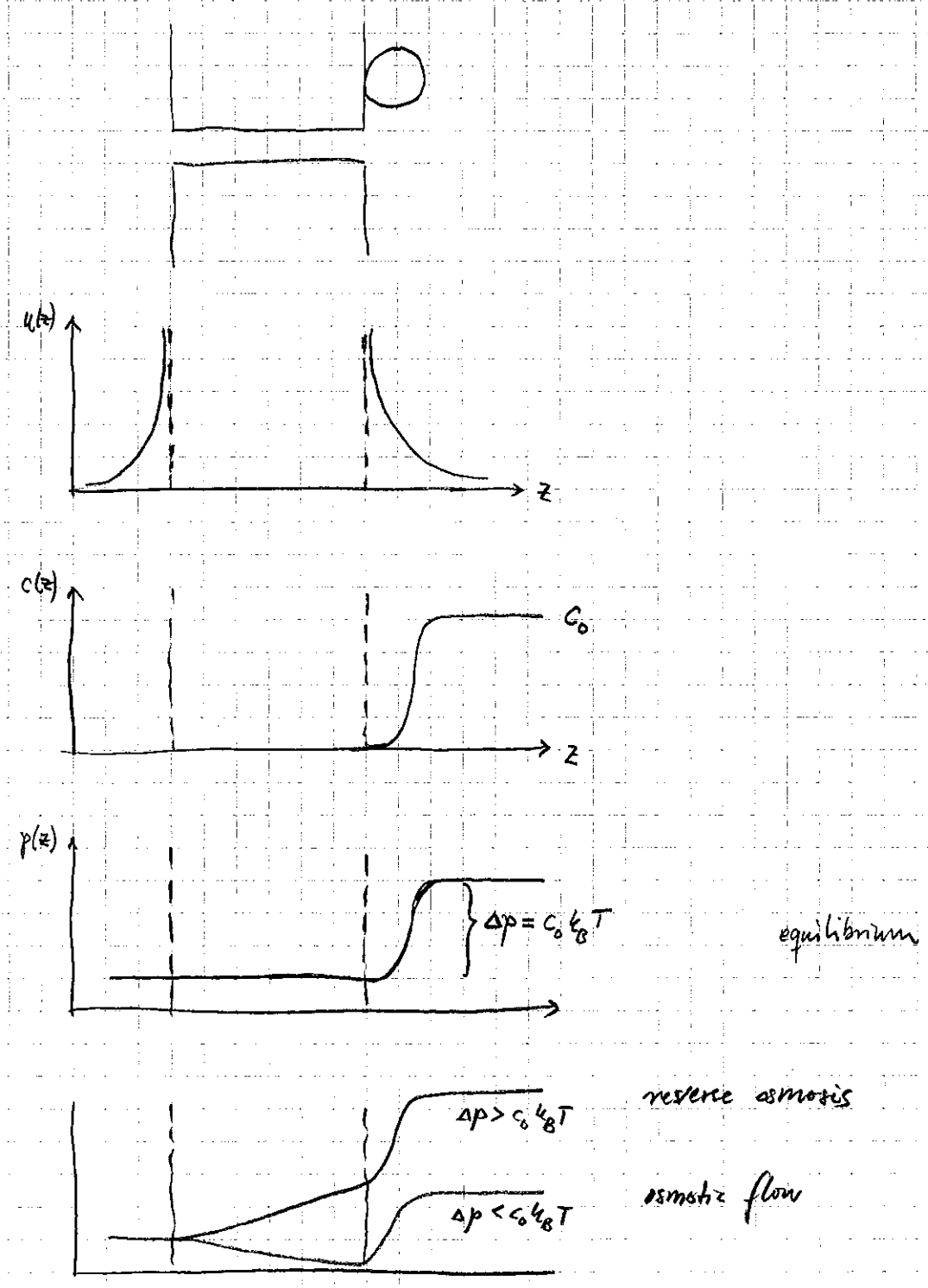
Now we have two unknown fcns ($c(z)$ & $f(z)$) instead of one ($F(z)$). However, $c(z)$ and $f(z)$ are connected. To see this introduce $U(z)$ = potential energy of solutes.

$$f(z) = -\frac{dU}{dz} \qquad c(z) = c_0 e^{-U(z)/k_B T} \qquad U = 0 \text{ far from membrane}$$

$$\Rightarrow c(z) = c_0 \text{ when } z \to \infty$$

$$\frac{dp}{dz} = -c_0 e^{-U(z)/k_B T} \frac{dU}{dz} = k_B T \frac{d}{dz}\left(c_0 e^{-U(z)/k_B T}\right)$$

$$\Rightarrow \boxed{\frac{dp}{dz} = k_B T \frac{dc}{dz}} \qquad \Rightarrow \Delta p = c_0 k_B T \quad \text{van't Hoff.}$$

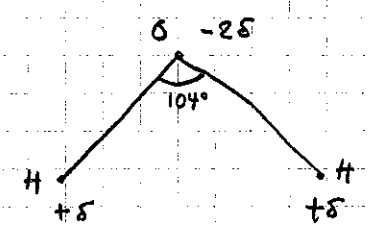


Pressure across channel : $\Delta p_{ch} = \Delta p - c_0 k_B T$

Leads to flow $j = - L_p (\Delta p - c_0 k_B T)$

↑ filtration coefficient

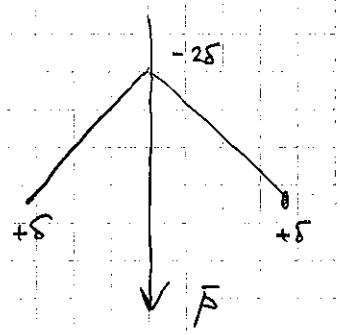
Properties of water (7.5, the rest of chap. 7)



I. Polar (= permanent separation of charges)

The molecules making up fat and oils are examples of nonpolar molecules.

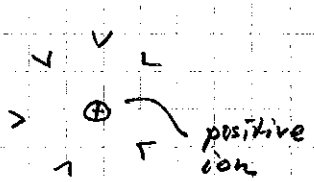
Water is polar because O is strongly electronegative



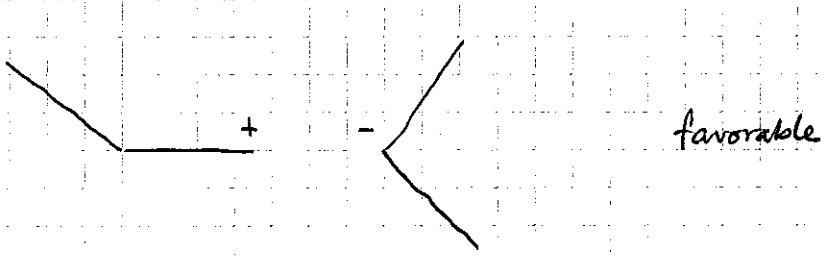
II. Assymetric ⇒ Water is a dipole

(not the case for linear molecules, +δ — (-2δ) — +δ)

- The strong dipole character gives rise to the large value of the permittivity constant ε. Water is a highly polarizable medium.



Interactions between water molecules



- Because positive atom is H, the interaction is relatively strong (partial loss of only electron of H ⇒ large reduction in size ⇒ opposite charges can come close ⇒ strong interaction)
- The interaction is called a hydrogen bond (h-bond)
- Complete description requires QM.

- Because of particular geometry of water molecules, water can form a tetrahedral arrangement (Fig. 7.12, pg. 274)

⇒ for each water molecule, both H point at other molecules O

⇒ each H_2O participates in 4 h-bonds.

Structure of ice crystals

- Water at room temperature: thermal motion make h-bonds break and form, but the network is still there.
(Problem 7.6, estimate heat of vaporization: ~3.5 h-bonds per H_2O)

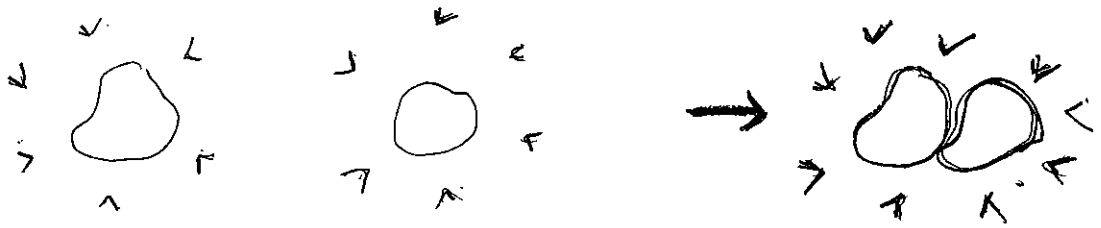
Hydrogen bonds and biological molecules

I. Macromolecules like DNA and proteins also make h-bonds
   - DNA double helix (complimentary base pairs)
   - α-helix and β-sheet structure in proteins (more in chap. 9)

II. H bond network in water affects solubility of small molecules in H_2O
   - Solubility of nonpolar molecules at room temperature is poor. (oil in water).
   - Hydrophobic effect. Major driving force in protein folding. Nonpolar amino acids of water soluable protein tend to cluster together in core of protein.

Nonpolar molecules in water

- cannot participate in H bonding
- disturb the H bond network of water



By clustering together, the nonpolar molecules disturb the network as little as possible.

⇒ <u>effective attraction</u> between nonpolar objects

How is the H bond network disrupted by a nonpolar molecule?

Two possibilities:

1) H bonds break — <u>costs energy</u>
2) H bonds remain intact, but to avoid breaking H bonds the water molecules must give up orientational freedom — <u>costs entropy</u> (possible only for small molecules)

Fig. 7.13

Exp. data (Fig. 7.14)

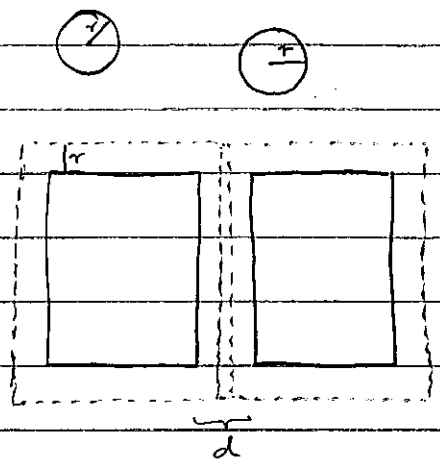
FIG 7.14

solubility of small nonpolar molecules ↓ as temperature ↑

⇒ a large part of the free energy cost of solvation is entropic.

Depletion interactions

Effective interaction that can occur in a mixture of small and large objects



- Dilute solution (# small >> # large)
- Volume of large objects V_L (incl. depletion zone)
- Small objects radius r
- Contact area A

Volume available to small objects

$$d > 2r \;:\; V = V_0 - 2V_L$$

$$d < 2r \;:\; V = V_0 - 2V_L + V_{overlap} \qquad V_{overlap} = (2r - d)A$$

Free energy $F(d)$

$$Z = V^N \times \{V\text{-indep. factor}\}$$

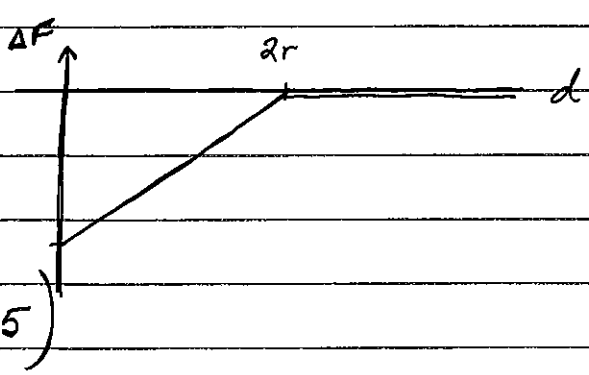
$$F(d) = -Nk_BT \ln V + \{V\text{-indep. term}\}$$

$$\Delta F = F(d) - F(2r)$$

$$= -Nk_BT \ln \frac{V_0 - 2V_L + V_{overlap}}{V_0 - 2V_L}$$

$$= -Nk_BT \ln\left(1 + \frac{V_{overlap}}{V_0 - 2V_L}\right) \approx -Nk_BT \frac{V_{overlap}}{V_0 - 2V_L}$$

$$\approx -ck_BT\,(2r - d)A$$



Distance $d < 2r \Rightarrow$ effective attractive force

(Significant in cells? See problem 7.5)

Ideal gas, osmosis, depletion force: assumed only entropic effects, i.e. interactions between particles negligible. In cells, electrostatic interactions can be important. But what is its "character" in solution?

Electrostatic vs. thermal energy

$+e$ 0 $\quad$ $-e$ 0 $\quad$ $V_c = \frac{-e^2}{4\pi\varepsilon r}$ Coulomb's law

ε permittivity

$$\frac{|V_c|}{k_B T} = \underbrace{\frac{e^2}{4\pi\varepsilon k_B T}}_{\text{Bjerrum length } l_B} \cdot \frac{1}{r}$$

The electrostatic interaction is weak ($|V_c| < k_B T$) if $r > l_B$

Air, room temperature $\quad \varepsilon = \varepsilon_0$

$$\begin{cases} \frac{e^2}{4\pi\varepsilon_0} = 2.3 \cdot 10^{-28}\ \text{Jm} \\ k_B T_r = 4.1 \cdot 10^{-21}\ \text{J} \end{cases} \Rightarrow l_B = \frac{2.3}{4.1} \cdot 10^{-7}\ \text{m} \approx \underline{56\ \text{nm}}$$

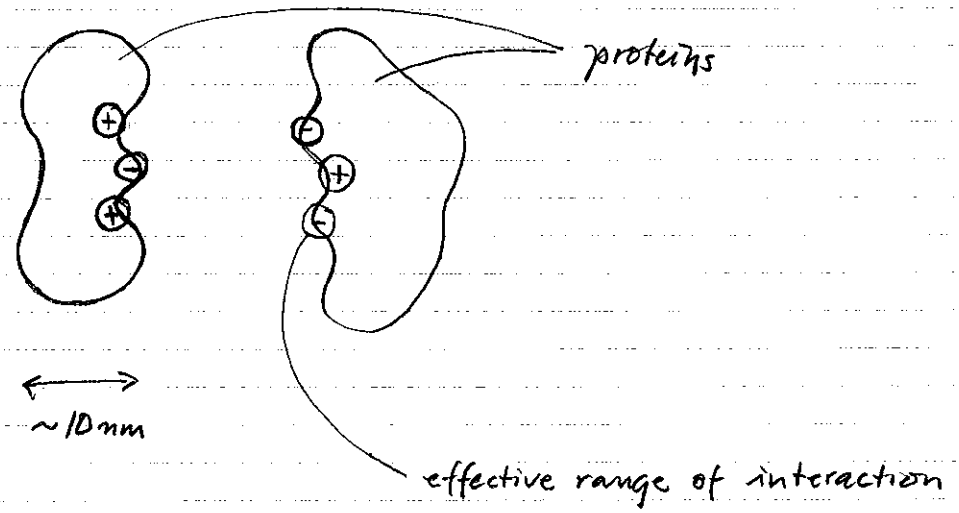
Water, room temperature $\quad \varepsilon = 80\,\varepsilon_0$

$$\underline{l_B \approx 0.7\ \text{nm}}$$

In the presence of salt, the electrostatic interaction is exponentially screened at $r > \lambda_D$ = the Debye length $(\sim e^{-r/\lambda_D})$

$\Rightarrow$ Electrostatic interactions are effectively short-ranged in cells

Electrostatic interactions are effectively short-ranged in cells. This has implications for <u>molecular recognition.</u>



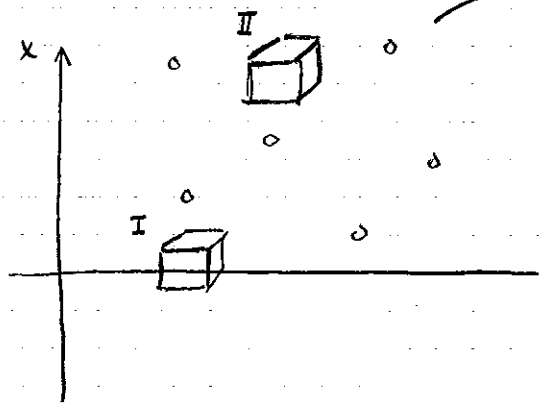
- electrostatic interactions <u>weak</u> and <u>short-ranged</u>
- many needed to get strong binding
- shapes of molecules and charges must match

→ specificity

Here, discussed distribution of charges. Some biomolecules or biomolecular assemblies have a net charge (often negative), like DNA and cell membrane. That generates a <u>cloud of counterions</u> around the molecular surface to maintain overall charge neutrality.

Cloud of counterions is also known as a <u>diffuse charge layer.</u>

To understand the formation of <u>diffuse charge layer</u>, examine a simple situation: negatively charged surface surrounded by positively charged counterions.



pos. charged <u>counterions</u>, each carrying charge $+e$

charge density ρ_q (C/m^3)

neg. charged surface (e.g. cell membrane) with charge density $-2\sigma_q$ (C/m^2)

How will the counterions be distributed?

Electric field $\bar{E}$ satisfies $\int_V \bar{E}\cdot d\bar{A} = q/\varepsilon$ (Gauss law)

I $E(0+) = -E(0-)$ symmetry

$E(0+)dA - E(0-)dA = -2\sigma_q dA/\varepsilon$

$E(0+) = -\sigma_q/\varepsilon$

II $E(x+\frac{\Delta x}{2})dA - E(x-\frac{\Delta x}{2})dA = \rho_q \Delta x\Delta y\Delta z/\varepsilon$

$$\frac{E(x+\frac{\Delta x}{2}) - E(x-\frac{\Delta x}{2})}{\Delta x} = \frac{\rho_q}{\varepsilon}$$

$$\frac{dE}{dx} = \frac{\rho_q}{\varepsilon} \qquad \Delta x \to 0$$

To find $\bar{E}$ we need ρ_q, but to find ρ_q we need $\bar{E}$.

Let
- ρ_q = average charge density
- V = electrostatic potential that results from this density and σ_q

<u>Mean-field approximation:</u> each ion move independently of the detailed location of the other ions, but under the influence of an electric potential created by the average charge density of all other ions.

$$\begin{cases} E = -\dfrac{dV}{dx} \\ \dfrac{dE}{dx} = \dfrac{\rho_q}{\varepsilon} \end{cases} \Rightarrow \quad \frac{d^2V}{dx^2} = -\frac{\rho_q}{\varepsilon} \qquad \text{Poisson equation}$$

We still have the same problem: need V to get ρ_q, and vice versa. After mean-field approximation, ρ_q is average charge density and so is determined by a Boltzmann distribution.

Let $c_+(x)$ = number density of counterions $(\rho_q = e c_+)$

$$\begin{cases} c_+(x) = c_0 e^{-\frac{eV}{k_B T}} \\ V(0) = 0 \quad \Rightarrow \quad c_+(0) = c_0 \end{cases} \qquad \text{convention}$$

Poisson-Boltzmann equation

$$\frac{d^2V}{dx^2} = -\frac{e}{\varepsilon} c_0 e^{-eV/k_B T}$$

Introduce (dimension-less and rescaled $V(x)$)

$$\bar{V} = \frac{eV}{k_B T} \quad \Rightarrow \quad \frac{d^2\bar{V}}{dx^2} = -4\pi \frac{e^2}{4\pi\varepsilon k_B T} c_0 e^{-\bar{V}} = -4\pi l_B c_0 e^{-\bar{V}}$$

Boundary conditions (σ_q not included above)

$x = 0$: $\quad \dfrac{dV(0)}{dx} = \dfrac{\sigma_q}{\varepsilon} \Rightarrow \dfrac{d\bar{V}(0)}{dx} = \dfrac{e\sigma_q}{\varepsilon k_B T} = 4\pi l_B \dfrac{\sigma_q}{e}$

$x \to \infty$: $\quad \dfrac{d\bar{V}(\infty)}{dx} = 0$ no charges far from the surface

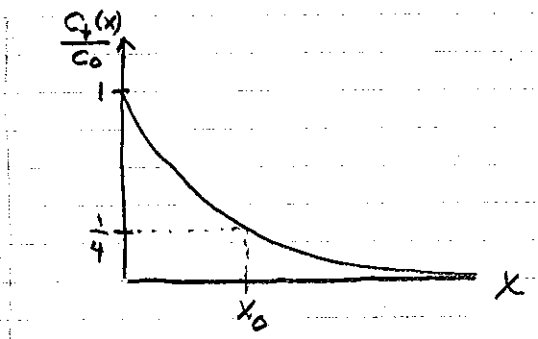
$$\boxed{\frac{d^2\bar{V}}{dx^2} = -4\pi l_B c_0 e^{-\bar{V}} \qquad \frac{d\bar{V}(0)}{dx} = 4\pi l_B \frac{\sigma_q}{e} \qquad \frac{d\bar{V}(\infty)}{dx} = 0 \qquad \bar{V}(0) = 0}$$

Solution (by trial and error)

$$V(x) = 2\frac{k_B T}{e}\ln(1 + x/x_0) \qquad x_0 = \frac{e}{2\pi l_B \sigma_f} \qquad \text{Verify this.}$$

Counterion distribution

$$c_+(x) = c_0 e^{-2\ln(1+x/x_0)} = \frac{c_0}{(1+x/x_0)^2}$$



$x_0 \propto T$: low T counterions collapse onto surface

high T broad distribution

$\Rightarrow$ competition between energy and entropy

How big is x_0?

bilayer membrane can have $\left|\frac{\sigma_f}{e}\right| \approx 0.7\ nm^{-2}$ (one charge per lipid head group)

$l_B = 0.7\ nm$

$x_0 = \frac{1}{2\pi \cdot 0.7^2}\ nm \approx 0.3\ nm$

Solving the PB equation analytically is difficult for more complicated geometries.

Numerical solution.

Protein folding and aggregation 8.6.2

- Building blocks: amino acids, arranged in a chain. ~ 50-10^3 aa ⇒ macromolecules.

3D structure is called a conformation

Astronomical number of possible conformations

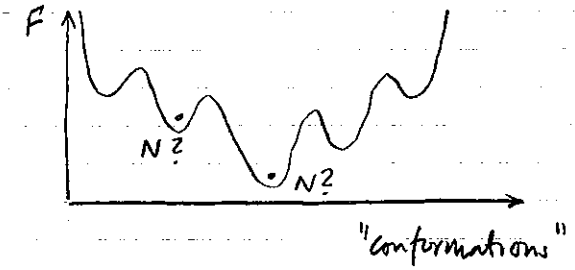
The biologically active state typically corresponds to an essentially unique, folded 3D structure called the native conformation.

- Uniqueness should not be taken too literally
  - limited structural flexibility often part of biological function
  - there are actually disordered or unstructured proteins that nonetheless are functional

Q: Is the native conformation just a local free energy-minimum from which it cannot escape,

or

is it the global free energy-minimum?



For many proteins, there are experiments that suggest that the native conformation is the global free energy minimum.

Refolding experiments:

- Denature protein. Change T, pH, etc.
- Restore physiological conditions
- Spontaneous refolding to the native state

Christian B. Anfinsen did such experiments in 1960s — Nobel prize.

Forces that drive folding

- **H bonding**

  Stabilizes α-helix and β-sheet structure.

- **Hydrophobic effect.** We know it is important because:
  - Proteins have a **hydrophobic core**. Polar and charged aa on surface.
  - Hydrophobicities of amino acids in the core are highly conserved between different species. Align amino acid sequences of related proteins (with similar 3D structure): common with variations but hydrophobicities conserved.
  - Cold unfolding.

    Know that proteins unfold at high T but some unfold also at low T. May seem surprising, but hydrophobic interactions actually get weaker with decreasing T (solubility of small nonpolar molecules increases as T decreases). So cold unfolding makes sense if the hydrophobic effect is important for protein stability.

- Attraction between positively and negatively charged amino acids. Not as important as one may think, because of the shielding effect of water (high ε).

Aggregation

Typically, the surface of proteins <u>not perfectly polar</u> but there are also some sticky nonpolar amino acids.

$\Rightarrow$ attraction between different proteins which can lead to the aggregation of proteins.

Nelson gives examples of both <u>unwanted</u> and <u>functional</u> aggregation driven by hydrophobicity.

A special and important example of protein aggregation not mentioned by Nelson is so-called <u>amyloid structure</u>.

formation involves two steps:

1) Misfolding or unfolding
2) Aggregation into "amyloid fibrils"
   (β-sheet rich structures in which proteins are connected by intermolecular h-bonds)

Amyloid aggregation is currently studied intensively by many research groups, primarily because it has been discovered that this type of aggregation occur in a number of diseases such as Alzheimer's and Parkinson's.

Together, they are sometimes called <u>protein misfolding diseases</u>.