Generalized Poisson-Boltzmann equations: applications to biological systems

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Coulombic systems and biology

- Biomolecules are charged (DNA, RNA, proteins)
- water is the solvent
- salts and small ions in solution
- membranes may be charged

It is thus important to understand the properties of systems with Coulombic interactions: electrolytes, polyelectrolytes, colloids, etc...

Outline

- Phenomenological derivation
- The double layer problem
- Debye-Huckel
- Field-Theory
- Steric effects
- The dipolar solvent
- Short range interactions

Consider a system of charges in a solution with dielectric constant ε *Nⁱ* molecules of charge *qie*

Poisson equation:
$$
-\nabla^2 \varphi(\vec{r}) = \frac{\rho_c(\vec{r})}{\varepsilon}
$$

where $\varphi(\vec{r})$ is the electrostatic potential and $\rho_c(\vec{r})$ is the charge density

At thermodynamical equilibrium, the charge density is given by the sum of the fixed charges and a Boltzmann distribution

$$
\rho_c(\vec{r}) = \rho_f(\vec{r}) + \sum_i N_i q_i e \frac{e^{-\beta q_i e \varphi(\vec{r})}}{Z_i}
$$

fixed charges

where
$$
Z_i = \int d^3 e^{-\beta q_i e\varphi(\vec{r})}
$$
 concentration of ion in
In an infinite system: $Z_i = V$

$$
-\nabla^2 \varphi(\vec{r}) = \frac{\rho_f(\vec{r})}{\varepsilon} + \sum_i \frac{c_i q_i e}{\varepsilon} e^{-\beta q_i e\varphi(\vec{r})}
$$

Example: (1:1) salt

$$
-\nabla^2 \varphi(\vec{r}) = \frac{\rho_f(\vec{r})}{\varepsilon} - 2\frac{ce}{\varepsilon} \sinh(\beta e \varphi(\vec{r}))
$$

Poisson-Boltzmann

- Very non-linear partial differential equation (PDE)
- Very few cases are exactly solvable
	- a charged plane with counterions (double layer problem)
	- a charged cylinder with counterions (Manning condensation)
	- a charged plane wih salt (implicit solution very complicated)
- Usually must resort to numerical solution

The double layer: a charged plane with counterions

- consider a plane with charge density σ
- counterions of charge -1

$$
-\varphi''(z) = \frac{\sigma}{\varepsilon}\delta(z) - \frac{\lambda}{\varepsilon}e^{+\beta e\varphi(z)}
$$

- note that λ as it can be absorbed in λ as it can be absorbed in φ
- Boundary condition

$$
\varphi'(0)=-\frac{\sigma}{\varepsilon}
$$

Try a solution of the type:
$$
\varphi(z) = A \log(z + \mu)
$$

\nSolution: $A = -\frac{2}{\beta e}$
\n $\lambda = \frac{2\varepsilon}{\beta e}$
\n $\mu = \frac{2\varepsilon}{\beta e \sigma}$
\n
\nCounterion density
\n $\rho_c(z) = -\frac{2\varepsilon}{\beta e} \frac{1}{(z + \mu)^2}$
\n $\int_0^{+\infty} dz \rho(z) = -\sigma$

All couterions are bound to the plane: charge neutrality

The cylindrical case: Manning condensation

- Consider an infinite cylinder with charge density $-\sigma$ surrounded by its counterions.
- There is an exact solution.
- There is a critical surface charge σ_c such that
	- if $\sigma < \sigma_c$, the couterions are unbound
	- if $\sigma > \sigma_c$, a fraction of the counterions are bound to the cylinder, and the rest is unbound.

Debye-Huckel approximation

Assume $\beta q_i e\varphi$ small. Expand to order 1 Charge neutrality implies $\sum c_i q_i e = 0$ *i* $\nabla^2\varphi = \kappa^2\varphi$

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- Debye-Huckel potential decays exponentially: electrostatic screening
- Debye-Huckel length proportional to the inverse of the square root of the ionic concentrations.

Numerical solution

- Standard numerical method: solve by iterations:
	- start from a guess φ_0
	- solve the equation $-\nabla^2 \varphi = V(\varphi_0)$
	- iterate the procedure until convergence
	- discretize the Laplacian
	- sometimes need to refine the grid near fixed charges
	- partition fixed charges on grid points

What is absent from PB

- Steric effects: ions are supposed to be punctual
- Water has no structure. It is a continuous medium. Necessary to treat is as dipoles
- Interactions of water molecules.
- PB is mean-field: need to introduce fluctuations.

Natural method to generalize PB: field theory of Coulombic systems.

Why Field-Theory?

- Statistical mechanics of Coulombic liquids
- Derivation of Mean-Field theories
- Calculation of fluctuations to all orders
- Non-perturbative approaches

Field Theory for Electrolytes

$$
Z = \frac{1}{N!} \int dr_1 \dots dr_N \exp\left(-\frac{\beta}{2} \int dr dr' \rho_c(r) v_c(r - r') \rho_c(r')\right)
$$

$$
v_c(r) = \frac{1}{4\pi\epsilon_0 r} \qquad \Delta v_c(r) = -\frac{\delta(r)}{\epsilon_0}
$$

$$
\rho_c(r) = \sum_{i=1}^{N} q_i \delta(r - r_i)
$$

Gaussian integrals

$$
\int_{-\infty}^{+\infty} dx e^{-\frac{a}{2}x^2 + ux} = \sqrt{\frac{2\pi}{a}} e^{\frac{u^2}{2a}}
$$

 $\int +\infty$ $-\infty$ $\prod_{i=1}^{N} dx_i e^{-\frac{1}{2}}$ 2 $\sum_{i,j} x_i A_{ij} x_j + \sum_i u_i x_i = \frac{(2\pi)^{N/2}}{(det A)^{1/2}}$ $\frac{(2\pi)^{7}}{(\det A)^{1/2}}$ e $\overline{1}$ 2 $\sum_{i,j} u_i A_{ij}^{-1} u_j$

generalize to a field:

$$
x_i \to \varphi(r)
$$

\n
$$
A_{ij} \to A(r, r')
$$

\n
$$
\int \prod_{i=1}^N dx_i \to \int \mathcal{D}\varphi(r)
$$

Stratanovich-Hubbard = Gaussian identity

$$
\exp\left(-\frac{\beta}{2}\int \rho(r)v(r-r')\rho(r')\right) =
$$

$$
\int \mathcal{D}\phi(r)\exp\left(-\frac{\beta}{2}\int dr dr' \phi(r)v^{-1}(r-r')\phi(r') + i\beta \int dr \rho(r)\phi(r)\right)
$$

Poisson equation for a unit point-like charge:

$$
\nabla^2 v_c(r) = -\frac{\delta(r)}{\varepsilon_0}
$$

$$
v_c^{-1}(r, r') = -\varepsilon_0 \nabla^2 \delta(r - r')
$$

Poisson-Boltzmann

$$
Z = \int \mathcal{D}\varphi(r)e^{-\frac{\beta \varepsilon_0}{2}\int dr(\nabla \varphi)^2 - i\beta \int dr \rho_c(r)\varphi(r)}
$$

$$
Z = \int D\varphi(r)e^{-\frac{\beta \varepsilon_0}{2}\int dr (\nabla \varphi)^2 + \sum_i \lambda_i e^{-i\beta q_i e\varphi(r)}}
$$

 $PB =$ Saddle-Point method on ϕ then $\phi \rightarrow i\phi$

Example: salt 1:1

$$
\Delta^2 \phi = \frac{2\lambda e}{\epsilon_0} \sinh(\beta e \phi)
$$

Poisson-Boltzmann with hard-cores up to a numerical property In order to descript by indicated the occupation of cells by indicated the occupation of cell in the occupation of cell in the occupation of cells by indicate the occupation of cells by indicate the occupation of cell in t Fig. 1. Schematic view of the adsorption of the adsorption of large in the adsorption of large ions to a charge in the adsorption of large in [18]. The surface charge is carried by amphiphilic molecules which are confined to changing the area per amplitude the area per ampli-

 \mathcal{S}

$$
\nabla^2 \psi = \frac{8\pi ze}{\varepsilon} \frac{c_b \sinh(z\beta e\psi)}{1 - \phi_0 + \phi_0 \cosh(z\beta e\psi)}
$$

$$
z : z \text{ salt}
$$

Poisson-Boltzmann with dipoles a fixed charge distribution of \mathbf{d} (\mathbf{r}). The charge distribution of \mathbf{r} **E** USSON-DOIL CHARGE WILL density core provides the point of the point α by $\mathbf{r} = \mathbf{r} \cdot \mathbf{r}$, the total charge density $\mathbf{r} = \mathbf{r} \cdot \mathbf{r}$, the total charge density $\mathbf{r} = \mathbf{r} \cdot \mathbf{r}$ *i*=1 *j*=1 *i*=1 (1) where r*ⁱ* denotes the position of dipoles of moment p*ⁱ* and *i* are the positions of the positions of the canonical contract \mathbf{r} partition is given by the set of \mathbf{u}

orated below), $\mathcal{L}(\mathcal{L})$ $\mathcal{L}(\mathcal{L})$ because the vacuum permittivity. $\mathcal{L}(\mathcal{L})$

⇤

^q^j ^e⇥(rR(*j*)

ⁱ)+⇧*^f* (r)

Represent water as point-dipoles \overline{a} *N* \overline{a} *n* as point-dipoles *i*=1*d*³R(*j*)

^p*ⁱ ·*⇤⇥(rr*i*)+⇤

$$
\rho(\mathbf{r}) = -\sum_{i=1}^{N_d} \mathbf{p}_i \cdot \nabla \delta(\mathbf{r} - \mathbf{r}_i) + \sum_{j=1}^{I} \sum_{i=1}^{N_j} q_j e \delta(\mathbf{r} - \mathbf{R}_i^{(j)}) + \rho_f(\mathbf{r})
$$

$$
Z = \int \mathcal{D}\phi(\mathbf{r}) \exp\left(-\frac{\beta \epsilon}{2} \int d^3 \mathbf{r} \left[\nabla \phi(\mathbf{r})\right]^2 + \lambda_d \int d^3 \mathbf{r} d^3 \mathbf{p} e^{-i\beta \mathbf{p} \cdot \nabla \phi} + \sum_{i=1}^I \lambda_i \int d^3 \mathbf{r} e^{-i\beta q_i e\phi} -i\beta \int d^3 \mathbf{r} \phi(\mathbf{r}) \rho_f(\mathbf{r})\right)
$$

$$
= \int d^3 \mathbf{r} \phi(\mathbf{r}) \rho_f(\mathbf{r}) \sum_{i \text{avril } 14} \int d^3 r \frac{\sin(\beta p_0 |\nabla \phi(r)|)}{\beta p_0 |\nabla \phi(r)|}
$$

2

⇧(r) =

⇤

distances, for example, between two charged plates (sur-

face force balance apparatus). These hydration phenom-

ena are very important in many biological processes such

as protein folding, protein crystallization and interactions

Most studies other than the PB rely on one of sev-

eral theoretical techniques. Monte Carlo (MC) [6] or

Molecular Dynamic (MD) [7] computer simulations take

MD simulations. However, all these methods are rather

cumbersome and involve heavy computation resources.

In addition, they lack the simple physical picture pro-

In this Letter we propose another approach called the

Dipolar Poisson-Boltzmann (DPB). Unlike the PB model

where the solution is characterized by a homogeneous

dielectric constant, in the DPB model we coarse grain

$r_{\rm{eff}}=r_{\rm{eff}}$ riÞ of the solute, all of them interacting solely Water + ions + vacancies

$$
\beta \mathcal{F} = -\frac{\beta}{2} \int d\vec{r} \,\epsilon_0 |\vec{\nabla} \Phi(\vec{r})|^2 + \beta \int d\vec{r} \,\rho_f(\vec{r}) \Phi(\vec{r}) -\frac{1}{a^3} \int_{\text{solvent}} d\vec{r} \ln \left(1 + 2\lambda_{\text{ion}} \text{cosh}(\beta e \mathbf{z} \Phi(\vec{r})) + \lambda_{\text{dip}} \frac{\text{sinh}(\beta p_{\text{o}} |\vec{\nabla} \Phi(\vec{r})|)}{\beta p_{\text{o}} |\vec{\nabla} \Phi(\vec{r})|} \right),
$$

dipoles and the ions create a local charge density in the sol-

On the modeling level, it would be very useful for quickly

computing the electrostatic part of solvation energies with a

more realistic model than PBE, especially as a molecular

understanding of the nature of the hydrophobic effect is still

lacking for macromolecules and remains a subject of active

research (30–33). The structure of water around both polar

and apolar solutes is also still actively studied (34–36).

Knowledge of the solvent density profile has clear implica-

tions for the calculation of solvation energies and the mod-

eling of the hydrophobic effect at different length scales (31).

Indeed, as included in the van der Waals theory of capillarity

 (37)

proportional to the integral of the squared gradient of the

$$
-\epsilon \nabla^2 \Psi = \sum_i \lambda_i q_i e \ e^{-\beta q_i e \Psi} + \rho_f(\mathbf{r}) + \lambda_d p_0 \nabla \cdot [(\nabla \Psi / |\nabla \Psi|) \mathcal{G} (\beta p_0 | \nabla \Psi|)]
$$

profile of the dipole density (dashed line) is rescaled by its bulk value. It can be seen that in the surface vicinity in the surface vicinity of \mathcal{L}_max

dipole density. In rescaled units, it saturates at a value of about 1.2 in the mid-region and reaches about 2.3 at α

Compared to a PB theory with the *same* bulk and

The ionic concentration is much less a⇤ected by the

In Fig. 2 we plot the relative osmotic pressure di⇤er-

ence (DBP PB)*/*PB as a function of the surface separation *d*. The pressure is a global quantity, and is sensitive to the strength of the electric field throughout τ system rather than to its value on the surface.

a result, DPB deviates strongly from PB for small *d*,

while DPB at larger separation.

presence of the dipoles. We have computed the ion densities as a function of the distance to the surface. Because of the different boundary condition the ionic density is in strongly suppressed at the surface with respect to PB (to about half original values). However, it comes back $\mathcal{L}_{\mathcal{B}}$ value at distances as $\mathcal{L}_{\mathcal{B}}$ from the distances as $\mathcal{L}_{\mathcal{B}}$

homogeneous ⇥^e taken as constant throughout the sys-

tem, the DPB demonstrates strong deviations, not only in the surface proximity but also in its saturated mid-

range value (for strong enough ⇤ and/or small *d*).

dard PB one may occur in the strong P field \mathcal{P} f

$$
\mathcal{G}(u) = \cosh u/u - \sinh u/u^2
$$

PB with dipoles and it is empty in the energy is a very sense of the energy is Y ukawa constant magnitude p⁰ at position r <u>is under the set of the</u> A as \mathcal{A} , we get \mathcal{A} as \mathcal{A} , we get \mathcal{A} , we get \mathcal{A} , we get \mathcal{A}

$$
Z = \frac{1}{N!} \int dr_1 \dots dr_N \exp\left(-\frac{\beta}{2} \int dr dr' \rho_c(r) v_c(r - r') \rho_c(r')\right)
$$

$$
\times \exp\left(-\frac{\beta}{2} \int dr dr' \rho(r) V_Y(r - r') \rho(r')\right)
$$

 $\rho_c(r) = \sum$

 $\rho(r) = \sum$

N

i=1

 $i = 1$

i

 $=\sum \delta(r-r_i)$

 $q_i\delta(r-r_i)$

 T the bulk dipole concentration concentration concentration concentration concentration concentration concentration concentration \mathcal{L}

¼ #

 $=\sum_{i=1}q_i o(r-r_i)$

 $\frac{d}{i}$

hard spheres representing the water $\frac{1}{2}$

 $d_{\rm 5.5\%}$ dip to 55% m to its value in solution, i.e., i.e

, i.e., to a fraction of the diameter $\mathcal{O}(\mathcal{E})$

water= dipoles hard-cores = lattice gas water-water interaction: Yukawa $\frac{1}{2}$ in the lattice. μ and cores to account for μ $\frac{1}{2}$ right conto in the rection $\frac{1}{2}$ $\frac{1}{2}$ $\frac{1}{3}$ water interaction. This $\frac{1}{3}$

$$
V_Y(r) = -v_0(e^{-r/b}/r) \nvert_{V_Y^{-1}(r-r')} = -\frac{1}{v_0} \left(-\nabla^2 + \frac{1}{b^2} \right) \delta(r-r')
$$

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envelope can be taken as the molecular surface or the

accessible surface of the solute.

PB with dipoles and Yukawa **PB WITH (** The free energy functional for the whole lattice includes \blacksquare \mathbf{r} the electrostatic energy, the functional form form for the energy, the energy \mathbf{r} of the Yukawa field, the energy of the field charges, and the figure system of the fixed charges, and the figure system of the figure syst \mathbf{p}_1 in the lattice. A similar approach was used by \mathbf{p}_1 Coalson and colleagues to account for free ions steric republika in the internal problem in the internal problem in the internal problem in the internal problem in t
The internal problem in the internal problem in the internal problem in the internal problem in the internal p with a size particles \blacksquare this \blacksquare

 $\mathcal{L}_{\mathcal{P}}$ to the energy of a dipole present at the energy of a dipole present at

The two equations (3) and (4) are solved numerically on

 $\mathcal{A} = \mathcal{A} \cup \mathcal{A}$

 \mathbf{b}

 $s_{\rm eff}$ and the boundary is required to be at least 2lB,

 $T_{\rm eff}$

We use a self-consistent iterative algorithm to solve for

set to be large enough so that " ¼ 0, E

#lYb²N Acb

 \mathcal{L}

 $\frac{1}{2}$

for any position r

density of water.

!ðr

 \mathbb{R}^n is the Bjerrum length (equal to \mathbb{R}^n

 $v_{\rm eff}$

 \mathcal{L}^{b}

lished separately (see also [12]).

 $W_{\rm eff}$

$$
\beta \mathcal{F} = -\frac{\beta}{2} \int d\vec{r} \epsilon_0 |\vec{\nabla} \Phi(\vec{r})|^2
$$

+
$$
\frac{\beta}{2v_0} \int d\vec{r} \left(|\vec{\nabla} \Psi(\vec{r})|^2 + \frac{\Psi(\vec{r})^2}{b^2} \right)
$$

+
$$
\beta \int d\vec{r} \rho_f(\vec{r}) \Phi(\vec{r}) - \frac{1}{a^3} \int d\vec{r} \ln(Z_l(\vec{r})).
$$

$$
Z_{l}(\vec{r}) = 1 + \lambda_{\text{dip}} e^{-\beta \Psi(\vec{r})} \sinh(c(u))
$$

$$
u = \beta p_0 |\nabla \Phi|
$$

Yukawa field !ðr

$$
\begin{cases}\n\vec{\nabla}\Big(\epsilon_0\vec{\nabla}\Phi(\vec{r}) + \gamma(\vec{r})\beta p_0^2 \frac{\lambda_{\text{dip}}e^{-\beta\Psi(\vec{r})}F_1(u)}{a^3 Z_l(\vec{r})}\vec{\nabla}\Phi(\vec{r})\Big) = -\rho_f(\vec{r}) \\
\frac{1}{v_0}\Big(\Delta\Psi - \frac{\Psi(\vec{r})}{b^2}\Big) = \gamma(\vec{r})\frac{1}{a^3}\frac{\lambda_{\text{dip}}e^{-\beta\Psi(\vec{r})}\sinh(c(u))}{Z_l(\vec{r})}.\n\end{cases}
$$
\n
$$
F_1(u) = \frac{\sinh(c(u))}{u} \mathcal{L}(u); \ \mathcal{L}(u) = 1/\tanh(u) - 1/u
$$
\n
$$
u = \beta p_0 |\nabla \Phi|
$$

$$
u=\beta p_0 |\nabla \Phi|
$$

dip verifies and the verifies of the verifies

size a, strength political concentration concentration concentration concentration concentration concentration
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dip. These water dipoles are dis-

tributed on a lattice to approximate the excluded-volume

effects in the lattice gas formalism, the domain outside the

boundary of the molecule is represented as a three-

constant magnitude p⁰ at position r~ is obtained as the

 $B_{\rm eff}$ and $B_{\rm eff}$ interaction $B_{\rm eff}$

 $\mathcal{O}(\mathcal{O})$ or $\mathcal{O}(\mathcal{O})$ is the local electric that

field. To mimic correlation effects between dipoles in a

 \mathbb{R}^n

way compatible with a mean-field approach, we add a

inside the envelope of the solute and one otherwise. This

dip. These water dipoles are dis-

tributed on a lattice to approximate the excluded-volume

effects in the lattice gas formalism, the domain outside the

boundary of the molecule is represented as a three-

dimensional lattice with N uniformly sized cuboids, of

size a3, where a, the lattice spacing, is set to the geomet-

rical dimension of the dipoles. As a first approximation, we

assume that the dipoles are hard spheres of fixed sizes. The

solute is described by a constant charge density !^f and a

inside the envelope of the solute and one otherwise. This

envelope can be taken as the molecular surface or the

it is empty, its energy is zero. The energy of one dipole of

 $E_{\rm eff}$ site in the lattice can contain at \sim

Application: hydratation of proteins

- Fixed protein (taken from the PDB)
- water: dipoles+ Yukawa
- small ions: Na, CI, ...
- Web Server: PDB Hydro

http://lorentz.immstr.pasteur.fr/pdb hydro.php

Program available: Aquasol (P. Koehl and M. Delarue)

membrane protein: molecular surface at protein: $\mathbf{r} = \mathbf{r}$ (http://pymol.sourceforge.net). [Supple-Hydrophobic regions (red) of a Thymidine Kinase

Figure 2. (A) Colored molecular surface of thymidine kinase 4TMK (as a monomer) as a function of surface area buried upon addition of surface area buried upon addition of water molecules in the peaks of water molecules in of the solvent density map. The dimerization area appears as the largest poorly solvated (red) patch. Drawn with P

TABLE 1: Computed versus Experimental Solvation Free Energies of Ions

