Lectures 11-13: Electrostatics of Salty Solutions

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Water as a medium of life: $\text{H}_2\text{O}$ dissociation into $\text{H}^+$ and $\text{OH}^-$

- in pure water: 1 $\text{H}_2\text{O}$ molecule out of $10^7$ is dissociated

- definition of the $\text{pH} = -\log_{10} [\text{H}^+]$

- thus, for pure water $\text{pH} = 7$

- the presence of ions or other molecules in $\text{H}_2\text{O}$ can change pH

- different amino acids can donate or accept $\text{H}^+$, thus their charged state depends on pH and that affects the protein structure

- example of an influenza virus uptake by a cell:
Variation of pH inside the body:

- pH of the blood is at 7.3
- inside the cell, e.g. lysosome (protein degradation) pH<4
- cells manipulate pH by H⁺ transport across the membrane
- in bacterium: $2 \times 10^{10}$ H₂O molecules
- $10^7$ ions (mM concentrations): Na⁺, K⁺, ...
- equilibrium constant and pH: charge separation in H₂O dictated by a competition between energetic and entropic effects

$$H_2O \leftrightarrow H^+ + OH^-$$
law of mass action using $\nu_{H_2O} = -1, \nu_{H^+} = 1, \nu_{OH^-} = 1$:

$$\frac{[H^+] [OH^-]}{[H_2O]} = \frac{[H^+]_0 [OH^-]_0}{[H_2O]_0} \exp[-\beta(\mu_{H^+}^0 + \mu_{OH^-}^0 - \mu_{H_2O}^0)]$$

$[A]_0$ ... the concentration of species A in some standard state

$\mu_A^0$ ... the chemical potential of species A in the standard state

pure water: presence of H+ is due to dissociation only

$$[H^+] = [OH^-]$$

$[H_2O] = [H_2O]_0$ (only 1 in $10^7$ molecules dissociated)

$[H_2O]_0 = 55 \text{ M}; [H^+]_0 = [OH^-]_0 = 1\text{ M};$

$$\mu_{H^+}^0 + \mu_{OH^-}^0 - \mu_{H_2O}^0 = 79.9 \text{ kcal/mol}$$

$$[H^+] [OH^-] = [H^+]^2 = 1.0 \times 10^{-14} \text{ M}^2 \rightarrow [H^+] = 10^{-7} \text{ M}$$
An average distance between the H+ ions as a function of pH
The charge state of macromolecules M and the pH of the solution

\[ HM \leftrightarrow H^+ + M^- \]

Dissociation constant \( K_d \):

\[ K_d = [H^+][M^-]/[HM] \]

A measure of the tendency of a macromolecule to undergo the dissociation reaction is known as pK of the molecule:

\[ pK = - \log_{10} K_d \]

Henderson-Hasselbalch equation:

\[ pH = pK + \log_{10} \frac{[M^-]}{[MH]} \]

pK is equal to pH, at which half of macromolecules has dissociated.
For example:
- pK = 1 for DNA;
- at pH = 7, the phosphates on the DNA backbone dissociated
  (each phosphate group carries 2 negative charges)
- different amino acids have different pK values
Salt concentration dependence of equilibrium constants $K$: (A) binding of Lac repressor to nonspecific DNA (B) binding of bovine pancreatic ribonuclease to DNA

The larger the $K$, the higher the binding probability

Figure 9.3 Physical Biology of the Cell (© Garland Science 2009)
Electrostatics for Salty Solutions: Review of EIs between charges
- a force between two charges $q_1$ and $q_2$:

$$F = (4\pi \varepsilon_0 D)^{-1} \frac{q_1 q_2}{r^2}$$

- $D$ ... a dielectric constant ($D=1$ for vacuum or air, $D=80$ for water)
- water molecules are polar, they arrange with respect to a local electric field

![Diagram](Image)
\[ E(r) = (4\pi\varepsilon_0 D)^{-1} \frac{Q}{r^2} e \]

\[ E_{\text{tot}}(r) = \sum_i E_i = \sum_i E(r - r_i) \rightarrow \text{superposition} \]

Instead of discrete distribution of charges (which results in individual electric fields), we will introduce continuous charge distribution \( \rho(r) \) within a small volume \( \Delta V \)

\[ \Delta Q = \rho(r) \Delta V \]
Electric field caused by A) a single charge, B) three charges, C) a local charge density

\[ E = \frac{1}{4\pi\varepsilon_0D} \frac{Q}{r^2} \hat{r} \]

\[ E_{\text{tot}} = E_1 + E_2 + E_3 \]

\[ \Delta E = \frac{1}{4\pi\varepsilon_0D} \frac{\rho\Delta V}{r^2} \hat{r} \]

Figure 9.6 Physical Biology of the Cell (© Garland Science 2009)
The relationship between the charge density and the electric field using the concept of the flux $\Phi$ of the electric field (flux = the # of electric field lines per unit area, perpendicular to the field direction):

$$\Phi = \int \mathbf{E}(\mathbf{r}) \cdot \mathbf{n} \, dA = \int (4\pi \varepsilon_0 D)^{-1} \frac{Q}{r^2} \mathbf{e}_r \cdot \mathbf{e}_r \, dA = \frac{Q}{(\varepsilon_0 D)}$$
Electric Flux and Gauss's Law

(A) point charge

\[ \Phi = \frac{Q}{\varepsilon_0 D} \]

(B) point charge

\[ \Phi = \frac{Q_1 - Q_2 + Q_3 - Q_4}{\varepsilon_0 D} \]

Figure 9.7 Physical Biology of the Cell (© Garland Science 2009)
Let the charge density depend only on x: Calculate the flux through a closed surface:
\[ \Phi = E_x (x + \Delta x) \Delta y \Delta z - E_x (x) \Delta y \Delta z = \frac{dE_x}{dx} \Delta x \Delta y \Delta z \]
so the Gauss's law is expressed as:
\[ \frac{dE_x (x)}{dx} = \frac{\rho (x)}{D\varepsilon_0} \]
or in general \( E = E(x,y,z) \)
for each component \( x,y,z \):
\[ \frac{\partial E_x}{\partial x} + \frac{\partial E_y}{\partial y} + \frac{\partial E_z}{\partial z} = \frac{\rho (x)}{D\varepsilon_0} \]
the most general form of Gauss's law.
From the electric field $E(r)$ description to the electrostatic potential $V(r)$

$V(r)$ … electrostatic potential = work per unit charge done to bring a test charge from infinity to $r$ very slowly

Example in 1D:

$E(x)$ as a result of a charge distribution $\rho(x)$:

$$V(x) = \int_{\infty}^{x} -(E(x') e_x) - (e_x dx')$$

$$= \int_{\infty}^{x} E(x') dx'$$

$$E_x(x) = \frac{dV(x)}{dx}$$
For each component of \( \mathbf{E}(\mathbf{r}) \):

\[
(E_x(x,y,z), E_y(x,y,z), E_z(x,y,z)) = (-\frac{\partial V(x,y,x)}{\partial x}, -\frac{\partial V(x,y,x)}{\partial y}, -\frac{\partial V(x,y,x)}{\partial z})
\]

Express the relationship between \( V(\mathbf{r}) \) and \( \mathbf{E}(\mathbf{r}) \) into Gauss's law:

\[
\nabla^2 V(x,y,x)/\partial x^2 + \nabla^2 V(x,y,x)/\partial y^2 + \nabla^2 V(x,y,x)/\partial z^2
= -\rho(x,y,x)/(D\varepsilon_0)
\]

We derived the Poisson equation that relates electrostatic potential to the charge density.

\[
\nabla^2 V(\mathbf{r}) = -\rho(\mathbf{r})/(D\varepsilon_0)
\]

\[\nabla^2 \ldots \text{Laplacian of the scalar function } V(\mathbf{r})\]
Energy cost associated with assembly a charged sphere
- for a general charge distribution:
  \[ U_{\text{EL}} = \frac{1}{2} \sum q_i V_i = \frac{1}{2} \int V(r) \rho(r) \, d^3r \]
  (bring charge 1 to the vicinity of charge 2 and the other way around → \(\frac{1}{2}\))
- for a sphere (to the right):
  \[ dU_{\text{EL}} = V(r) \, dq \]
  \[ V(r) = \int_r^\infty E(r')dr' = q/(4\pi \varepsilon_0 D) \int_r^\infty r'^{-2} \, dr' \]
  \[ = q/(4\pi \varepsilon_0 Dr) \]
  \[ dU_{\text{EL}} = V(r) \, dq \]
  \[ = 1/(4\pi \varepsilon_0 Dr) \rho \, 4/3\pi r^3 \rho 4\pi r^2dr \rightarrow \]
  \[ U_{\text{EL}} = \int_0^R 16\pi^2 \rho^2/(12\pi \varepsilon_0 D) \, r^4dr \]
  \[ = 3Q^2/(20\pi \varepsilon_0 DR) \]
What is an energy cost of separation of two charges (a) in vacuum and (b) in water?

- in water the charges are largely free (non-interacting)

**Bjerrum length** $l_B =$ length at which the electrostatic interaction energy between two oppositely charged charges is equal to the thermal energy $k_B T$: $e^2/(4\pi \varepsilon_0 D l_B) = k_B T$ or

$$l_B = \frac{e^2}{(4\pi \varepsilon_0 D k_B T)} \sim 0.7 \text{ nm (in water with } D=80)$$

![Diagram of Bjerrum length](image)
A simple globular protein = a ball of radius R made of amino acids: small beads with radii r
- all hydrophobic residues: inside the ball
- all polar (hydrophilic) residues: on the surface
- each of polar residues can release one unit charge into the solution

What is the self energy of the sphere if all charge is concentrated on a shell of radius R?
- if the # of polar residues as a function of R is \( Q_T \), then:

\[
U = \frac{Q_T^2}{(4\pi \varepsilon_0 D) 2R}
\]

\[
Q_T = Ne = \left(\frac{4\pi R^2}{\pi r^2}\right) e
\]

\[
U = \frac{e^2}{(4\pi \varepsilon_0 D)} 8 R^3/r^4 = k_B T \frac{8R^3 I_B}{(D r^4)}
\]
Energy cost to charge a protein:
- $I_B \sim 0.7 \text{ nm}$
- $r \sim 0.5 \text{ nm}$
- $U = k_B T R^3 \times 8 \times 0.7/(0.5)^4$ for $R \text{ [nm]}$
Electrostatics in Salty Solutions: Negatively Charged DNA in Ionic Solution with Counterions

- salty solutions are physiologically relevant

- DNA backbone is negatively charged

- positive ions in solution form a screening cloud because it lowers their electrostatic energy

- the thickness of the "cloud": interplay between lower EI energy and entropy loss
ESTIMATE: The size of the screening cloud $\lambda_D$
- concentration of + ions: $c_{\text{positive}} = c_\infty + \frac{1}{2} \Delta c$

where $\Delta c = c_{\text{positive}} - c_{\text{negative}}$
- the net charge of the screening cloud:
  $$Q = e \Delta c A \lambda_D$$
  ($A$ ... surface area of the biomolecule)
- the total charge of a biomolecule and the surrounding cloud is zero
  $$\Delta c = \frac{Q}{e A \lambda_D}$$
- electric field: $E = \frac{Q}{D \varepsilon_0 A}$
- electric potential: $V = \frac{Q \lambda_D}{2 D \varepsilon_0 A}$
In equilibrium the chemical potential away from the cloud is:
\[ \mu = \mu_0 + k_B T \ln(c_\infty/c_0) \]
The chemical potential of an ion inside the cloud:
\[ \mu = \mu_0 + k_B T \ln[(c_\infty + \frac{1}{2} \Delta c)/c_0] + e V \]
\[ = \mu_0 + k_B T \ln(c_\infty/c_0) \]
The two chemical potentials are the same in equilibrium:
\[ k_B T \ln(c_\infty/c_0) = k_B T \ln[(c_\infty + \frac{1}{2} \Delta c)/c_0] + eQ\lambda_D/(2D\varepsilon_0A) \]
So assuming that \( \Delta c \ll c_\infty \) we can write
\[ \ln(c_\infty + \frac{1}{2} \Delta c) - \ln(c_\infty) = \ln(1 + \frac{1}{2} \Delta c/c_\infty) \sim \frac{1}{2} \Delta c/c_\infty \]
and obtain the Debye screening length \( \lambda_D \) expressed by \( I_B \):
\[ \lambda_D = (4\pi I_B c_\infty)^{-\lambda_2} \]
Remember that \( I_B = e^2/(4\pi \varepsilon_0 D k_B T) \) ... Bjerrum length
The Poisson-Boltzmann Equation

- Poisson Eq.: relates the EI potential to the charge density
- Boltzmann distribution:
  - probability of different microstates
- far from the biomolecule:
  \[ c_{\text{positive}} = c_{\text{negative}} = c_\infty \]
- consider a negatively charged membrane with \( \sigma \) as a charge per unit area: only variation in the \( x \)-direction
  \[ c_{\text{positive}}(x) = c_\infty e^{-\beta z e V(x)} \]
  \[ c_{\text{negative}}(x) = c_\infty e^{+\beta z e V(x)} \]
- \( \pm z e V(x) \) ... the EI energy of \( \pm \) ions

Figure 9.16 Physical Biology of the Cell (© Garland Science 2009)
The total charge density \( \rho(x) \): 
\[
\rho(x) = z e c_{\text{positive}}(x) - z e c_{\text{negative}}(x)
\]
is related to the electric potential through the Poisson equation:
\[
\frac{d^2 V(x)}{dx^2} = -\frac{\rho(x)}{D \varepsilon_0}
\]
Resulting in the non-linear differential equation for salty solution which is the Poisson-Boltzmann equation:
\[
\frac{d^2 V(x)}{dx^2} = \frac{z e c_{\infty}}{D \varepsilon_0} \left[ e^{\beta z e V(x)} - e^{-\beta z e V(x)} \right]
\]
When the charge density on a biomolecule does not produce a too large electric potential \( V(x) \), we can use a linearized form:
\[
\frac{d^2 V(x)}{dx^2} = \frac{2 z^2 e^2 c_{\infty}}{D \varepsilon . k_B T} V(x)
\]
Known as the Debye-Huckel equation. Solution is well-known:
\[
V(x) = A e^{-x/\lambda_D} + B e^{+x/\lambda_D} \\
\lambda_D = \sqrt{\frac{D \varepsilon_0 k_B T}{2 z^2 e^2 c_{\infty}}} \\
\text{Debye screening length}
\]
Solution:

\[ V(x) = \frac{\sigma \lambda_D}{D \varepsilon_0} e^{-x/\lambda_D} \]

\[ \rho(x) = \frac{-\sigma}{\lambda_D} e^{-x/\lambda_D} \]

For a charged protein in a salt solution with charge density \( c_\infty = 200 \text{ mM} \) (typical for potassium ions inside a cell),

\( \lambda_D = 0.7 \text{ nm} \)
Viruses as Charged Spheres in a Salty Solution:
Debye-Hückel Model

What are viruses?

→ *virus*: an example of a macromolecular assembly of sizes ~10s to ~100s of nanometers

→ highly ordered and symmetrical objects made of proteins and nucleic acids

→ *capsid*: protein shell (repetitive packing of the same protein unit resulting in icosahedron: 12 vertices, 20 faces each with 3 edges)

→ *viral genome*: once in a host cell, command the construction of its own inventory of parts that further assemble into virus copies
Examples of Viral Capsid Structures

HIV virus (electron micrograph)
The energy cost for assembling a spherical shell of charge $Q$ and radius $R$ is: $\frac{1}{2} Q V(R)$

$V(R)$ ... the potential on the surface of the sphere

For spherically symmetric charge distribution, the flux:

$\Phi(r) = E_r(r) 4\pi r^2$

The charge within a sphere of radius $r$ is: $q(r) = \int_0^r \rho(r') 4\pi r'^2 dr'$

Using Gauss's law relating the flux and the charge: $\Phi(r) = \frac{q(r)}{D \varepsilon_0}$

We then get the Poisson equation for a spherically symmetric case:

$$\frac{1}{r} \frac{d}{dr} [r V(r)] = -\frac{\rho(r)}{D \varepsilon_0}$$

Using linearized version of the Boltzmann equation:

$$\rho(r) \approx -\frac{2 z^2 e^2 c_{\infty}}{k_B T} V(r)$$
We then derive the Debye-Hückel equation:
\[
\frac{d}{dr} \left[ r V(r) \right] = \frac{r V(r)}{\lambda_D^2} \quad \lambda_D \ldots \text{the Debye screening length}
\]

Known solution for the function \( rV(r) \) is:
\[
V(r) = A \frac{e^{-r/\lambda_D}}{r}
\]

The constant \( A \) is determined by taking into account that
\[
\left( \frac{dV(r)}{dr} \right)_{r=R} = E(R) = \frac{Q}{4\pi \varepsilon_0 DR^2} \quad A = \frac{Qe^{R/\lambda_D}}{4\pi D (1 + \frac{R}{\lambda_D})}
\]

\[
V(R) = \frac{1}{4\pi \varepsilon_0 D} \left( \frac{Q}{R} \right) \frac{\lambda_D}{R + \lambda_D}
\]

The electrostatic energy of the spherical shell (virus capsid):
\[
U(R) = \frac{1}{2} Q V(R) = \frac{1}{2} k_B T \left( \frac{Q}{e} \right)^2 \frac{l_B \lambda_D}{R(R + \lambda_D)}
\]
Capsomers arranged into a triangular face of the icosahedral capsid are held together by hydrophobic forces that need to overcome the electrostatic interactions ($Q = N \ z \ e$ & $R + \lambda_D \sim R$):

$$\Delta G_{\text{capsid}} = \Delta G_{\text{contact}} + \frac{1}{2} k_B T \frac{N^2 Z^2 l_B \lambda_D}{R^2}$$

Salt concentration dependence is via the Debye screening length $\lambda_D$. 
Equilibrium constant can be measured and compared to:

\[
\ln K_{\text{capsid}} = -\frac{\Delta G_{\text{capsid}}}{k_B T} = -\frac{\Delta G_{\text{contact}}}{k_B T} - \frac{1}{2} N^2 z^2 \frac{l_B \lambda_D}{R^2}
\]

→ measured equilibrium constant = concentration of capsids in solution as a function versus concentration of capsomers squared

→ temperature dependence: (hydrophobic effect)
Equilibrium constant depends on the salt concentration:

$$\ln K_{\text{capsid}} \propto \frac{1}{\sqrt{C}}$$