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

N_i molecules of charge $q_i e$

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 i

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 φ
- Boundary condition

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

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

Solution: $A = -\dfrac{2}{\beta e}$

$$\lambda = \frac{2\varepsilon}{\beta e}$$

$$\mu = \frac{2\varepsilon}{\beta e \sigma}$$

Gouy-Chapmann length: size of the double layer

Counterion density

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

$$\rho_c(z) = -\frac{2\varepsilon}{\beta e}\frac{1}{(z+\mu)^2}$$

$$\int_0^{+\infty} dz\ \rho(z) = -\sigma$$

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

$$-\nabla^2 \varphi = \sum_i \frac{c_i q_i e}{\varepsilon} e^{-\beta q_i e \varphi}$$

Assume $\beta q_i e \varphi$ small. Expand to order 1

Charge neutrality implies $\sum_i c_i q_i e = 0$

$$\nabla^2 \varphi = \kappa^2 \varphi$$

$$\kappa^2 = \frac{1}{l_{DH}^2} = \frac{\beta e^2}{\varepsilon} \sum_i c_i q_i^2$$

Debye-Huckel length → l_{DH}

- 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

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

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

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

Gaussian integrals

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

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

generalize to a field:

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

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

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

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:

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

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

Poisson-Boltzmann

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

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

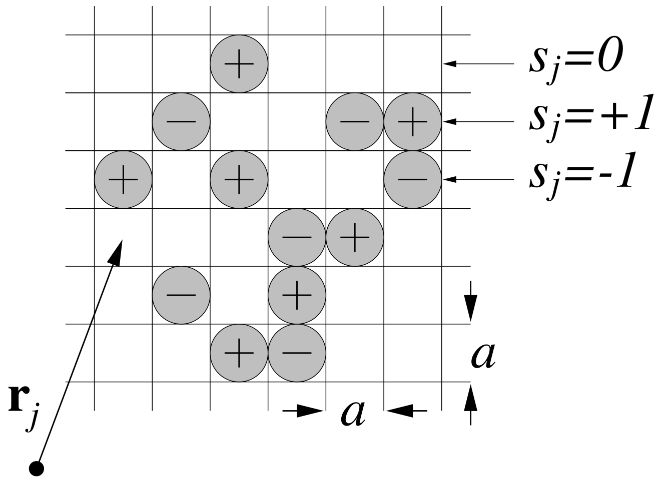
PB = Saddle-Point method on ϕ then $\phi \to i\phi$

Example: salt 1:1

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

Poisson-Boltzmann with hard-cores

Lattice Gas



$$Z = \sum_{s_j=0,\pm 1} \exp\left(-\frac{\beta}{2} z^2 e^2 \sum_{j,j'} s_j v_c(\mathbf{r}_j - \mathbf{r}_{j'}) s_{j'} + \sum_j \beta \mu_j s_j^2 \right)$$

Note: CGS units!!

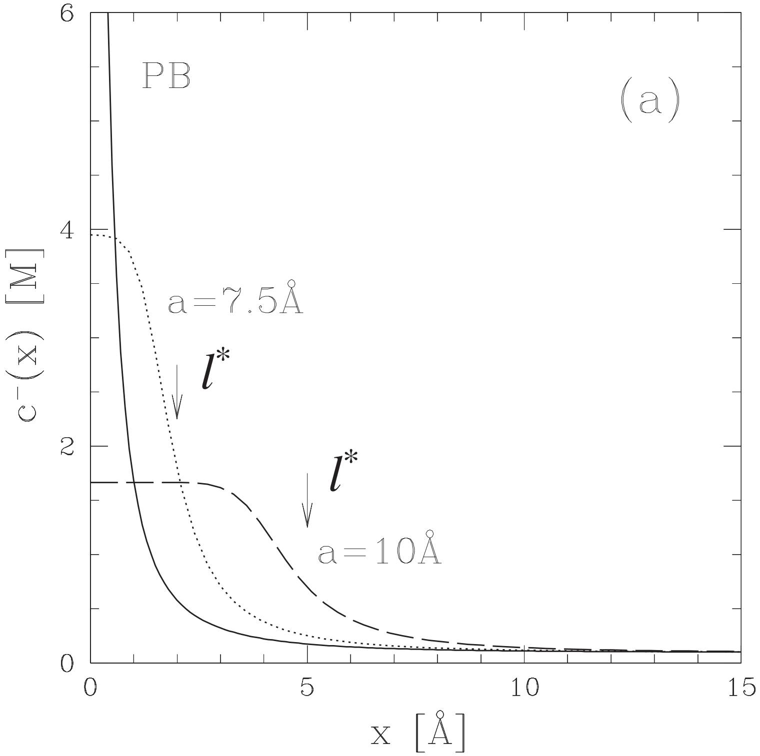
$$Z = \int \mathcal{D}\varphi_c \ \exp\Big(-\frac{\beta\varepsilon}{8\pi} \int \mathrm{d}\mathbf{r} \ |\nabla \varphi_c|^2$$

$$+ \frac{1}{a^3} \int \mathrm{d}\mathbf{r} \ \ln\{1 +^{\beta\mu_+ - iz\beta e \varphi_c(\mathbf{r})} +^{\beta\mu_- + iz\beta e \varphi_c(\mathbf{r})}\} \Big)$$

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

$z : z$ salt

$$\nabla^2\psi = \frac{8\pi z e}{\varepsilon} c_b \sinh(z\beta e\psi)$$



Poisson-Boltzmann with dipoles

Represent water as point-dipoles

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

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

$$\int d^3 r \frac{\sin(\beta p_0 |\nabla\phi(r)|)}{\beta p_0 |\nabla\phi(r)|}$$

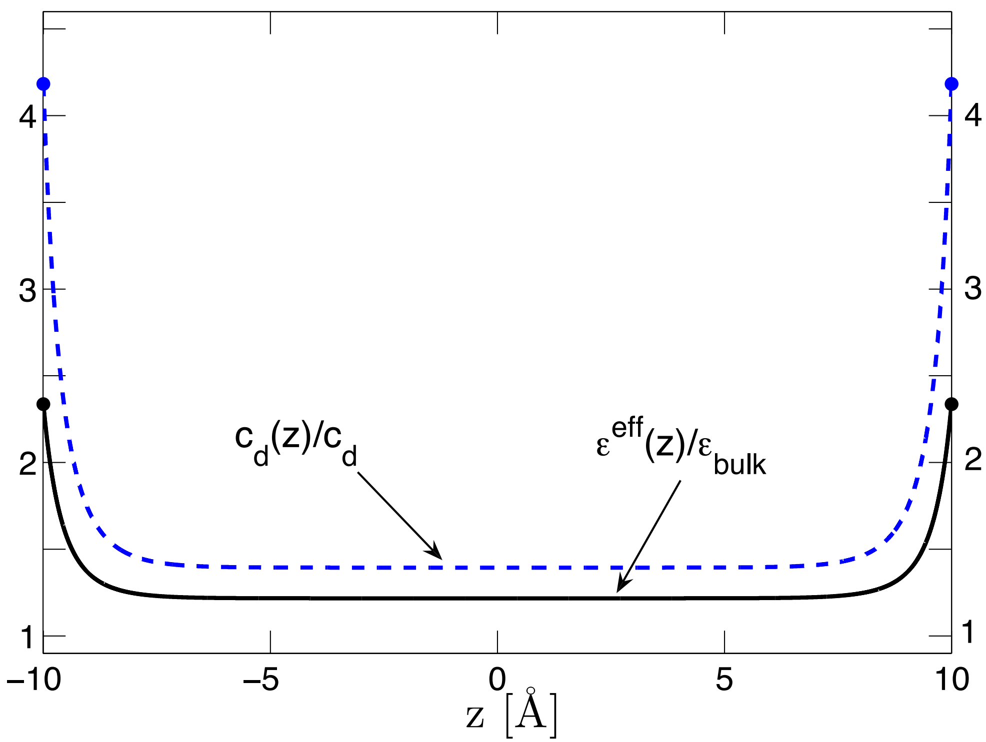
Water + ions + vacancies

$$\beta\mathcal{F} = -\frac{\beta}{2}\int d\vec{r}\,\boldsymbol{\epsilon}_0|\vec{\nabla}\Phi(\vec{r})|^2 + \beta\int d\vec{r}\,\boldsymbol{\rho}_{\mathrm{f}}(\vec{r})\Phi(\vec{r})$$
$$-\frac{1}{a^3}\int_{\mathrm{Solvent}} d\vec{r}\,\ln\left(1 + 2\lambda_{\mathrm{ion}}\cosh(\beta ez\Phi(\vec{r}))\right.$$
$$\left.+\lambda_{\mathrm{dip}}\frac{\sinh(\beta p_{\mathrm{o}}|\vec{\nabla}\Phi(\vec{r})|)}{\beta p_{\mathrm{o}}|\vec{\nabla}\Phi(\vec{r})|}\right),$$

$$-\epsilon\nabla^2\Psi = \sum_i \lambda_i q_i e \, \mathrm{e}^{-\beta q_i e \Psi} + \rho_f(\mathbf{r})$$

$$+ \lambda_d p_0 \nabla \cdot \left[(\nabla\Psi/|\nabla\Psi|)\mathcal{G}\left(\beta p_0 |\nabla\Psi|\right) \right]$$

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



PB with dipoles and Yukawa

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

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

water= dipoles
hard-cores = lattice gas
water-water interaction: Yukawa

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

$$\rho(r) = \sum_i \delta(r-r_i)$$

$$V_Y(r) = -v_0(e^{-r/b}/r)$$

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

PB with dipoles and Yukawa

$$\beta\mathcal{F} = -\frac{\beta}{2}\int d\vec{r}\epsilon_0|\vec{\nabla}\Phi(\vec{r})|^2 + \frac{\beta}{2v_0}\int d\vec{r}\left(|\vec{\nabla}\Psi(\vec{r})|^2 + \frac{\Psi(\vec{r})^2}{b^2}\right) + \beta\int d\vec{r}\rho_f(\vec{r})\Phi(\vec{r}) - \frac{1}{a^3}\int d\vec{r}\ln(Z_l(\vec{r})).$$

$$\mathcal{Z}_l(\vec{r}) = 1 + \lambda_{\text{dip}}e^{-\beta\Psi(\vec{r})}\,\text{sinh}c(u)$$

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

$$
\left\{
\begin{array}{l}
\vec{\nabla}\left(\epsilon_0 \vec{\nabla}\Phi(\vec{r}) + \gamma(\vec{r})\beta p_0^2 \frac{\lambda_{\mathrm{dip}} e^{-\beta\Psi(\vec{r})} F_1(u)}{a^3 Z_l(\vec{r})} \vec{\nabla}\Phi(\vec{r})\right) = -\rho_f(\vec{r}) \\
\\
\frac{1}{v_0}\left(\Delta\Psi - \frac{\Psi(\vec{r})}{b^2}\right) = \gamma(\vec{r}) \frac{1}{a^3} \frac{\lambda_{\mathrm{dip}} e^{-\beta\Psi(\vec{r})} \,\mathrm{sinhc}(u)}{Z_l(\vec{r})}.
\end{array}
\right.
$$

$$
F_1(u) = \frac{\mathrm{sinhc}(u)}{u} \mathcal{L}(u); \;\; \mathcal{L}(u) = 1/\tanh(u) - 1/u
$$

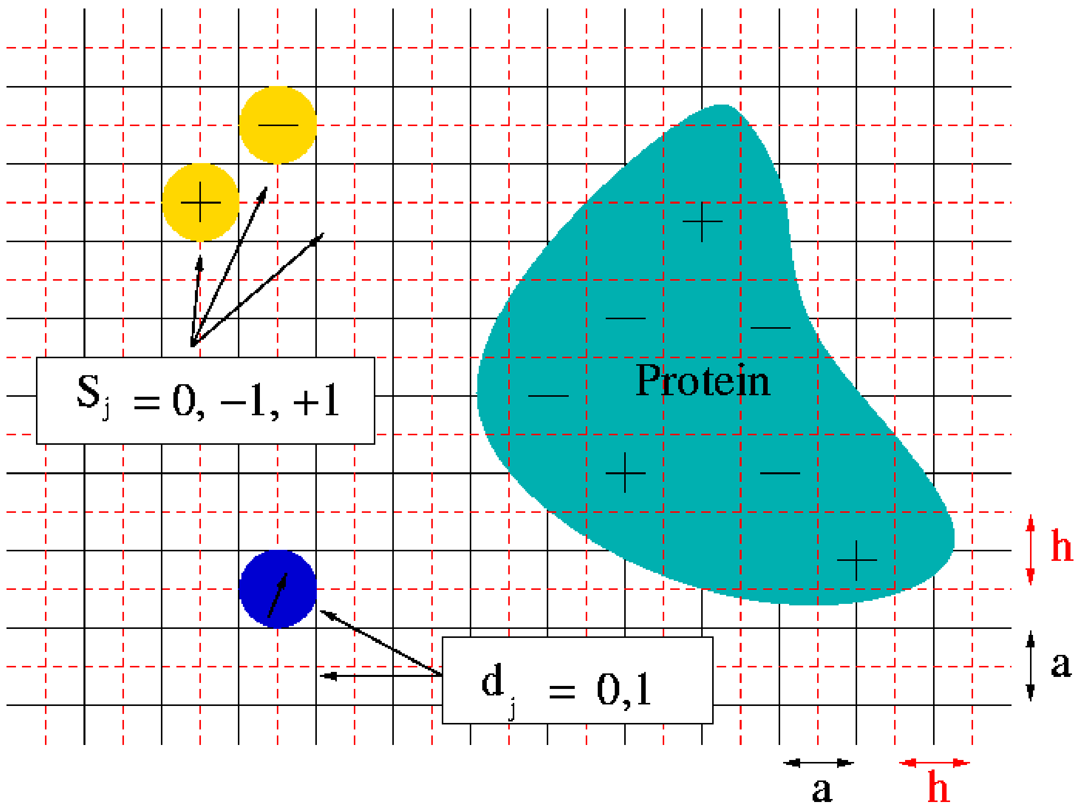
$$
u = \beta p_0 |\nabla\Phi|
$$

Application: hydratation of proteins

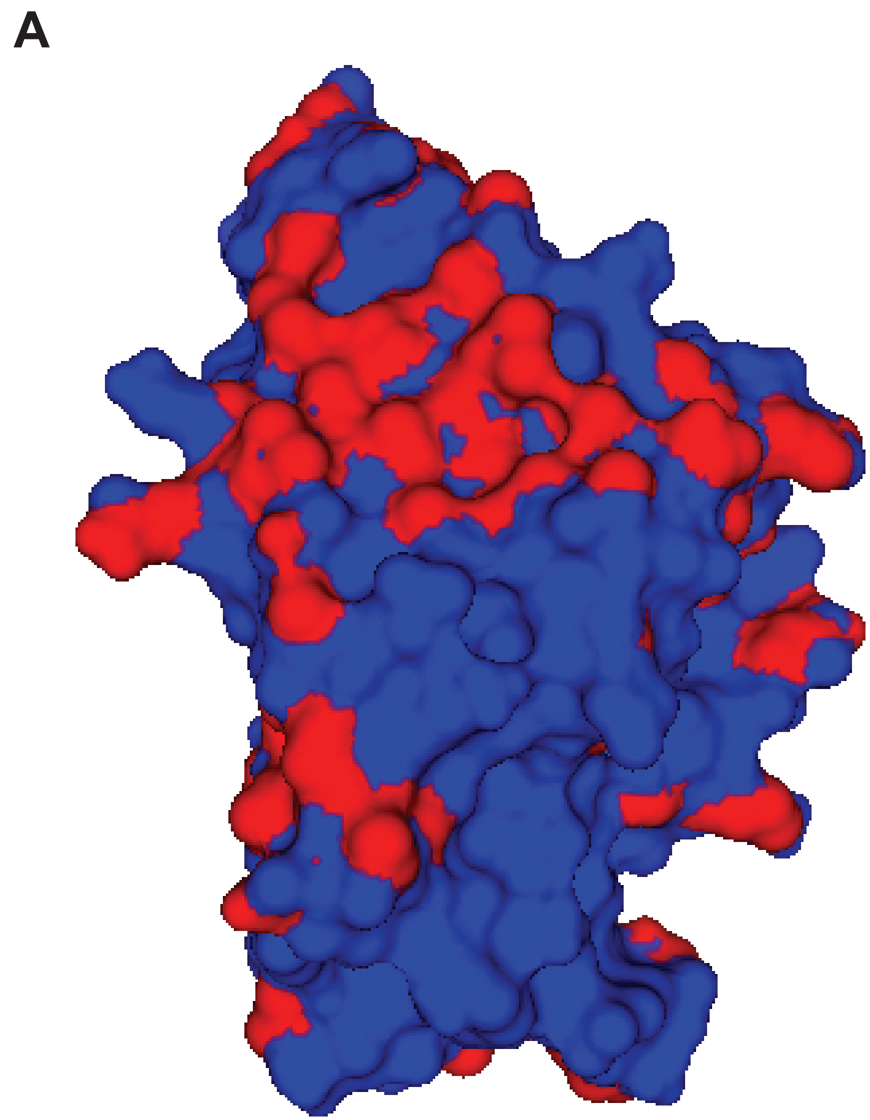
- Fixed protein (taken from the PDB)
- water: dipoles+ Yukawa
- small ions: Na, Cl, ...
- Web Server: PDB Hydro

http://lorentz.immstr.pasteur.fr/pdb_hydro.php

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



$S_j = 0, -1, +1$
Protein
$d_j = 0,1$
h
a
a
h



Hydrophobic regions (red) of a Thymidine Kinase

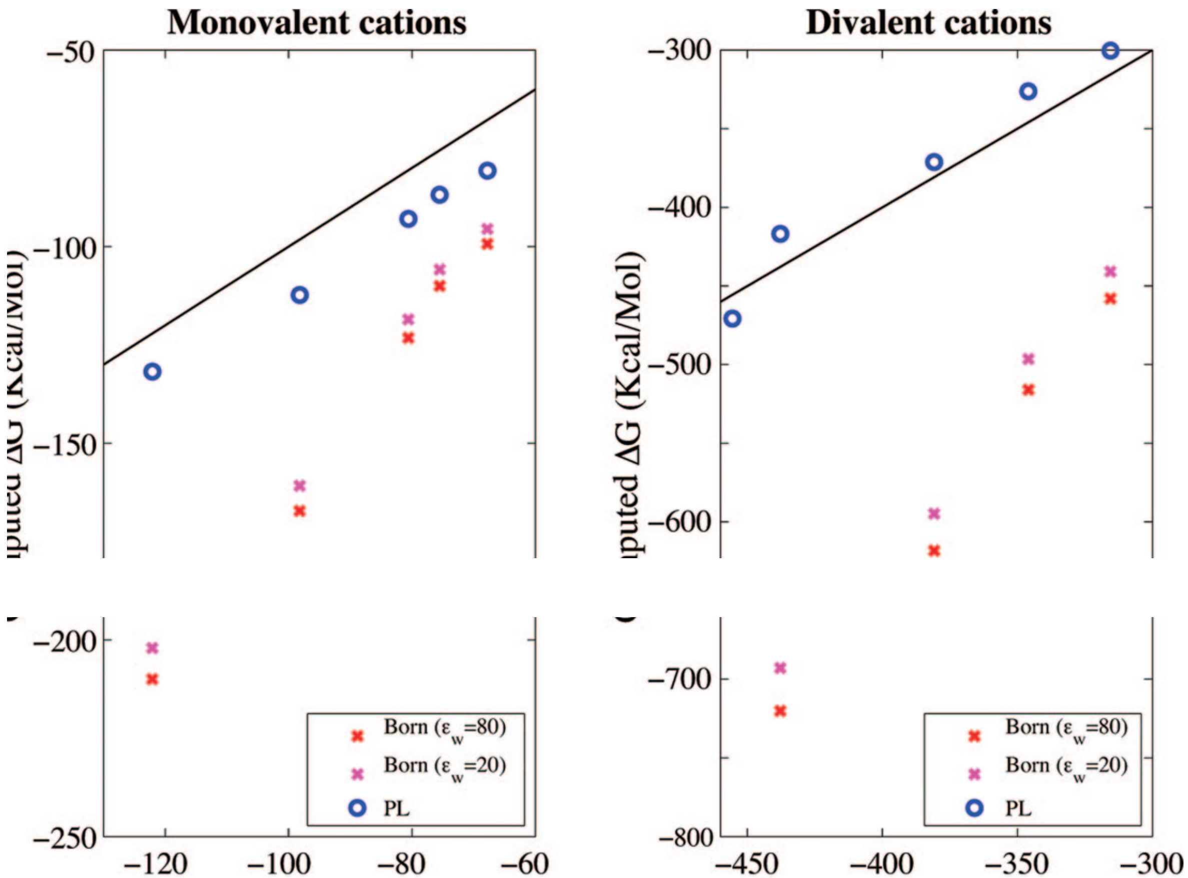


TABLE 1: Computed versus Experimental Solvation Free Energies of Ions

ion	radius[a] (Å)	ΔG_{exp}[b] (kcal/mol)	ΔG_{PL}[c] (kcal/mol)	ΔG_{Born80}[d] (kcal/mol)	ΔG_{Born20}[e] (kcal/mol)	ΔG_{W}[f] (kcal/mol)	ΔG_{MSA}[g] (kcal/mol)	ΔG_{qLD}[h] (kcal/mol)
Li^{+}	0.78	−122.1	−132.7	−210.0	−202.1	−223.1	−122.0	−142.5
Na^{+}	0.98	−98.2	−114.1	−167.2	−160.8	−210.8	−106.0	−121.5
K^{+}	1.33	−80.6	−94.8	−123.2	−118.5	−177.3	−86.5	−98.2
Rb^{+}	1.49	−75.5	−88.5	−110.0	−105.0	−162.3	−79.8	−90.6
Cs^{+}	1.65	−67.8	−82.4	−99.3	−95.5	−149.4	−74.0	−84.1
Mg^{2+}	0.78	−455.5	−474.5	−840.2	−808.3	−555.5	−487.9	−517.2
Mn^{2+}	0.91	−437.8	−422.4	−720.2	−692.9	−552.5	−444.8	−462.0
Ca^{2+}	1.06	−380.8	−377.3	−618.3	−594.8	−537.5	−403.8	−414.3
Sr^{2+}	1.27	−345.9	−333.0	−516.0	−496.5	−517.3	−357.5	−365.1
Ba^{2+}	1.43	−315.5	−307.5	−458.0	−440.9	−493.0	−328.8	−336.4
RMS[i] (kcal/mol)			14	187	169	124	15	28