7. Relevant interactions for biopolymers

Biopolymers in the cell do not take random conformations. Instead, they take up specific shapes that lead to their functional properties.
For example, proteins can fold spontaneously (that is, without any help), after translation, in their three-dimensional shape (Anfinsen '59, '60, '63 → Nobel prize 1973). They can do so only because their folding is driven by interactions between the amino-acids. We must therefore first describe the relevant interactions between monomers in an acqueous solution.

1) Van der Waals interactions

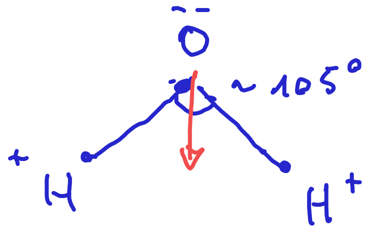
These interactions stem from the mutual polarization between molecules. As long as there is a convenient polarisation, which of course grows stronger at shorter distances, the Van der Waals interaction is always attractive, although rather weak compared to the others.

2) Hydrogen bond

This is a very peculiar interaction, that is typical of water and whose ubiquitous relevance for biopolymers is a testament for their evolution in acqueous solutions.

2.a) Between water molecules

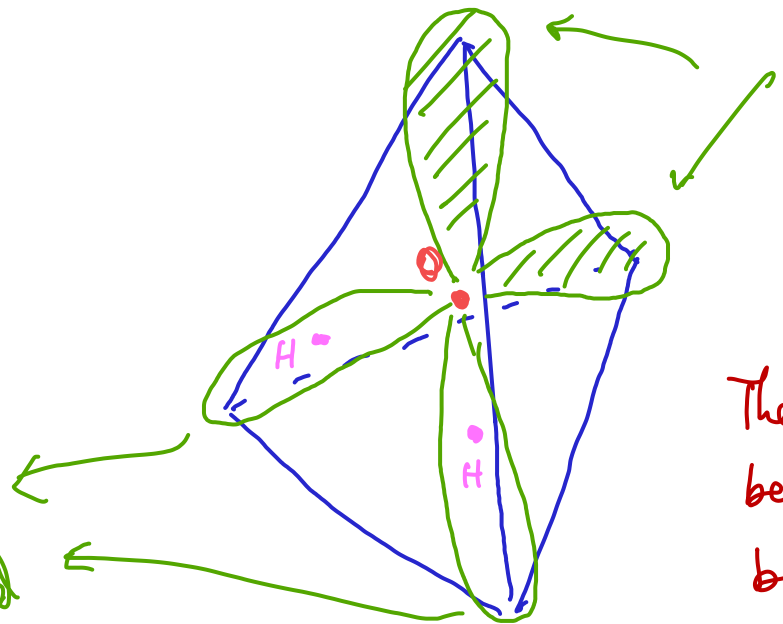
A water molecule is typically represented as a "wedge" with the oxygen in the middle



The centers of mass of the positive and negative charges do not coincide, and as a consequence there is a dipole ⇒ water molecules are polar.

Actually, the situation is a little more complex: recall that we must think "quantum" when we look at the molecular orbitals.

Detailed calculations show that the electronic orbitals are made of four lobes, roughly pointing at the vertices of a tetrahedron, with the oxygen in the middle:

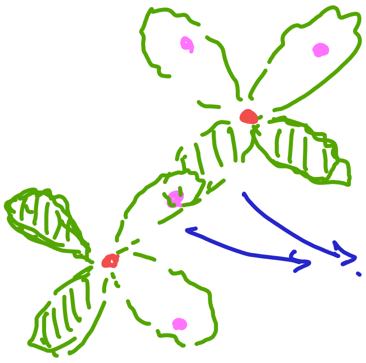


excess of electrons ⇒ - charge

defect of electrons ⇒ H is unscreened ⇒ + charge

There is thus a mismatch between the centers of mass, but from a more complex setting than initially believed.

The tetrahedral geometry also gives constraints on the interactions between water molecules. In a 2D rendering,



excess and defect lobes overlap

⇒ electrostatic interaction

⇒ overlap of electronic orbitals (covalent)

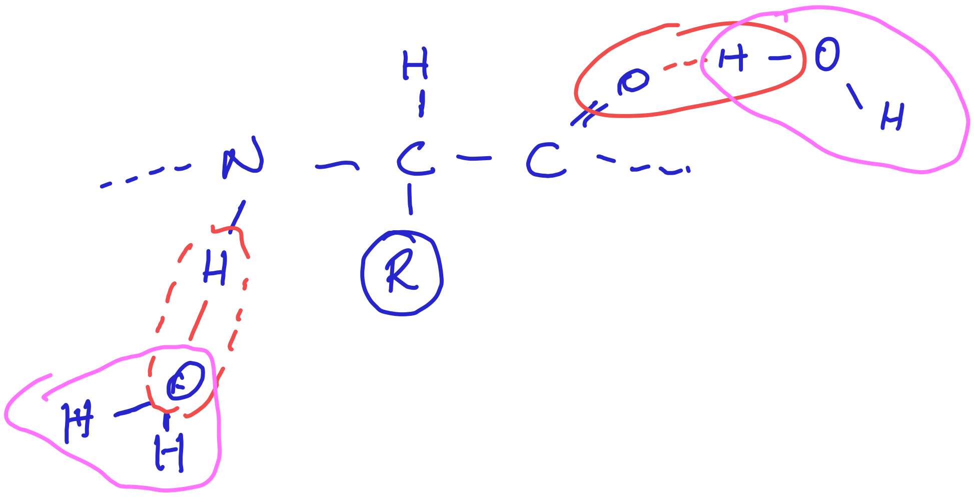
The hydrogen bond is partially electrostatic and partially covalent (quantum), which explains its strength.

But :
- highly orientation dependent
- very short range (orbital densities fall off exponentially fast)

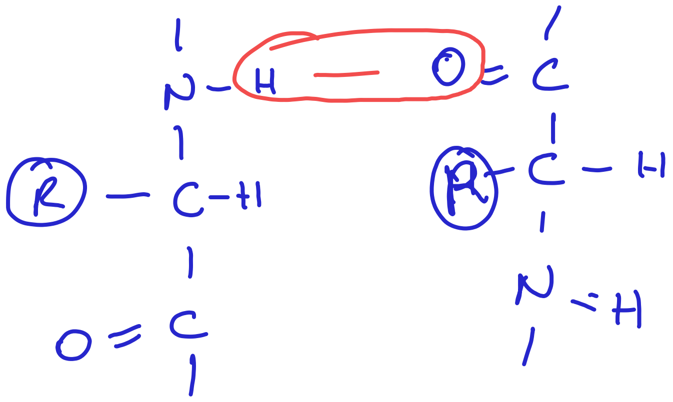
Satisfying the hydrogen bond is energetically convenient at low temperatures, but its high directionality imposes special spatial arrangements

⇒ that's why ice is less dense than water: at lower T, water molecule must take a tetrahedral arrangement, with selective interactions, at the cost of density.

2.b Between amino-acids and water



2.c Between amino-acids



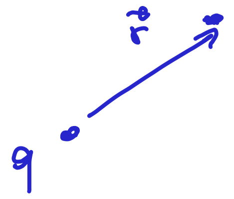
Is it better than amino-acid/water?

The hydrogen bond between amino-acids gives a lot of "order" to collapsed proteins, but it is unlikely to induce the collapse in the first place, because to form it, the protein gives up two hydrogen bonds with water

3. Electrostatics

How does electrostatics work in a medium with charged particles that can move around?

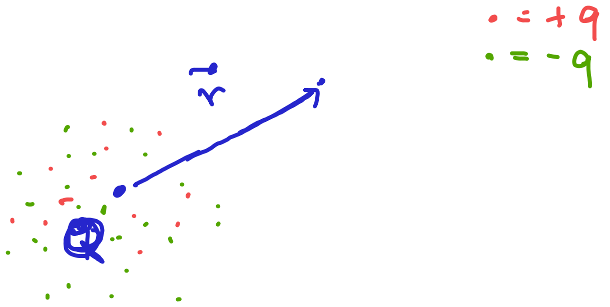
In a dielectric we know that the electrostatic potential is just modified by the dielectric constant of the medium



$$V(\vec{r}) = \frac{q}{4\pi\varepsilon_0\varepsilon_r|\vec{r}|}$$

↳ due to the polarizability of the medium

We now let charges move around



We assume that the medium is globally neutral:

$$\int c_+(\vec{r})\, d\vec{r} = N_+ = N_- = \int c_-(\vec{r})\, d\vec{r}$$

density of positive charge carriers

density of negative charge carriers

tot. number of positive charge carriers in the volume

tot. number of negative charge carriers in the volume

Here we work in the assumption that the charge of positive and negative charge carriers is the same (opposite sign of course). If not, it can be generalized.

We also set the density at ∞: $c_+(\infty) = c_-(\infty)$ so that, infinitely far away from Q the concentration is constant and the medium locally neutral

To find the potential we use the Poisson equation:

$$\nabla^2 V = -\frac{1}{\varepsilon}\underbrace{\left[Q\,\delta(\vec{r}) + q\,c_+(\vec{r}) - q\,c_-(\vec{r}) \right]}_{\text{total charge density}}$$

We look at the problem at equilibrium:

The energy of a positive charge in $\vec{r}$ is $q\,V(\vec{r})$, and the energy of a negative charge is $-q\,V(\vec{r})$.

We thus know that

$$\left.\begin{aligned} c_+(\vec{r}) &= c_+(\infty)\, e^{-\beta q V(\vec{r})} \\ c_-(\vec{r}) &= c_-(\infty)\, e^{\beta q V(\vec{r})} \end{aligned}\right]$$

at infinite distance from Q, $V(\vec{r}) \to 0$, and the concentrations go to their values.

This leads to the Poisson-Boltzmann equation:

$$\nabla^2 V = -\frac{1}{\varepsilon}\left[Q\,\delta(\vec{r}) + q c_+(\infty)\, e^{-\beta q V} - q c_-(\infty)\, e^{\beta q V} \right]$$

This is a highly non-linear equation, but can be solved in some approximations: weak potential $\Rightarrow$ $\beta q V \ll 1$

$$\Rightarrow \quad e^{\pm \beta q V} \simeq 1 \pm \beta q V$$

and

$$\nabla^2 V \simeq -\frac{1}{\varepsilon}\left[Q\,\delta(\vec{r}) + \cancel{q\,c_+(\infty)} - \beta q^2 c_\infty V - \cancel{q\,c_-(\infty)} - \beta q^2 c_\infty V \right] =$$

$$= -\frac{1}{\varepsilon} Q\,\delta(\vec{r}) + 2\,\frac{\beta q^2}{\varepsilon}\, c_\infty V$$

Or

$$\nabla^2 V - 2\frac{\beta q^2}{\varepsilon} c_\infty V = -\frac{1}{\varepsilon} Q\, \delta(\vec{r})$$

This equation is solved by Fourier transform

$$\tilde{V}(\vec{k}) = \int d\vec{r}\, e^{-i\vec{k}\cdot\vec{r}}\, V(\vec{r}) \qquad V(\vec{r}) = \frac{1}{(2\pi)^3}\int d\vec{k}\, e^{i\vec{k}\vec{r}}\, \tilde{V}(\vec{k})$$

$\Downarrow$

$$\int d\vec{r}\, e^{-i\vec{k}\cdot\vec{r}}\delta(\vec{r}) = 1$$

$$-\left(k^2 + 2\frac{\beta q^2}{\varepsilon}c_\infty\right)\tilde{V} = -\frac{1}{\varepsilon} Q \cdot 1$$

$$\Rightarrow \quad \tilde{V}(\vec{k}) = \frac{Q}{\varepsilon}\,\frac{1}{k^2 + 2\frac{\beta q^2}{\varepsilon}c_\infty} = \frac{Q}{\varepsilon}\,\frac{1}{k^2 + k_0^2}$$

with $k_0 = \sqrt{2\frac{\beta q^2}{\varepsilon}c_\infty}$

Then we anti-transform

$$V(\vec{r}) = \frac{1}{(2\pi)^3}\int d\vec{k}\, \frac{Q}{\varepsilon}\,\frac{1}{k^2+k_0^2}\, e^{+i\vec{k}\cdot\vec{r}} =$$

$$= \frac{1}{(2\pi)^3}\int_0^{2\pi} d\varphi \int_0^{\pi} d\theta \sin\theta \int_0^{\infty} k^2 dk\, \frac{Q}{\varepsilon}\,\frac{1}{k^2+k_0^2}\, e^{ikr\cos\theta} =$$

$$= \frac{1}{(2\pi)^2}\int_0^{\infty} dk\, k^2\, \frac{Q}{\varepsilon}\,\frac{1}{k^2+k_0^2}\int_0^{\pi} d\theta \sin\theta\, e^{ikr\cos\theta} =$$

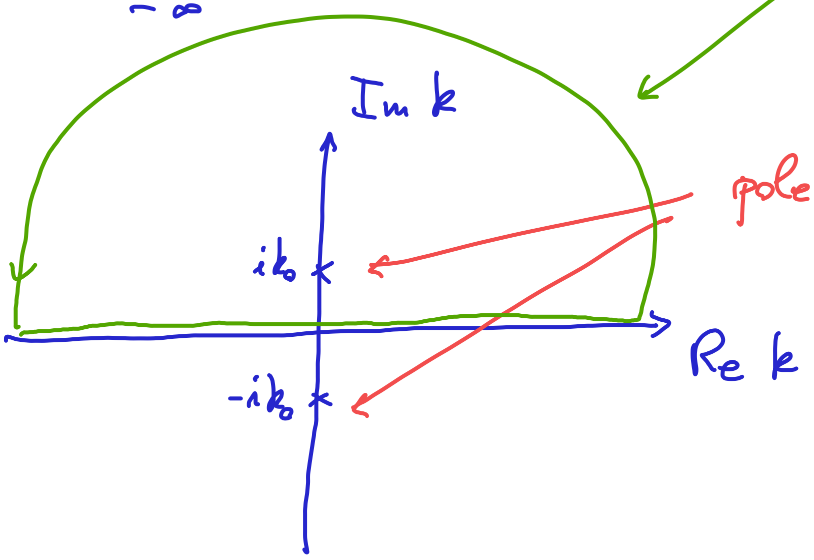
$$= \frac{1}{(2\pi)^2}\frac{Q}{\varepsilon}\int_0^\infty dk\, k^2 \frac{1}{k^2+k_0^2}\left[-\frac{1}{ikr}\, e^{ikr\cos\theta}\right]_0^\pi =$$

$$= \frac{1}{(2\pi)^2}\frac{Q}{\varepsilon}\int_0^\infty dk\, k^2\frac{1}{k^2+k_0^2}\left(+\frac{1}{ikr}\right)\left(e^{+ikr}-e^{-ikr}\right)=$$

$$=\frac{1}{(2\pi)^2}\frac{Q}{\varepsilon}\frac{1}{ir}\left[\int_0^\infty dk\,\frac{k}{k^2+k_0^2}\,e^{ikr} - \underbrace{\int_0^\infty dk\, \frac{k}{k^2+k_0^2}\,e^{-ikr}}_{k\to -k}\right]=$$

$$=\frac{1}{(2\pi)^2}\frac{Q}{\varepsilon}\frac{1}{ir}\left[\int_0^\infty dk\,\frac{k}{k^2+k_0^2}\,e^{ikr}+\int_{-\infty}^0 dk\,\frac{k}{k^2+k_0^2}\,e^{ikr}\right]=$$

$$=\frac{1}{(2\pi)^2}\frac{Q}{\varepsilon}\frac{1}{ir}\int_{-\infty}^{+\infty}dk\,\frac{k}{k^2+k_0^2}\,e^{ikr}$$



By Jordan's lemma, we close in the upper plane

poles of the integrand

$$\int_{-\infty}^{+\infty}dk\,\frac{k}{k^2+k_0^2}\,e^{ikr} = 2\pi i\,\mathrm{Res}\left(\frac{k}{k+ik_0}\,e^{ikr}\right)_{ik_0}=$$

$$=2\pi i\,\frac{ik_0}{2ik_0}\,e^{-k_0r}=\frac{2\pi i}{2}\,e^{-k_0r}=\pi i\, e^{-k_0 r}$$

$$\Rightarrow \quad V(\vec r)=\frac{Q}{\varepsilon}\frac{1}{(2\pi)^2}\frac{i\pi}{ir}\,e^{-k_0r}$$

Finally

$$V(\vec{r}) = \frac{Q}{4\pi\varepsilon r} e^{-k_0 r}$$

with $k_0 = \sqrt{2 \frac{q^2}{\varepsilon k_B T} c_\infty} \Rightarrow \lambda_D = \sqrt{\frac{\varepsilon k_B T}{2 q^2 c_\infty}}$

Debey length

$$V(\vec{r}) = \frac{Q}{4\pi\varepsilon r} e^{-r/\lambda_D}$$

no screening

If $c_\infty = 0 \Rightarrow \lambda_D = \infty \Rightarrow V(\vec{r}) = \frac{Q}{4\pi\varepsilon r}$ ok

If $c_\infty = \infty \Rightarrow \lambda_D = 0 \Rightarrow V(\vec{r}) = 0 \quad \forall \vec{r} \neq 0$ ok

perfect screening

If $T \to \infty \Rightarrow \lambda_D \to 0 \Rightarrow$ no screening

If $T \to 0 \Rightarrow \lambda_D \to \infty \Rightarrow$ perfect screening

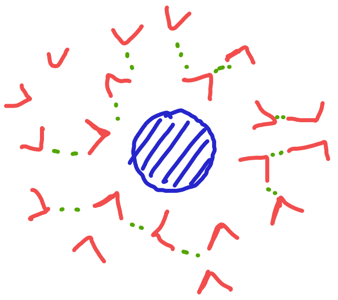
Summarizing: electrostatics in a ionic solution is relevant only at very short distances, smaller than the Debey length, which, in biological fluids as the cytoplasm, is about 2 nm $\Rightarrow$ short range!

4. Hydrophobic interactions

The hydrophobic interaction is likely the most important interaction for biological polymers. As its name suggests, it is due to the "fear for water" of some molecules. Which ones?

It is well known that oil does not dissolve in water, as if its molecules where attracting each other. Oil is one of a large category of substances, hydrophobic ones, that share the property of being by-and-large neutral: no net charge, no dipole. Essentially, they do not interact with water.

What are the consequences?



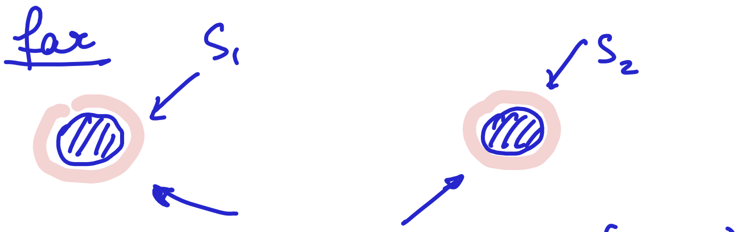
water molecules in "bulk", far from the non polar molecule, can form hydrogen bonds in any direction.

Water molecules close to the interface lose some of the potential binding partners ⇒ less convenient.

Water pays a penalty at being in contact with a non-polar molecule. This penalty can be quantified as proportional to the contact surface ⇒ it's a surface tension (free-energy per unit surface) which is positive: the larger the surface, the larger the penalty.

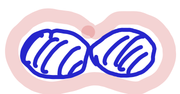
Let's examine what happens with 2 molecules

① far



$\Delta G_{far} = \gamma\, S_{far} = \gamma (S_1 + S_2)$

② close



$\Delta G_{close} = \gamma\, S_{close}$

But it is pretty clear, geometrically, that

$$S_{close} < S_1 + S_2$$

as a consequence

$$\Delta G_{far} > \Delta G_{close}$$

Since at equilibrium a system tends toward the minimum of the free energy, it implies that there is an effective attraction between hydrophobic molecules.

From a more formal approach, we can say that we have two hydrophobic molecules in $\vec{R}_1$ and $\vec{R}_2$ and many water molecules in $\{\vec{r}_i\}$, then the partition function of the system, for definite $\vec{R}_1$ and $\vec{R}_2$, is

$$Z(\vec{R}_1, \vec{R}_2) = \int \prod_i d\vec{r}_i \quad e^{-\beta E(\{\vec{r}_i\}, \vec{R}_1, \vec{R}_2)} =$$

$$= e^{-\beta G(\vec{R}_1, \vec{R}_2)}$$

with

$$G(\vec{R}_1, \vec{R}_2) = -k_B T \ln Z(\vec{R}_1, \vec{R}_2)$$

and it clear that $G(\vec{R}_1, \vec{R}_2)$, namely the hydrophobic interaction, depends in a non-trivial way from the temperature.