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 compared to the thermal energy k_BT at room temperature. Much higher energies freeze the corresponding degrees of freedom, while lower energies are irrelevant and ignored in comparison to the ubiquitous thermal fluctuations. Since entropic contributions to the free energy are also of the order of k_BT, entropic considerations play a major role at molecular and cellular levels. The following two sections emphasize the role of entropy in the context of ionic interactions and polymer conformations.

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

$$\Delta F = \Delta E - T\Delta S = -\mathcal{E}_b + k_BT\log\left(\frac{V}{Nv_0}\right). \tag{2.1}$$

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. (A systematic evaluation of the partition function reproduces the above result with $v_0 = \lambda^3$, 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 of opposite charges, $\mathcal{E}_c$, can be estimated from Coulomb's law, as

$$\mathcal{E}_c = \frac{q_1q_2}{\epsilon r} = -\frac{e^2z^2}{\epsilon r}, \tag{2.3}$$

where ϵ is the dielectric constant of medium- water in cases of interest to us, 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_BT, 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 at room temperature. Very roughly, we may surmise that at separations larger than l_B, the Coulomb interaction between unit charges in water is insignificant compared to the thermal energy.

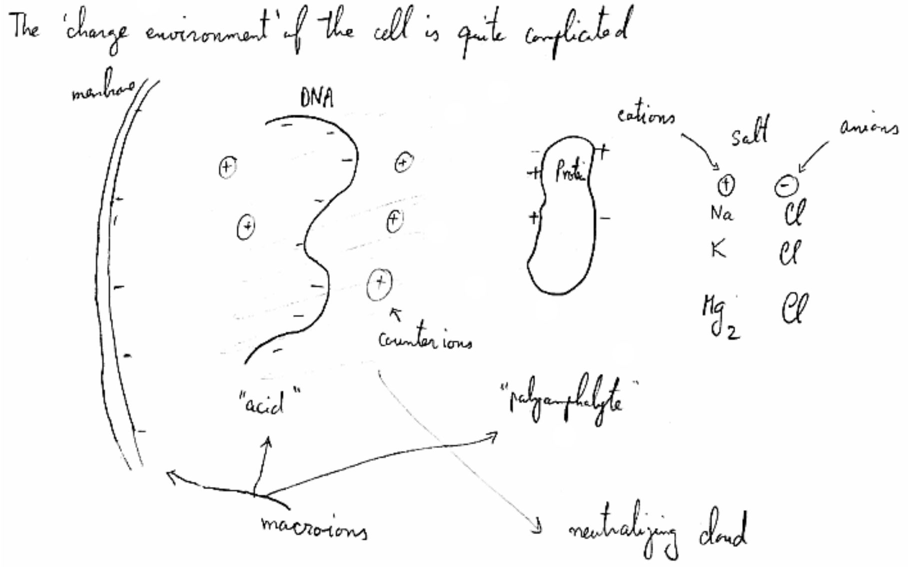

Figure 1: The charge environment of a cell.

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, expressed in terms of the concentrations of the different components as

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

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.* Generically, both types 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 influence 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 Coulomb 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 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 (with valence z_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 when the density is integrated over $\vec{r}$ the correct number of counterions is obtained. 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 for study of ionic solutions. 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). Expanding the Boltzmann weight in powers of ϕ is actually a quite good strategy when the Coulomb interaction between macroions is *screened* by a high concentration of salt ions. The first step is to linearize the exponential such that the local counterion charge density is

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

We note that at this order the local variations in counterion charge density and potential are simply proportional. Integrating the linearized equation for $n_\alpha(\vec{r})$, we find the total number $N_\alpha = \bar{n}_\alpha V\left[1 - \beta e z_\alpha \bar{\phi}\right]$. The value of the potential is in fact arbitrary up to a constant which can be absorbed into $\bar{n}$. Thus without loss of generality we can set $\bar{\phi} = 0$, in which case we can replace $\bar{n}_\alpha$ with the overall density $n_\alpha = N/V$. The mobile ions are a mixture of cations and anions from the dissociation of salt molecules in the solution, and counterions (typical H^+ and OH^{-1}) from dissociation of the macroions. The contribution of salt ions to the first term in Eq. (2.13) vanishes due to their overall charge neutrality, and neglecting the much smaller contribution from counterions released by the macroions (at high salt concentrations), we find

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

where

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

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 single point charge $Q = ze$, with

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

the solution is the exponentially damped version of the Coulomb potential

$$\phi(\vec{r}) = k_B T \frac{z l_B}{|\vec{r}|} \exp\left[-\frac{|\vec{r}|}{\lambda}\right] + \phi_0\,. \tag{2.17}$$

(The added constant ϕ_0 can be used to ensure $\overline{\phi} = 0$.) Since Eq. (2.14) is linear, its solution for a general distribution of charges is obtained by simple superposition, leading to the interaction energy

$$\beta E_{\text{interactions}}(\text{macroions}) = l_B \sum_{m<n} \frac{z_m z_n}{|\vec{r}_{mn}|} \exp\left[-\frac{|\vec{r}_{mn}|}{\lambda}\right]\,, \tag{2.18}$$

where $\vec{r}_{mn} = \vec{r}_m - \vec{r}_n$ is the distance between ions m and n.

2.1.4 Dissociation from a plate

The Debye-Hückel approximation is not applicable at low salt density. For example, consider the simple geometry of a flat plate, reminiscent of a membrane, with no salt in the ambient water solution. Upon dissociation the membrane is negatively charged; its charge density denoted by $\sigma = -e/d^2$ (i.e. the negative charges are on average a distance d apart, and their discreteness is ignored). 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 full Poisson–Boltzmann 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

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

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

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

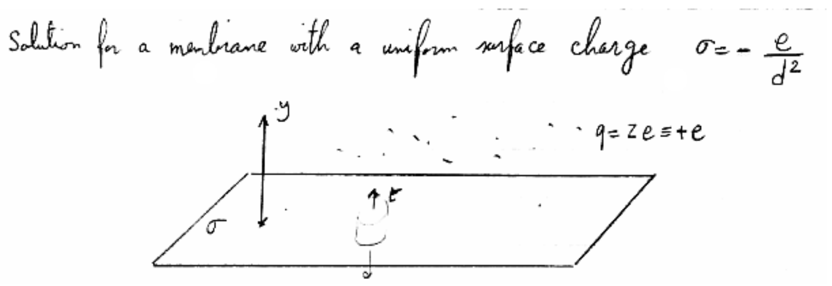

Figure 2: Membrane with a uniform surface charge.

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

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

where, without loss of generality, we have 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)

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

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, known as the *Guoy-Chapman length*, determines the thickness of the so-called "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 $\left(2\pi l_B y^2\right)^{-1}$. 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.