Coulombic systems in mean-field and beyond

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- Phenomenological derivation of PB
- Introduction to Statistical Field-Theory for Coulombic systems
- Steric effects
- The dipolar solvent
- Short range interactions
- Hydration of biopolymers
- SAXS profiles
- Fluctuations: Sampling the partition function

Coulombic systems and biology

- Biopolymers are charged (DNA, RNA, proteins)
- Water is the solvent (dipolar)
- Salts and small ions in solution, in channels
- Membranes may be charged

Coulomb interaction drives shape, function, interaction, organization, etc. of living matter

Important to understand properties of systems with Coulombic interactions: electrolytes, polyelectrolytes, colloids, aggregation, amyloids,etc…

- MD simulations require hundred of thousands of water molecules, ions, etc…
- relaxation time of small ions and molecules << relaxation times of biopolymers
- can one simplify the picture by avoiding simulation of small ions and molecules?

Consider a system of charges in a solution with dielectric constant ε

N_i molecules of charge $q_i e$ Fixed charges $\rho_f(\vec{r})$

Poisson equation:

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

dielectric constant

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 $Z_i = \int d^3 r e^{-\beta q_i e \varphi(\vec{r})}$

concentration of ion *i*

In an infinite neutral 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

Poisson-Boltzmann equation

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

Poisson-Boltzmann

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

What is absent from PB

- Steric effects: ions are supposed to be point-like
- Water has no structure. It is a continuous medium. Necessary to treat is as dipoles
- Non Electrostatic interactions of water molecules.
- PB is mean-field: may need to include fluctuations.
  - no overcharging, no same charge attraction

Natural framework to generalize
Poisson-Boltzmann:
Statistical Field Theory of
Coulombic systems.

Why Field-Theory?

- Exact Statistical Mechanics formulation of Coulombic liquids
- Derivation of Mean-Field theories
- Calculation of fluctuations to all orders
- Non-perturbative approaches, Monte Carlo, …

Statistical Physics of charges and dipoles

$$Z_N = \frac{\lambda^{3N}}{N!} \int \prod_{i=1}^{N} d^3 r_i \exp\left(-\frac{\beta q^2 e^2}{2} \sum_{i \neq j} v_c(\mathbf{r_i} - \mathbf{r_j}) \;-\; \beta q e \sum_{i=1}^{N} \int d^3 r \; v_c(\mathbf{r_i} - \mathbf{r}) \rho_f(\mathbf{r}) \right)$$

where

$$v_c(\mathbf{r}) = \frac{1}{4\pi\varepsilon_0 r}$$

Charge density

$$\rho_c(\mathbf{r}) = qe \sum_{i=1}^{N} \delta(\mathbf{r} - \mathbf{r_i}) + \rho_f(\mathbf{r})$$

Field Theory for Electrolytes

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

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

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

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:

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

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

Exact Field-Theoretical representation

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

Replace $\rho_c(r)$ by its expression, then can do integrals on $\{r_i\}$

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

Poisson-Boltzmann theory

Do Saddle-Point Method on functional integral= Poisson-Boltzmann equation

Possibility to compute fluctuations systematically to all orders: the loop-expansion

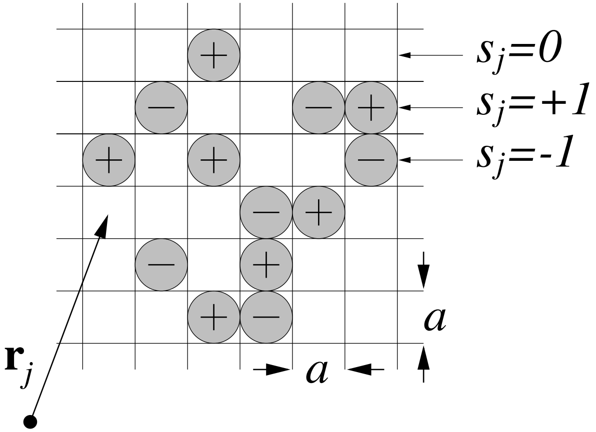
$$\Xi = \left(\frac{2\beta}{\varepsilon_0}\right)^{3/2} q^3 e^3 c^{1/2}$$

Dimensionless coupling constant

plays the role of $\hbar$

Poisson-Boltzmann with hard-cores

Lattice Gas



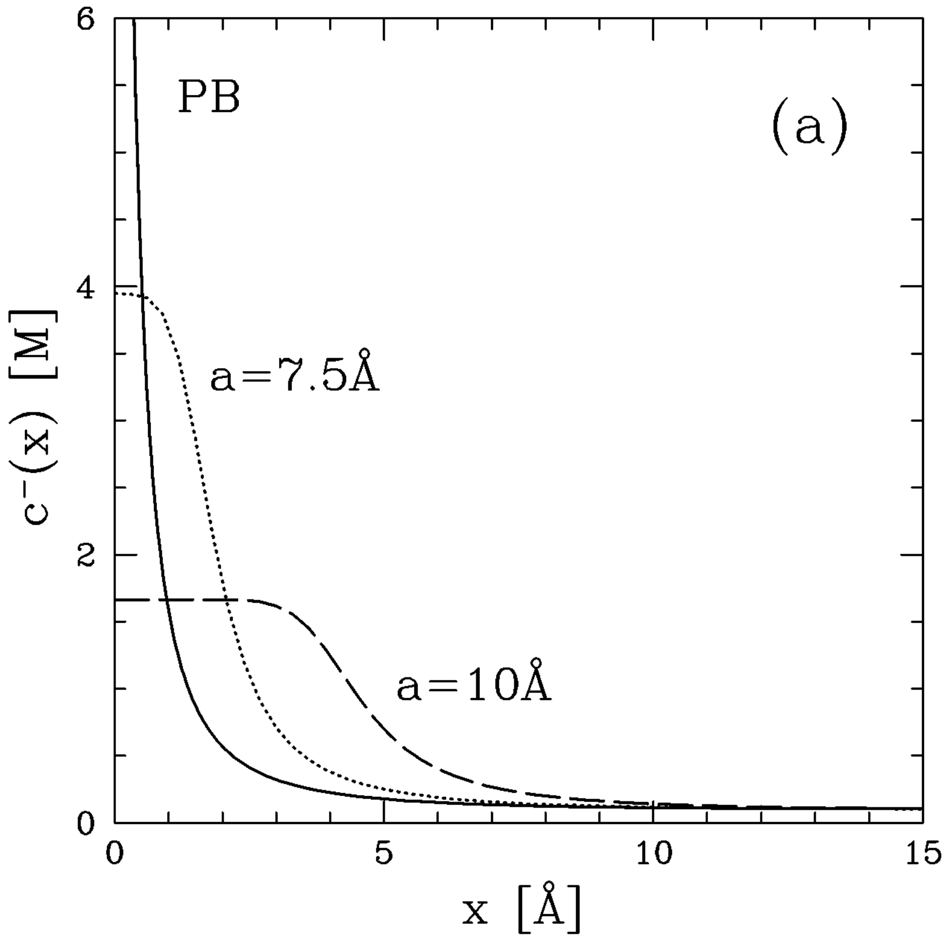
$$Z = \sum_{s_j=0,\pm1} \exp\left(-\frac{\beta}{2} z^2 e^2 \sum_{j,j'} s_j v_c(\mathbf{r}_j - \mathbf{r}_{j'}) s_{j'} + \sum_j \beta\mu_j s_j^2\right)$$

$$Z = \int \mathcal{D}\varphi \exp\Big(- \frac{\beta\varepsilon}{2} \int d^3r \, (\nabla\varphi)^2 + \frac{1}{a^3} \int d^3r \log\big(1 + e^{\beta\mu_+ - iz\beta e\varphi(\mathbf{r})} + e^{\beta\mu_- + iz\beta e\varphi(\mathbf{r})}\big)\Big)$$

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

$z : z$ salt

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



- No need for Stern layer
- Possibility to add dipolar nature of water (see later)

Poisson-Boltzmann with dipoles

Represent water as permanent point-dipoles $(\vec{p}_i, \vec{r}_i)$

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

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

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

Water + finite size ions

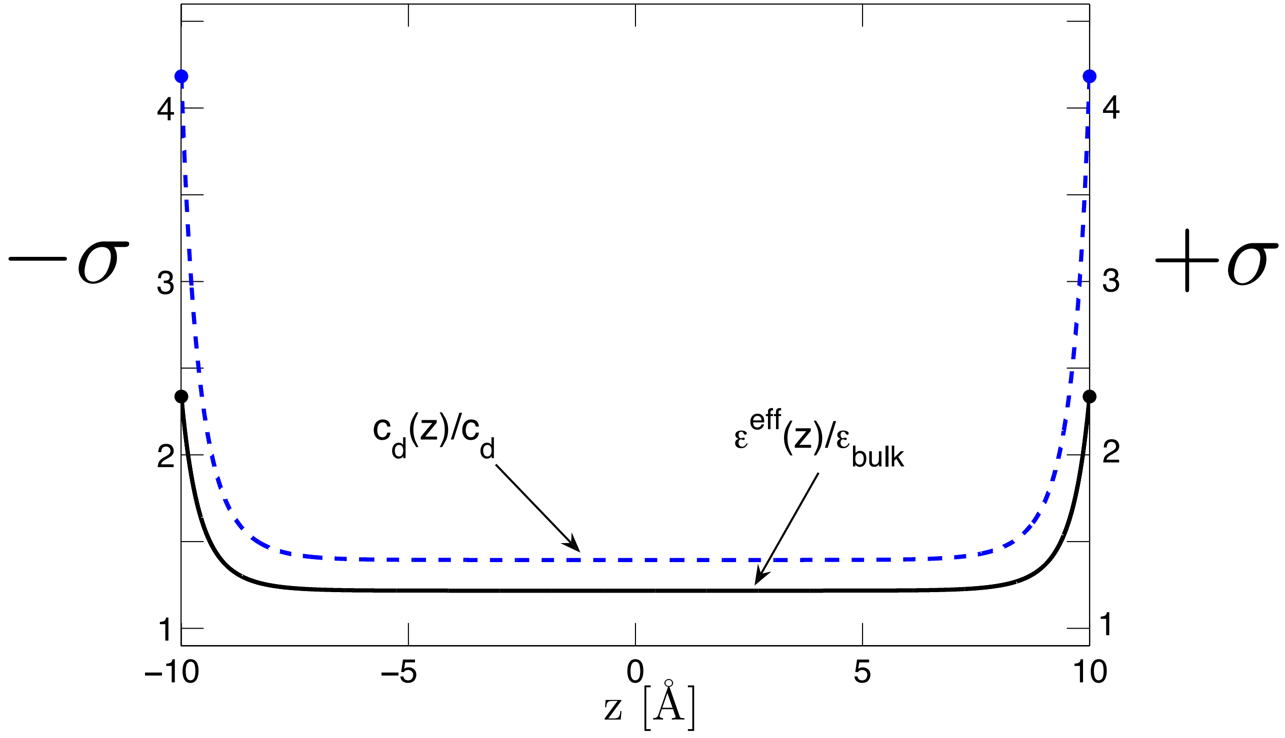
$$\beta\mathcal{F} = -\frac{\beta}{2}\int d\vec{r}\,\epsilon_0|\vec{\nabla}\Phi(\vec{r})|^2 + \beta\int d\vec{r}\,\rho_{\mathrm{f}}(\vec{r})\Phi(\vec{r})$$

$$-\frac{1}{a^3}\int_{\mathrm{Solvent}} d\vec{r}\,\ln\left(1 + 2\lambda_{\mathrm{ion}}\cosh(\beta ez\Phi(\vec{r}))\right.$$

$$\left.+\lambda_{\mathrm{dip}}\frac{\sinh(\beta p_{\mathrm{o}}|\vec{\nabla}\Phi(\vec{r})|)}{\beta p_{\mathrm{o}}|\vec{\nabla}\Phi(\vec{r})|}\right),$$

$$
\begin{aligned}
-\epsilon\nabla^2\Psi \;&=\; \sum_i \lambda_i q_i e\ \mathrm{e}^{-\beta q_i e \Psi} + \rho_f(\mathbf{r}) \\
&+\;\; \lambda_d p_0 \nabla\cdot\left[(\nabla\Psi/|\nabla\Psi|)\mathcal{G}\left(\beta p_0|\nabla\Psi|\right)\right]
\end{aligned}
$$

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



- With point-like dipolar water, no cation-anion asymmetry

- By taking finite-size dipoles for water, one gets a theory similar to non-local electrostatics (but positive susceptibilities)

- Possibility to generalize to non-permanent dipoles

PB with dipoles and Yukawa

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

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

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

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

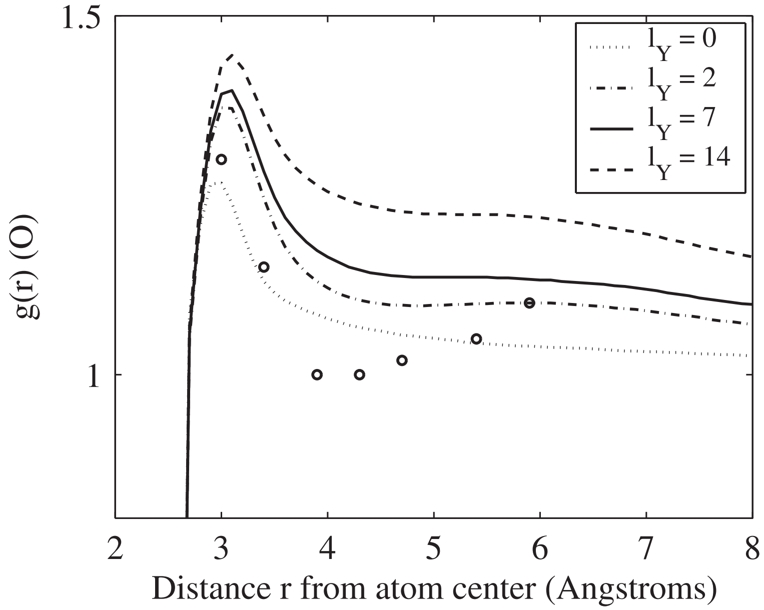
$$\mathcal{Z}_l(\vec{r}) = 1 + \lambda_{\text{dip}}e^{-\beta\Psi(\vec{r})}\,\text{sinhc}(u)$$

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

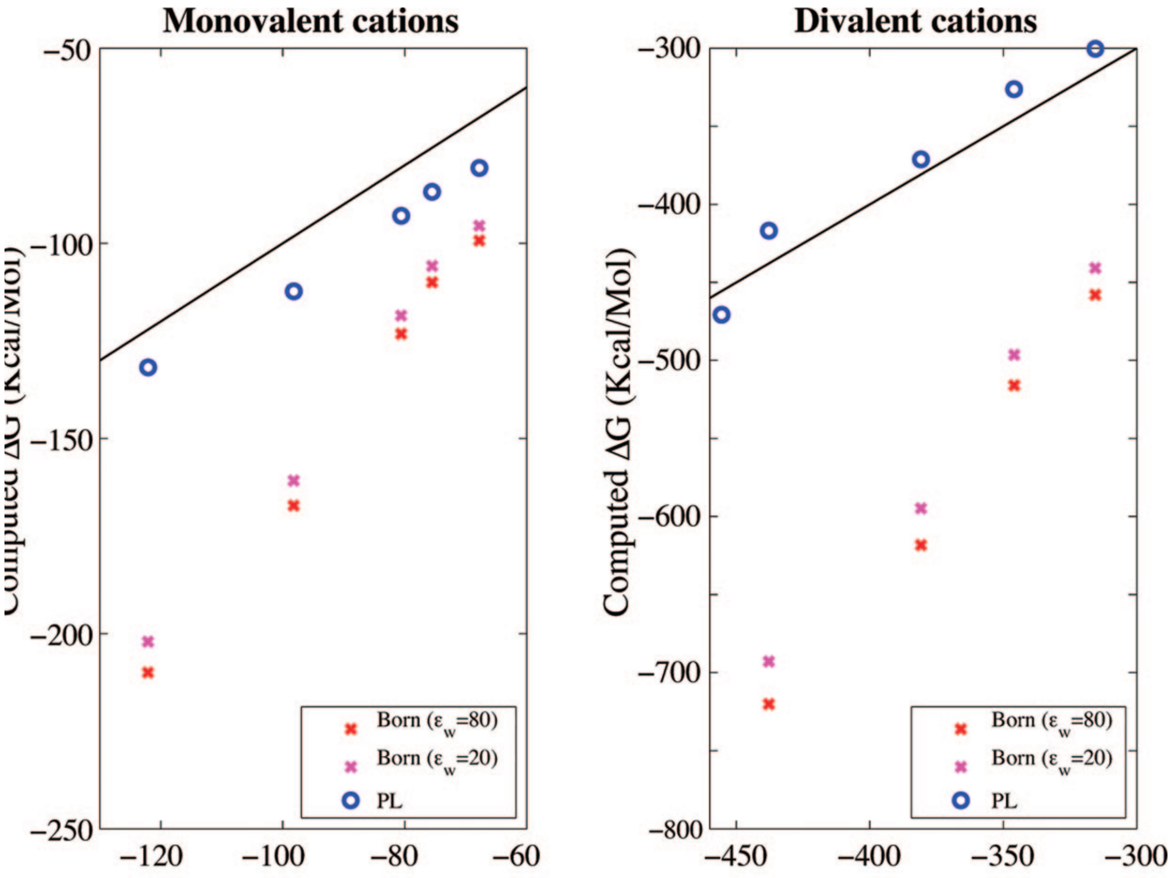
$$\left\{\begin{array}{l}\vec{\nabla}\left(\epsilon_0\vec{\nabla}\Phi(\vec{r})+\gamma(\vec{r})\beta p_0^2\dfrac{\lambda_{\mathrm{dip}}e^{-\beta\Psi(\vec{r})}F_1(u)}{a^3\mathcal{Z}_l(\vec{r})}\vec{\nabla}\Phi(\vec{r})\right)=-\rho_f(\vec{r})\\[3em] \dfrac{1}{v_0}\left(\Delta\Psi-\dfrac{\Psi(\vec{r})}{b^2}\right)=\gamma(\vec{r})\dfrac{1}{a^3}\,\dfrac{\lambda_{\mat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

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

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



Li^+
Na^+
K^+
Rb^+
Cs^+

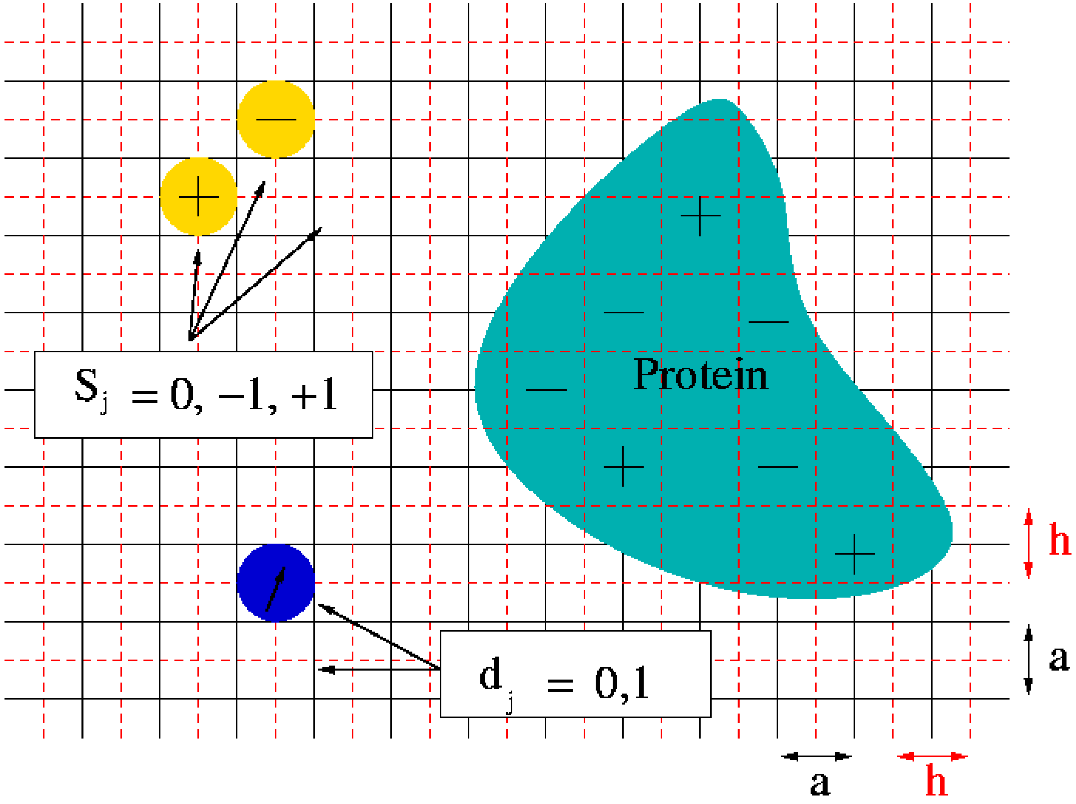


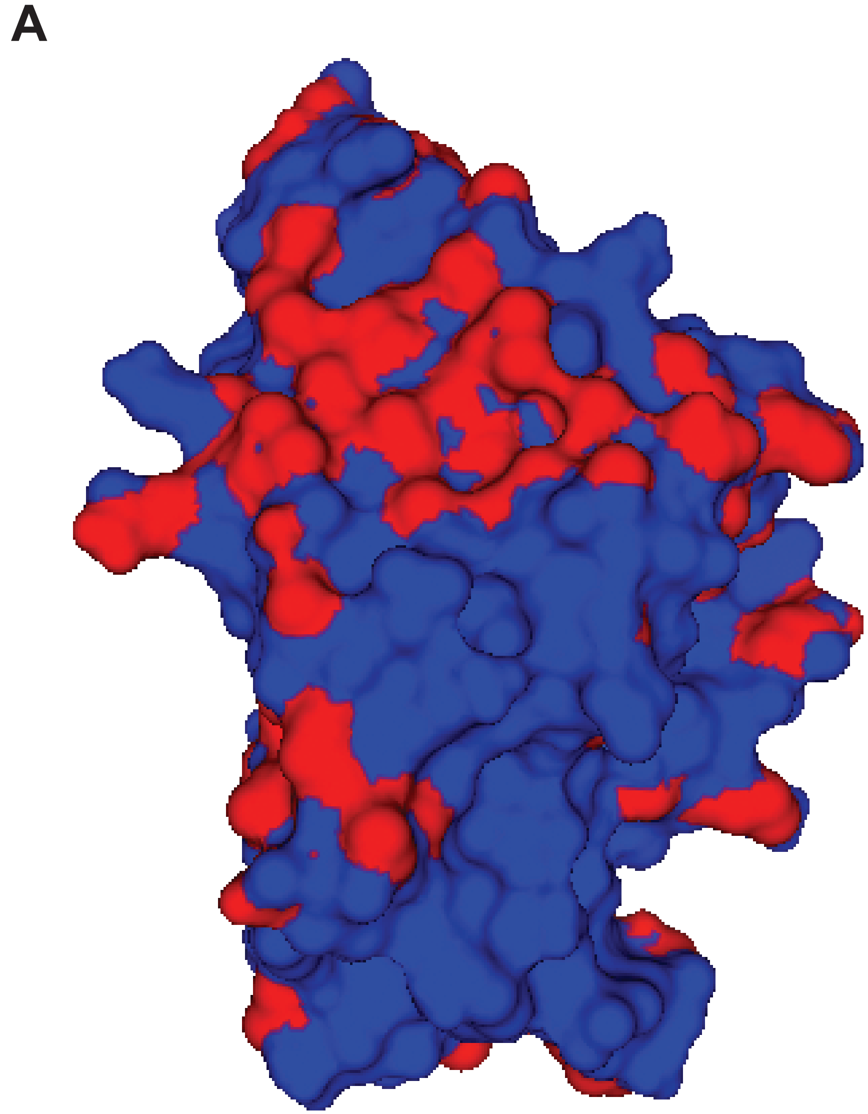
Mg^{2+}
Mn^{2+}
Ca^{2+}
Sr^{2+}
Ba^{2+}

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

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



Compute:
-hydrophobicity profiles
-ion profiles
-solvation free energies

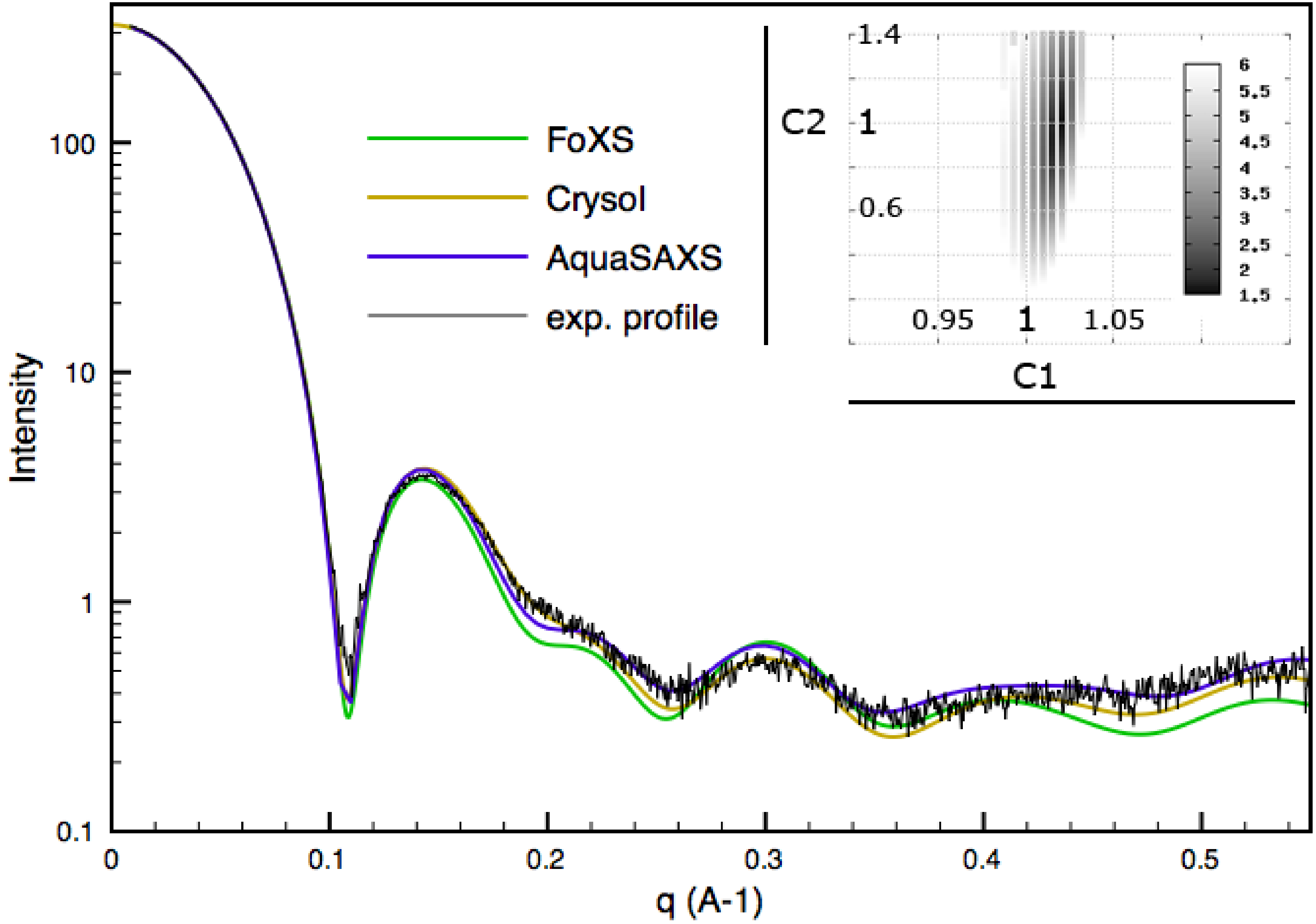
Hydrophobic regions (red) of a Thymidine Kinase
Validated by comparison with all atom MD simulations

Working include Gaussian vibrations of protein

Aquasax

- Compute SAXS profiles of given protein structures.
- Given a protein structure, compute the hydration layer
- Compute the corresponding SAXS profile
- Web server:

http://lorentz.dynstr.pasteur.fr/aquasaxs.php



FoXS
Crysol
AquaSAXS
exp. profile
Intensity
100
10
1
0.1
q (A-1)
0
0.1
0.2
0.3
0.4
0.5
C2
1.4
1
0.6
C1
0.95
1
1.05
6
5,5
5
4,5
4
3,5
3
2,5
2
1,5

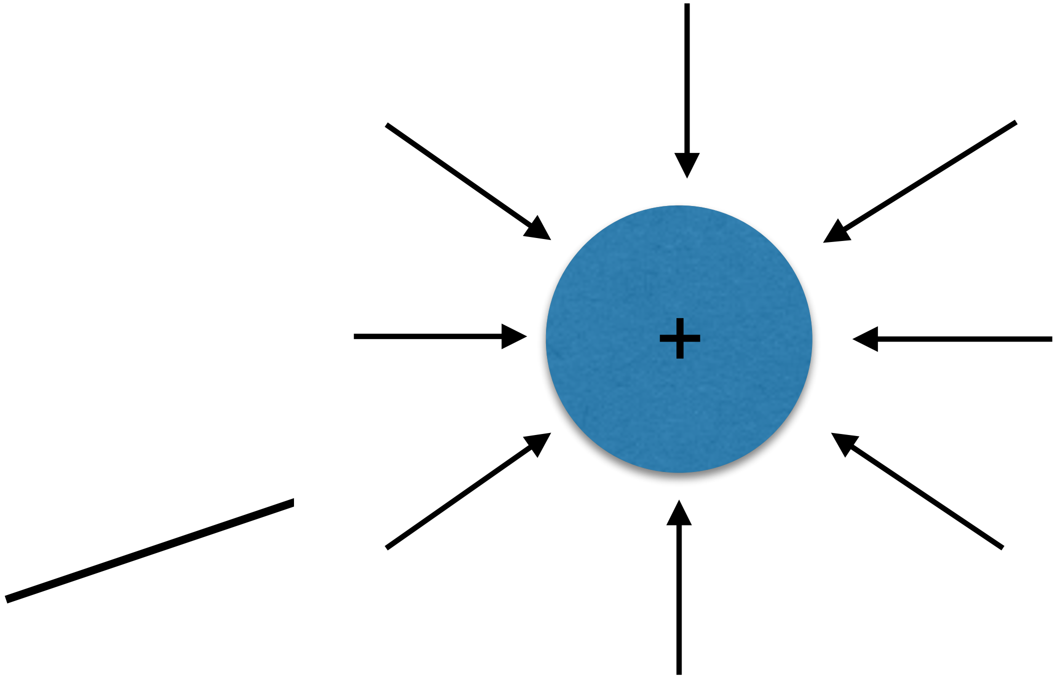
Effects of fluctuations: Beyond Poisson-Boltzmann

It is possible to compute the corrections to one loop order in simple cases:
EDL (with R. Netz), …

What happens when one adds salt to a dielectric fluid?

- Dielectric constant is the response of the system to an external electric field.
- Water has a high dielectric constant because water molecules are dipoles and can orient in an external electric field.

- When one adds ions in the solution, they polarize the water molecules



Hydration shell

Polarized water molecules are less orientable and contribute less to the dielectric constant

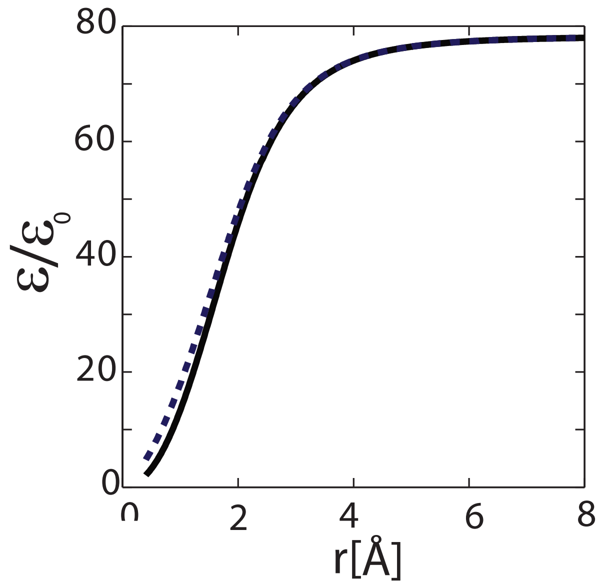
➡ dielectric constant decrement

A single ion in a dipolar liquid

- Assume low ion concentration. One can look at a single ion in water

$$-\epsilon_0 \nabla \mathbf{E} = n_d p_0 \nabla \cdot \left[\hat{E} G(\beta p_0 E) \right] + \rho_f(\mathbf{r}).$$

$$\rho_f(\mathbf{r}) = q\delta(\mathbf{r}).$$



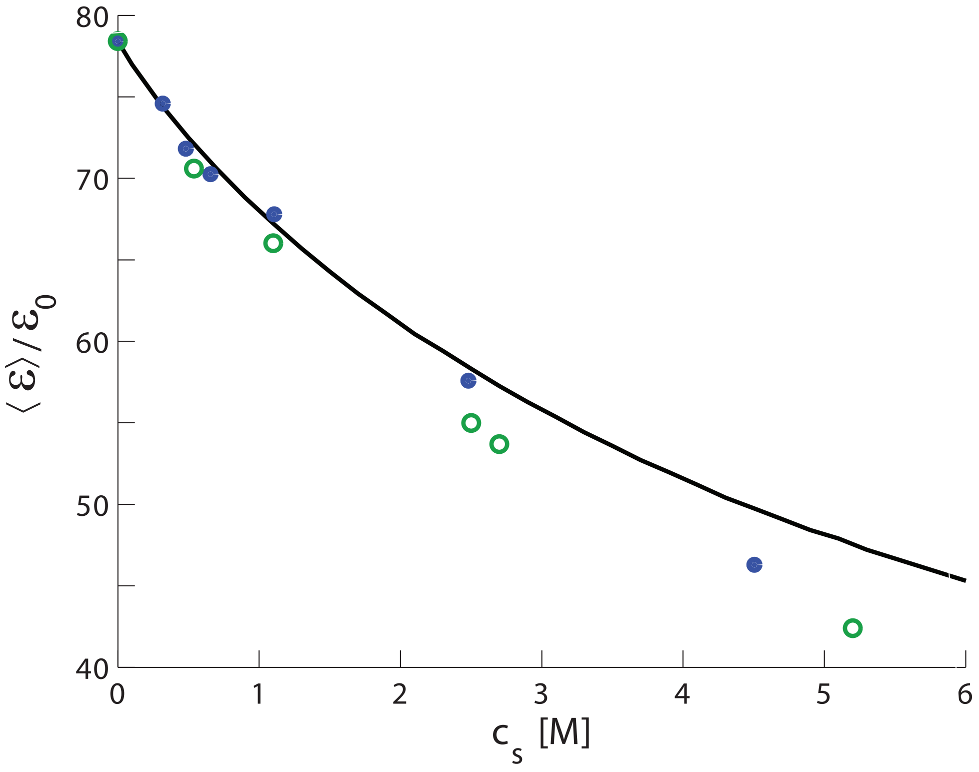
$$G(u) = \frac{\cosh u}{u} - \frac{\sinh u}{u^2}$$

$$l_h^2 = l_B d$$

Scale of hydration shell

Average dielectric constant over a sphere of radius equal to the typical distance between ions

$$R = \frac{1}{2}(2c_s)^{-1/3}$$



RbCl and CsCl in water

The field-theoretic approach

No ion interaction effect

$$Z[\rho(\mathbf{r})] \;=\; \int \mathcal{D}\phi(\mathbf{r}) \exp\left(-\beta \int \mathrm{d}^3\mathbf{r}\; f(\phi(\mathbf{r})) - i\beta \int \mathrm{d}^3\mathbf{r}\, \phi(\mathbf{r})\rho(\mathbf{r})\right)$$

$$\beta f(\phi(\mathbf{r})) \;=\; \frac{\beta\varepsilon_0}{2}[\nabla\phi(\mathbf{r})]^2 \;-\; 2\lambda_s \cos[\beta e\phi(\mathbf{r})] - \lambda_d \frac{\sin(\beta p_0|\nabla\phi(\mathbf{r})|)}{\beta p_0|\nabla\phi(\mathbf{r})|}$$

$$\begin{aligned} \frac{\lambda_s}{V}\frac{\partial}{\partial\lambda_s}\log Z &= c_s \\ \frac{\lambda_d}{V}\frac{\partial}{\partial\lambda_d}\log Z &= c_d \end{aligned}$$

The electrostatic potential $\Psi(\mathbf{r})$ is given by

$$\Psi(\mathbf{r}) = -\frac{1}{\beta}\frac{\delta \log Z[\rho(\mathbf{r})]}{\delta\rho(\mathbf{r})} = i\langle\phi(\mathbf{r})\rangle \;,$$

Gibbs free energy

$$\begin{aligned} G[\Psi(\mathbf{r})] &= F[\rho(\mathbf{r})] - \int \mathrm{d}^3\mathbf{r}\ \Psi(\mathbf{r})\rho(\mathbf{r}) \\ \Psi(\mathbf{r}) &= \frac{\delta F[\rho(\mathbf{r})]}{\delta\rho(\mathbf{r})}\ , \\ \rho(\mathbf{r}) &= -\frac{\delta G[\Psi(\mathbf{r})]}{\delta\Psi(\mathbf{r})} \end{aligned}$$

Dielectric tensor

$$\varepsilon_{\alpha\beta} = \frac{\partial^2}{\partial p_\alpha \partial p_\beta} \int \mathrm{d}^3\mathbf{r}\ \mathrm{e}^{i\mathbf{p}\cdot\mathbf{r}} \frac{\delta^2 G[\Psi(\mathbf{r})]}{\delta\Psi(\mathbf{r})\delta\Psi(0)}\bigg|_{\Psi=0,\mathbf{p}=0}$$

Here, dielectric tensor is diagonal

Mean-Field level

$$\beta G_{\mathrm{DPB}}[\Psi] \;=\; -\frac{\beta\varepsilon_0}{2}(\nabla\Psi)^2 - 2c_s\cosh(\beta e\Psi) - \; c_d g(u),$$

$\mathbf{u} = \beta p_0 \nabla\Psi(\mathbf{r})$, $u = |\mathbf{u}|$, and $g(u) = \sinh u/u$.

$$\epsilon_0\nabla^2\Psi \;=\; 2c_s e\sinh\left(\beta e\Psi\right) - \; c_d p_0 \nabla\cdot\left[\frac{\nabla\Psi}{|\nabla\Psi|}\mathcal{G}(\beta p_0|\nabla\Psi|)\right]$$

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

$$\varepsilon_{\mathrm{DPB}} = \varepsilon_0 + \beta p_0^2 c_d/3$$

The dielectric constant is the coefficient of the square gradient term.

No effect of the ions on the dielectric constant at mean-field level

One loop correction

$$\begin{aligned}\Delta G[\Psi(\mathbf{r})] &= \frac{1}{2\beta}\mathrm{Tr}\log\left[-\varepsilon_0\nabla^2 + 2\lambda_s\beta e^2\cosh(\beta e\Psi(\mathbf{r}))\right.\\ &+ \left.\lambda_d\beta p_0^2\left(\partial_\alpha\Gamma_{\alpha\gamma}(\mathbf{r})\partial_\gamma + \Gamma_{\alpha\gamma}(\mathbf{r})\partial_\alpha\cdot\partial_\gamma\right)\right]\end{aligned}$$

$$\Gamma_{\alpha\gamma}(\mathbf{r}) = \delta_{\alpha\gamma}\frac{g'(u)}{u} - \frac{u_\alpha u_\gamma}{u^2}\left(\frac{g'(u)}{u} - g''(u)\right)$$

Ions and dipole fugacities must be also computed to one-loop order

$$\begin{aligned}\lambda_d &= c_d - \frac{2\pi}{3a^3}\frac{\varepsilon_{\mathrm{DPB}} - \varepsilon_0}{\varepsilon_{\mathrm{DPB}}}\left[1 - \frac{3}{4\pi^2}(\kappa_{\mathrm{D}}a)^2\right.\\ &+ \left.\frac{3}{8\pi^3}(\kappa_{\mathrm{D}}a)^3\tan^{-1}\frac{2\pi}{\kappa_{\mathrm{D}}a}\right],\end{aligned}$$

$\kappa_{\mathrm{D}} = \sqrt{8\pi l_{\mathrm{B}} c_s}$ Inverse Debye length

- Regularization of short distance divergences through cut-off *a*. Final one-loop result

Fluctuations of water

$$\varepsilon - \varepsilon_{\mathrm{DPB}} = \Delta\varepsilon_d + \Delta\varepsilon_s :$$

$$\begin{aligned}
\Delta\varepsilon_d &= \frac{(\varepsilon_{\mathrm{DPB}} - \varepsilon_0)^2}{\varepsilon_{\mathrm{DPB}}} \frac{4\pi}{3 c_d a^3} \\
\Delta\varepsilon_s &= -\frac{(\varepsilon_{\mathrm{DPB}} - \varepsilon_0)^2}{\varepsilon_{\mathrm{DPB}}} \frac{\kappa_{\mathrm{D}}^2}{\pi c_d a} \left(1 - \frac{\kappa_{\mathrm{D}} a}{2\pi} \tan^{-1} \frac{2\pi}{\kappa_{\mathrm{D}} a}\right)
\end{aligned}$$

Effect of Salt

Results

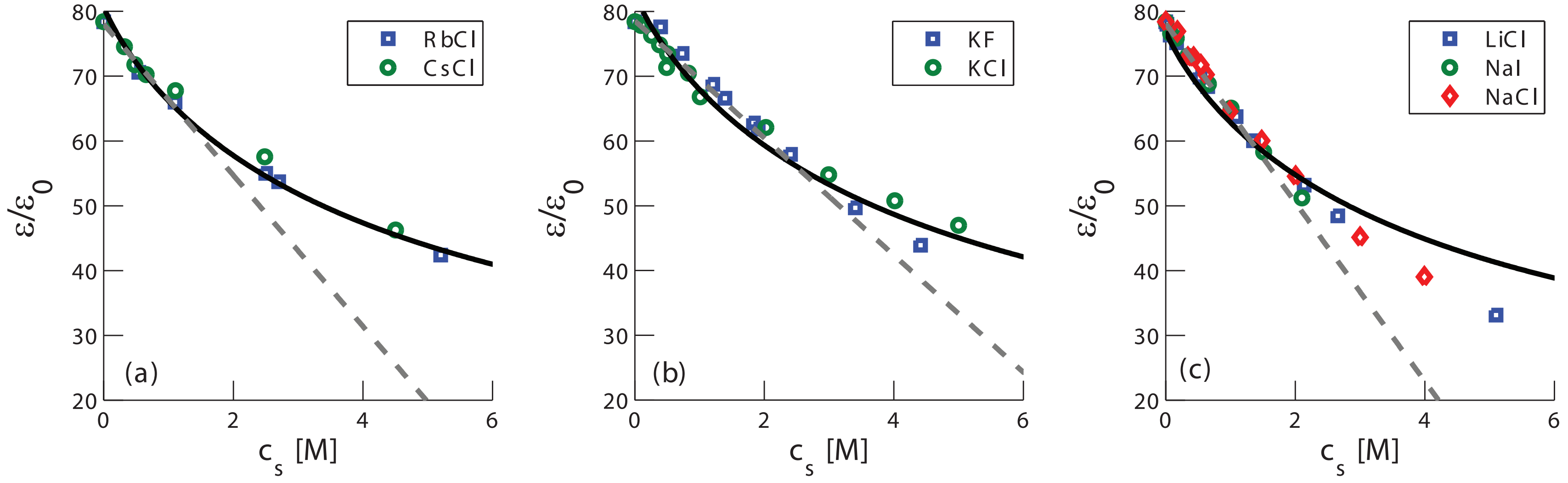


FIG. 2: (color online). Comparison of the predicted dielectric constant, ε, from Eq. (16) with experimental data from Ref. [19], as function of ionic concentration, c_s, for various salts. The theoretical prediction (solid line) was calculated using a as a fitting parameter. In (a) the fit is for RbCl and CsCl salts with $a = 2.66\,\text{Å}$; in (b) the fit is for KF and KCl with $a = 2.64\,\text{Å}$; while in (c) the fit is for LiCl, NaI and NaCl with $a = 2.71\,\text{Å}$. The dashed lines are the linear fit to the data in the low $c_s \leq 1\,\text{M}$ range. The slope of the linear fit is $\gamma/\varepsilon_0 = 11.7\,\text{M}^{-1}$ in (a), $9.0\,\text{M}^{-1}$ in (b) and $13.8\,\text{M}^{-1}$ in (c). The value of γ for each salt varies by about 10-20 % and the linear fit should be taken as representative of the low c_s behavior.

Beyond one-loop

- Quadratic fluctuations are OK if coupling constant not too strong.
- For large coupling constant, no good theory. Perform Monte Carlo or Langevin simulations.
- Action is complex!

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

Local Langevin dynamics for Electrolytes

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

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

$$n_i(r) = \sum_j \delta(r - r_j^{(i)})$$

$$\rho_c(r) = \sum_i q_i n_i(r) + \rho_f(r)$$

Constrain the integration over $n_i(r)$ by a δ function

$$Z = \int \prod_i \mathcal{D}\varphi_i(r)\mathcal{D}n_i(r) \exp\left(-\frac{\beta}{2}\int dr dr' \rho_c(r) v_c(r-r')\rho_c(r') + i\sum_i \int dr \varphi_i(r) n_i(r) + \sum_i \lambda_i \int dr e^{-i\varphi_i(r)}\right)$$

The integral on $\varphi_i(r)$ can be done to any order by the saddle-point method. To lowest-order:

$$Z = \int \prod_i \mathcal{D}n_i(r) \exp\left(-S(n_i(r))\right)$$

with

Coulomb energy

DFT

$$S(n_i(r)) = \frac{\beta}{2}\int dr dr' \left(\sum_i q_i n_i(r) + \rho_f(r)\right) v_c(r-r') \left(\sum_j q_i n_j(r') + \rho_f(r')\right)$$

$$+\sum_i \int dr n_i(r) \log\frac{n_i(r)}{\lambda e}$$

Entropy

and $n_i(r) \geq 0$ for all *i* and all *r*

$$\frac{\delta S}{\delta n_i(r)} = \beta q_i \int dr' v_c(r-r') \Big(\sum_j q_j n_j(r') + \rho_f(r')\Big) + \log\frac{n_i(r)}{\lambda_i}$$

General Langevin Equation

$$\frac{dn_i(r,t)}{dt} = -\int dr dr' D(r,r') \frac{\delta S(n_i(r,t))}{\delta n_i(r,t)} + \eta_i(r,t)$$

with $\langle \eta_i(r,t) \rangle = 0$

$$\langle \eta_i(r,t) \eta_j(r',t') \rangle = 2\delta_{ij}\delta(t-t')D(r,r')$$

where $D(r,r')$ is any positive definite operator

One can then prove that detailed balance is satisfied

So one can sample the Boltzmann distribution with this equation

Model A : $D(r,r') = D\delta(r-r')$

$$\frac{dn_i}{dt} = -D\left(\beta q_i \int dr' v_c(r-r')\Big(\sum_j q_j n_j(r') + \rho_f(r')\Big) + \log\frac{n_i(r)}{\lambda_i}\right) + \eta_i(r,t)$$

Problem: VERY non local due to Coulomb interaction

Model B : $D(r,r') = Dv_c^{-1}(r-r')$

Everything becomes local!!!

$$\frac{dn_i(r,t)}{dt} = D\left(\nabla\left(\varepsilon(r)\left(\nabla\log\frac{n_i(r,t)}{\lambda_i}\right)\right) - \beta q_i(\sum_j q_j n_j(r,t) + \rho_f(r))\right) + \nabla\vec{\xi}_i(r,t)$$

$$\langle \xi_i^{(\alpha)}(r,t)\xi_j^{(\alpha')}(r',t')\rangle = 2D\delta_{ij}\delta_{\alpha\alpha'}\delta(r-r')\delta(t-t')$$

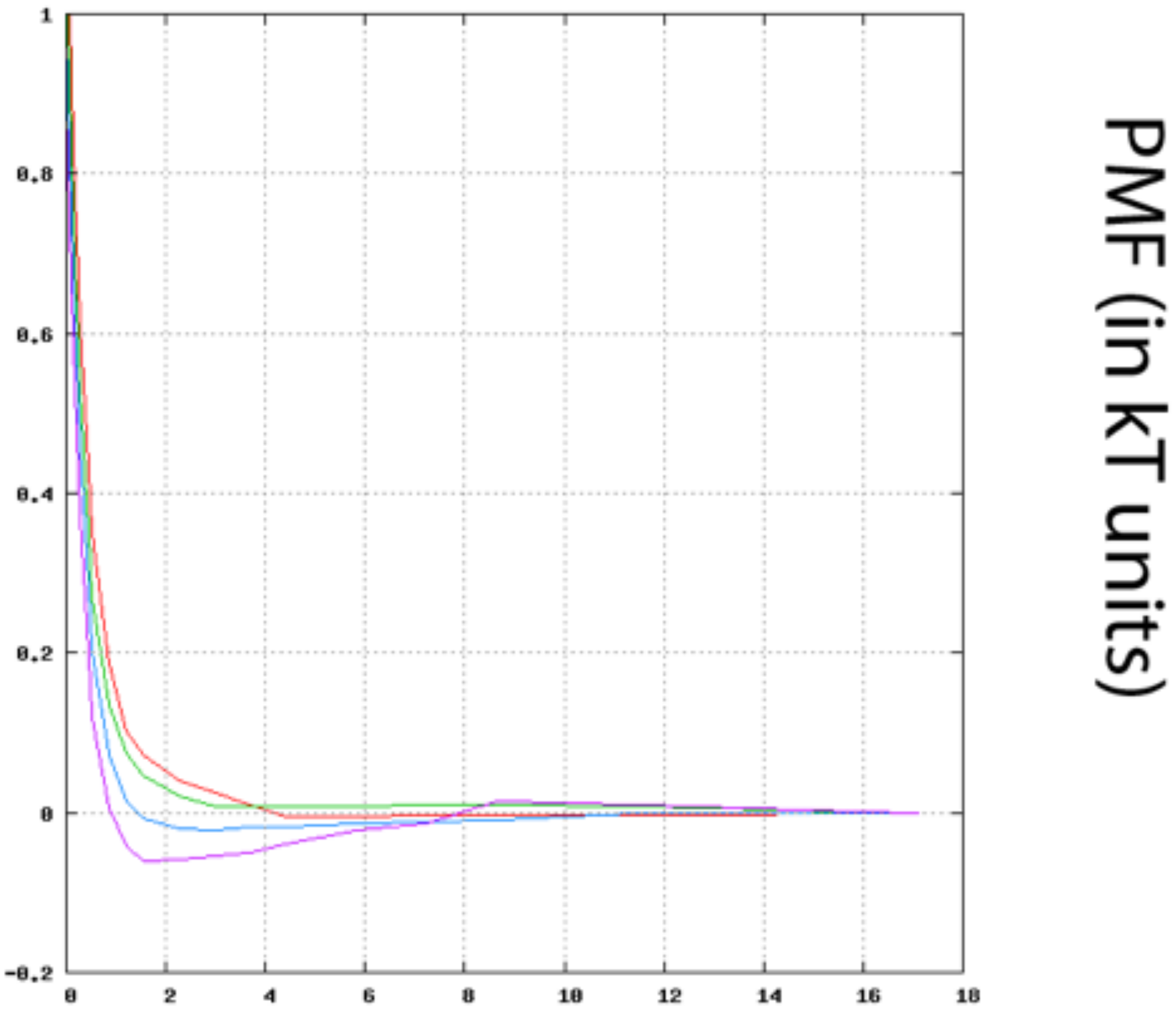
No Ewald sums

Non locality = Laplacian

Application: like-charge attraction

Two ions of same charge *q* in a multivalent *3:1* salt

q=3



Conclusion

- It is possible to include ion-size, dipolar water, etc…at mean-field level, for any geometry
- It is possible to account for fluctuations with local Langevin equations
- Apply to more systems, in particular biopolymers
- Apply to Molecular Dynamics of biopolymers
- Exact dynamics in local formulation