2 Structure

2.1 Coulomb interactions

While the information needed for reproduction of living systems is chiefly maintained in the sequence of macromolecules, any practical use of this information must rely on the physical forces that shape the molecules into functioning, sequence-dependent, structures. These forces and the resulting structures are the topic of the second segment of this course.

Since neither gravity, nor nuclear interactions, are particularly relevant to most organisms, the forces that shape the molecules of life are various manifestations of the electromagnetic interactions between electrons and nuclei. These include the strong covalent bonds (maintaining the primary connectivity of a molecule), the weaker hydrogen bonds (sensitive to orientations of the participating moieties), and the even weaker (and roughly direction independent) van der Waals forces. However, for these molecules to properly fold and function in the cell environment, their functionally relevant energy scales should be of the order of the thermal energy $k_B T$ at room temperature. Higher energies would freeze the corresponding degrees of freedom, while lower energies would be irrelevant and ignored in comparison to the ubiquitous thermal fluctuations. Thus entropic considerations play a major role in biomolecules, as will be emphasized in the much simpler systems considered in the following sections.

2.1.1 Charge dissociation in solution

Entropy is indeed the reason why many molecules (electrolytes) dissociate and ionize in solution. The opposing charges making up an ion clearly minimize the Coulomb energy by being in close proximity in a bound (molecular) state. The loss of this electrostatic energy in the dissociated (ionized) state is balanced by the gain in configurational entropy. We can quantify this by an approximate evaluation of the change in free energy upon dissociation, as

$$\Delta F = \Delta E - T \Delta S = -\mathcal{E}_b + k_B T \log \left(\frac{V}{N v_0} \right). \tag{2.1}$$

Here, $\mathcal{E}_b$ is the binding energy, T is the temperature, k_B is the Boltzmann constant, and v_0 is some characteristic volume. The gain in entropy is estimated from the number of positions available for each of N particles in the volume V. In a more systematic evaluation of the partition function, $v_0 = \lambda^3$, where λ is the "thermal wavelength". Setting the free energy change to zero, gives the equilibrium concentration

$$c = \frac{N}{V} = \frac{1}{\lambda^3} e^{-\beta \mathcal{E}_b}. \tag{2.2}$$

The electrostaic contribution to the binding energy, $\mathcal{E}_c$, can be computed from Coulomb's law, as

$$\mathcal{E}_c = \frac{q_1 q_2}{\epsilon r} = \frac{e^2 z^2}{\epsilon r}, \tag{2.3}$$

where ϵ denotes the dielectric constant of water, z is the valence, and e is the electron charge. The physically significant quantity is the ratio of this energy to the thermal energy $k_B T$, which can be expressed as

$$\beta \mathcal{E}_c = \frac{\beta e^2 z^2}{\epsilon r} = z^2 \frac{l_B}{r}, \tag{2.4}$$

where we have defined the *Bjerrum length*

$$l_B = \frac{e^2}{\epsilon k_B T}. \tag{2.5}$$

For water, $\epsilon \approx 81$, and the Bjerrum length is about 7.1 Å. Very roughly, we can say that at separations larger than l_B, the Coulomb interaction between unit charges in water is insignificant compared to thermal energy.
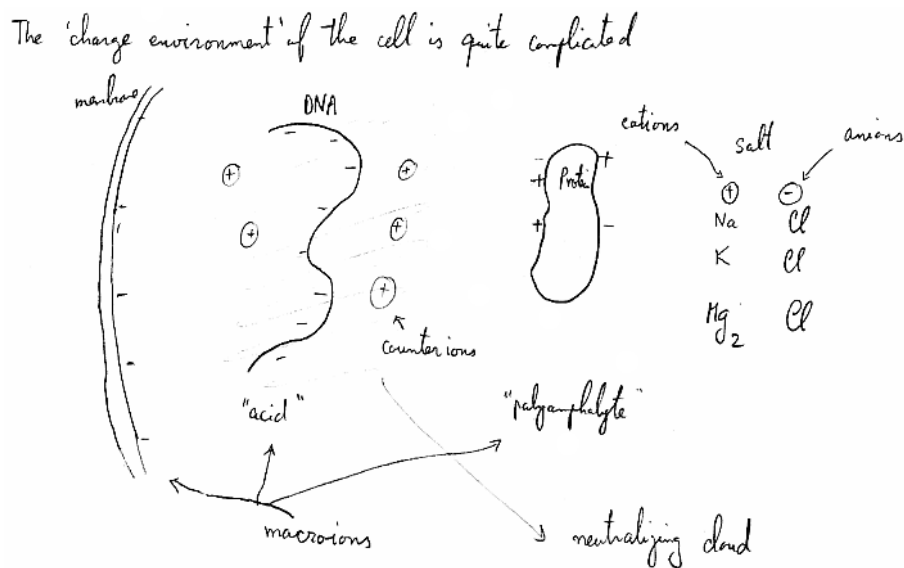
We can also think of dissociation as the chemical reaction

$$CA \rightleftharpoons C_+ + A_-. \tag{2.6}$$

(The dissociated positive charge is called a *cation*, the negative one an *anion*.) The *equilibrium constant* of the reaction

$$K_{eq.} \equiv \frac{[C_+][A_-]}{[CA]} \propto e^{-\beta \mathcal{E}_b}, \tag{2.7}$$

is a measure of the ease with which ionization occurs. For strong electrolytes, such as $Na^+ Cl^-$ (salt), $Na^+ OH$ (base) and $H^+ Cl$ (acid), which dissociate almost totally, the net binding energy is small. Weaker electrolytes are more strongly bound and dissociate less readily. Water itself can dissociate into H^+ and OH^- ions, but at room temperature this process only produces about 10^{-7} hydrogen ions per mole.

Biological molecules also dissociate, and the 'charge environment' of a cell is quite complicated. The lipids forming the cell membrane become negatively charged upon dissociation, as does DNA. The latter is an acid that releases H^+ ions, leaving behind a negatively charged backbone. Proteins can also release H^+ ions, but some of the amino-acid side groups are actually *basic*, releasing OH^-. A molecule of this sort, which can develop regions both of positive and of negative charge upon dissociation, is called a *polyampholyte*. Molecules like the DNA backbone, which carry a uniform charge, are known as *polyelectrolytes*. Together, both sorts of macromolecules are referred to as *macroions*, and the small charged particles they give up into the cytoplasm are called *counterions*. The electrostatic interactions between the macromolecules are very important for their biological function– the repulsive forces prevent aggregation, while attractions are important for docking and recognition. However, calculating these interactions in the environment of the moving counterions is not an easy task.

2.1.2   The Poisson–Boltzmann Equation

We know that proteins bind to one another, and that some proteins bind to DNA. In principle, an effective interaction between such macroions can be obtained by holding them at fixed separation (and orientation). A constrained partition function is then evaluated by integrating over all the other degrees of freedom, e.g. the positions of the more mobile counterions, as

$$e^{-\beta F(\text{macroions})} = Z_{\text{res.}} = \int \prod_i d^3 r_i \, e^{-\beta \mathcal{H}_c}. \tag{2.8}$$

In addition to steric constraints (the excluded volume around each atom), the Hamiltonian $\mathcal{H}_c$ includes the direct Coulomb interactions between the macroions, their interactions with the counterions, as well as the interactions amongst counterions. The restricted partition function is too hard to compute directly, and we shall instead resort to a "mean-field" approximation in which each counterion is assumed to experience an effective potential $\phi(\vec{r})$ due to the macroion, as well as all the other counterions. The effective potential is then computed self-consistently.

In this approximation, the position-dependent density of counterion species α adjusts to the potential through the Boltzmann weight, as

$$n_\alpha(\vec{r}) = \bar{n}_\alpha \exp\left[-\beta \phi(\vec{r}) z_\alpha e\right]. \tag{2.9}$$

Note that $\bar{n}_\alpha$ is in general not the particle density, but an overall parameter that needs to be adjusted so that the integral over $\vec{r}$ leads to the correct number of counterions. The potential $\phi(\vec{r})$ is in turn determined by the charge distribution, and satisfies the Poisson equation.

$$\nabla^2 \phi = -\frac{4\pi}{\epsilon} \rho(\vec{r}). \tag{2.10}$$

The charge density at each point has a contribution from the macroions, and from the

(fluctuation averaged) counterion density, and thus

$$\rho(\vec{r}) = \rho_{\text{macroions}}(\vec{r}) + \sum_\alpha z_\alpha e \bar{n}_\alpha e^{-\beta \phi z_\alpha e}. \tag{2.11}$$

Self-consistency then leads to the *Poisson-Boltzmann Equation*

$$\nabla^2 \phi = -\frac{4\pi}{\epsilon} \left[\rho_{\text{macroions}}(\vec{r}) + \sum_\alpha z_\alpha e \bar{n}_\alpha e^{-\beta \phi z_\alpha e} \right], \tag{2.12}$$

This equation, while a drastic simplification of the original problem, is commonly used. It is a *non-linear* partial differential equation, and exact solutions are available only for a few simple geometries. It does have the virtue of being at least numerically solvable.

2.1.3 Debye screening by salt ions

We expect physically that counterions will accumulate near regions of opposite charge to lower the electrostatic energy. As a result a charged macroion will be surrounded by a cloud of counterions, shielding and reducing its net charge. This effect is easily captured in a linearized version of Eq. (2.12). Linearizing the Boltzmann weight is actually a quite good approximation when the Coulomb interaction between macroions is *screened* by a high concentration of salt ions. The first step is to expand the exponential such that the local counterion charge density is

$$\sum_\alpha z_\alpha \bar{n}_\alpha e^{-\beta z_\alpha e \phi} \approx \sum_\alpha z_\alpha \bar{n}_\alpha \left[1 - \beta z_\alpha e \phi + \cdots \right]. \tag{2.13}$$

We note that at this order the local variations in counterion charge density and potential are simply proportional. Since the salt ions are overall neutral, we can then identify $\bar{n}_\alpha$ with the overall particle density of species α at this order. The condition of charge neutrality, $\sum_\alpha z_\alpha \bar{n}_\alpha = 0$, then leads to

$$\boxed{\nabla^2 \phi = -\frac{4\pi}{\epsilon} \rho_{\text{macro}}(\vec{r}) + \frac{\phi}{\lambda^2},} \tag{2.14}$$

where

$$\boxed{\lambda^{-2} = \sum_\alpha \frac{4\pi}{\epsilon} \beta e^2 z_\alpha^2 \bar{n}_\alpha = 4\pi l_B \sum_\alpha z_\alpha^2 \bar{n}_\alpha.} \tag{2.15}$$

This is the *Debye-Hückel* equation, and the parameter λ is the Debye *screening length*. In a typical biological environment λ is around 1nm.

For the case of a point charge $Q = ze$, i.e. for

$$\rho_{\text{macro}}(\vec{r}) = ze\delta^3(r), \tag{2.16}$$

the solution is the exponentially damped version of the Coulomb potential

$$\phi(\vec{r}) = k_B T \frac{z l_B}{|\vec{r}|} e^{-\frac{|\vec{r}|}{\lambda}}. \tag{2.17}$$

Since Eq. (2.14) is linear, its solution for a general distribution of charges is obtained by simple superposition, leading to the interaction energy

$$\beta E_{\text{interactions}}(\text{macroions}) = l_B \sum_{m<n} \frac{z_m z_n}{|\vec{r}_{mn}|} e^{-\frac{|\vec{r}_{mn}|}{\lambda}}. \tag{2.18}$$

2.1.4 Dissociation from a plate

Let us now consider the full Poisson–Boltzmann equation for the simple geometry of a flat plate, e.g. describing a membrane. Upon dissociation the membrane is negatively charged; its charge density denoted by $\sigma = -e/d^2$ (i.e. ignoring discreteness effects, the negative charges are on average a distance d apart). The neutralizing counterions, of charge $+e$ are present in the solution on both sides of the membrane. Due to translational symmetry, the average charge density (and potential) only depend on the separation from the plate, indicated by the coordinate y, and Eq. (2.12) now reads

$$\frac{d^2\phi}{dy^2} = -\frac{4\pi}{\epsilon} e\bar{n} e^{-\beta e\phi(y)}. \tag{2.19}$$
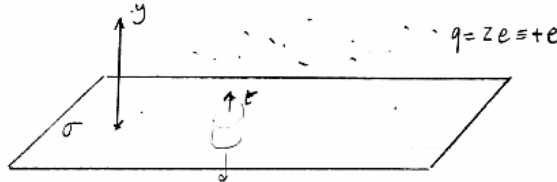
The following trick allows us to guess the solution to Eq. (2.19). We first make a transformation to

$$W(y) = e^{\beta e\phi/2} \implies \phi = \frac{2}{\beta e} \log W, \tag{2.20}$$

such that

$$\phi' = \frac{2}{\beta e} \frac{W'}{W}, \quad \text{and} \quad \phi'' = \frac{2}{\beta e} \cdot \frac{W''W - W'^2}{W^2}.$$

Multiplying both sides by W^2, Eq. (2.19) can be recast as

$$\frac{2}{\beta e} \left(W''W - W'^2 \right) = -\frac{4\pi}{\epsilon} e\bar{n}. \tag{2.21}$$

While still non-linear, it is easy to see that a linear function of y satisfies the above equation, and we set

$$W(y) = 1 + \frac{y}{y_0}, \tag{2.22}$$

where we have arbitrarily set $\phi(y \to 0) = 0$, such that $W(0) = 1$, and $y_0^{-2} = 2\pi\beta e^2 \bar{n}/\epsilon$. Note, however that $\bar{n}$ is simply a parameter that needs to be set by the requirement of charge neutrality. It is easier to trade in this parameter for y_0 and constrain the latter. The electrostatic potential thus has the form

$$\phi(y) = \frac{2}{\beta e} \log\left[1 + \frac{y}{y_0}\right]. \tag{2.23}$$

The undetermined length y_0, clearly sets the scale at which the counterion density changes significantly. It can be determined by examining the limit $y \ll y_0$, for which Eq. (2.23) becomes

$$\phi(y) \approx \frac{2}{\beta e}\frac{y}{y_0}. \tag{2.24}$$

Indeed, at distances close enough to the surface that screening is unimportant, we expect the electric field to be (e.g. by appealing to a Gaussian pillbox)

$$E = \frac{2\pi\sigma}{\epsilon},$$

and a corresponding potential

$$\phi = -\frac{2\pi\sigma}{\epsilon}y. \tag{2.25}$$

Comparing this result with Eq. (2.24) indicates that

$$y_0 = \frac{\epsilon}{e\sigma\pi\beta} = \frac{\epsilon}{\beta e^2}\frac{d^2}{\pi} = \frac{d^2}{\pi l_B}. \tag{2.26}$$

This characteristic scale is known as the *Guoy-Chapman length*, characterizing the thickness of the "diffusive boundary layer" of ions that shields a charged membrane.

Retracing the steps of algebra, it is easy to check that

$$\bar{n} = \frac{\pi}{2}\frac{l_B}{d^4},$$

and

$$n(y) = \frac{\bar{n}}{W^2} = \frac{\pi}{2}\frac{l_B}{d^4}\left(1 + \frac{y}{y_0}\right)^{-2}. \tag{2.27}$$

At large separations, $y \gg y_0$ from the plate, the counterion density falls off as $(2\pi l_B y^2)^{-1}$. The corresponding potential behaves as $\phi(y) \approx 2\ln(y)/(\beta e)$, very different from the linear potential in vacuum, and also quite distinct from an exponential decay that may have been surmised based on Debye-Huckel screening. Clearly this type of screening will lead to a quite

different interaction between charged plates, a question that will be taken up in the next problem set. In connection to that, we note that Eq. (2.21) also admits solutions of the form $\cos(y/y_1 + \theta)$ with parameters y_1 and θ that can be adjusted to conform to the boundary conditions corresponding to parallel charged plates.

While the solutions to the Poisson-Boltzmann equation are interesting and informative, they do not capture the entire physics of the problem. Fluctuations in charge density can be important in lowering the free energy. Indeed at high temperatures the correlated fluctuations around two similarly charged macroions further reduce the repulsion through a dipole-dipole interaction reminiscent of the van der Waals force. If strong enough these fluctuations can entirely reverse the sign of the force, leading to an attractive interaction between like-charged macroions. Such phenomena, not captured by the Poisson-Boltzmann equation, have received considerable attention in recent years.

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