Macroscopic Electrostatic Force in Molecular Conformational Dynamics

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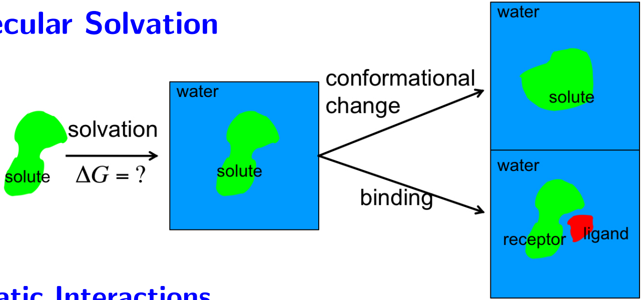
Biomolecular Solvation

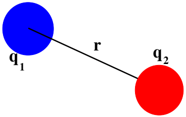


Electrostatic Interactions

- Solute partial charges
- Mobile ions in water
- Solvent polorization
- Dielectric response

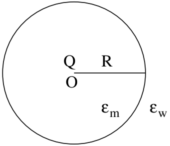
Coulomb's law

$$\mathbf{F}_{21} = -\frac{q_1 q_2}{4\pi\varepsilon r^2}\mathbf{r}_{21}$$



Poisson's equation

$$\nabla \cdot \varepsilon \nabla \psi = -\rho$$



Born's model (1920): $W = -\frac{Q^2}{8\pi R}\left(\frac{1}{\varepsilon_m} - \frac{1}{\varepsilon_w}\right)$

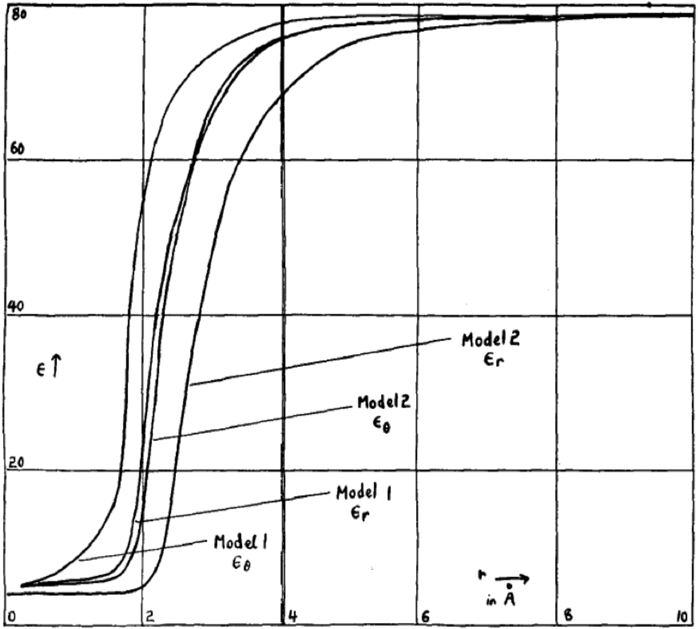


FIG. 1. Plot of dielectric constants ϵ_r, ϵ_θ against distance r in angstroms from an ion.

Hasted, Ritson, & Collie, JCP 1948)

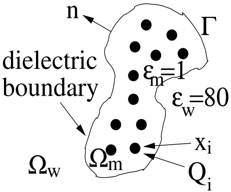
Variational Implicit-Solvent Model (VISM)

(Dzubiella, Swanson, & McCammon, PRL & JCP 2006)

Solvation free-energy functional

$$G[\Gamma] = \text{surface energy} + \text{solute-solvent interaction} + \text{electrostatics}$$

$$= \gamma_0 \,\text{Area}\,(\Gamma) + \rho_{\mathrm{w}} \int_{\Omega_{\mathrm{w}}} U_{\mathrm{vdW}}\, dV + G_{\mathrm{ele}}[\Gamma]$$



$$U_{\mathrm{vdW}}(x) = \sum_{i=1}^{N} U_{\mathrm{LJ}}^{(i)}(|x - x_i|)$$

Poisson–Boltzmann (PB) free energy and PBE

$$G_{\mathrm{ele}}[\Gamma] = \int_{\Omega} \left[-\frac{\varepsilon_\Gamma}{2} |\nabla \psi|^2 + f\psi - \chi_{\mathrm{w}} B(\psi) \right] dV$$

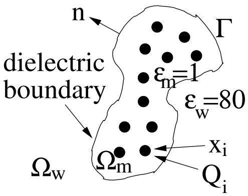
$$\varepsilon_\Gamma = \begin{cases} \varepsilon_{\mathrm{m}} & \text{in } \Omega_{\mathrm{m}} \\ \varepsilon_{\mathrm{w}} & \text{in } \Omega_{\mathrm{w}} \end{cases}$$

$$\nabla \cdot \varepsilon_\Gamma \nabla \psi - \chi_{\mathrm{w}} B'(\psi) = -f$$

$$B(\psi) = \beta^{-1} \sum_{j=1}^{M} c_j^{\infty} \left(e^{-\beta q_j \psi} - 1 \right)$$

Boundary force: $-\delta_\Gamma G[\Gamma] = -2\gamma_0 H + \rho_{\mathrm{w}} U_{\mathrm{vdW}} - \delta_\Gamma G_{\mathrm{ele}}[\Gamma]$

Dielectric boundary force (DBF): $-\delta_\Gamma G_{\mathrm{ele}}[\Gamma]$



$$\nabla \cdot \varepsilon_\Gamma \nabla \psi - \chi_{\mathrm{w}} B'(\psi) = -f$$

$$G_{\mathrm{ele}}[\Gamma] = \int_\Omega \left[-\frac{\varepsilon_\Gamma}{2} |\nabla \psi|^2 + f\psi - \chi_{\mathrm{w}} B(\psi) \right] dV$$

Define the DBF

$$\Gamma \Longrightarrow \Gamma_t \Longrightarrow \psi_{\Gamma_t} \Longrightarrow G_{\mathrm{ele}}[\Gamma_t] \Longrightarrow \delta_\Gamma G_{\mathrm{ele}}[\Gamma] := \left. \frac{d}{dt} \right|_{t=0} G_{\mathrm{ele}}[\Gamma_t]$$

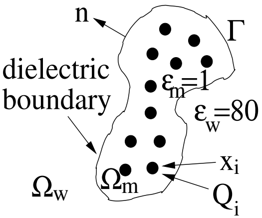
For any $V \in C_c^\infty(\mathbb{R}^3, \mathbb{R}^3)$, define $x : [0, \infty) \times \mathbb{R}^3 \to \mathbb{R}^3$ by $\dot{x} = V(x)$ and $x(0, X) = X$. Set $T_t(X) = x(t, X)$ and $\Gamma_t = T_t(\Gamma)$.

$$\delta_{\Gamma, V} G_{\mathrm{ele}}[\Gamma] := \lim_{t \to 0} \frac{G_{\mathrm{ele}}[\Gamma_t] - G_{\mathrm{ele}}[\Gamma]}{t} = \int_\Gamma (V \cdot n)\, h_\Gamma \, dS$$

Definition. $\delta_\Gamma G_{\mathrm{ele}}[\Gamma] = h_\Gamma : \Gamma \to \Gamma.$

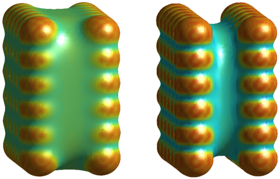
Theorem (Li, Cheng, & Zhang, SIAP 2011; Li, Zhang, & Zhou, J. Nonlinear Sci. 2021 (under review).) The DBF is given by

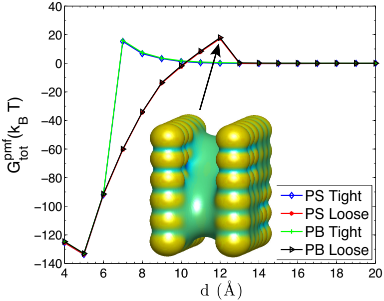
$$
\begin{aligned}
&-\delta_\Gamma G_{\mathrm{ele}}[\Gamma] \\
&= -\frac{1}{2}\left(\frac{1}{\varepsilon_{\mathrm{m}}} - \frac{1}{\varepsilon_{\mathrm{w}}}\right)|\varepsilon_\Gamma \nabla\psi\cdot n|^2 \\
&\quad - \frac{1}{2}(\varepsilon_{\mathrm{w}} - \varepsilon_{\mathrm{m}})\,|(I - n\otimes n)\nabla\psi|^2 - B(\psi) \\
&< 0.
\end{aligned}
$$

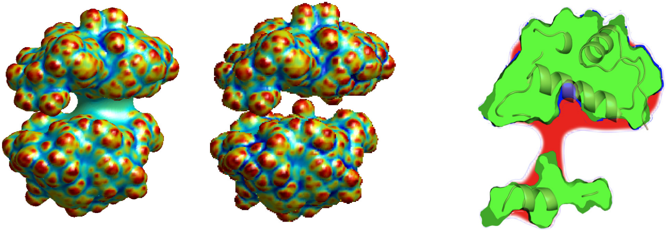


B. Chu, Molecular Forces. Based on the Baker Lectures of Peter J. W. Debye, John Wiley & Sons, 1967:

"Under the combined influence of electric field generated by solute charges and their polarization in the surrounding medium which is electrostatic neutral, an additional potential energy emerges and drives the surrounding molecules to the solutes."







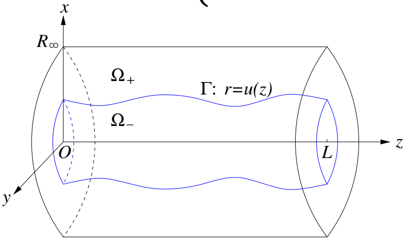
Wang *et al.* JCTC 2012, Guo *et al.* JCTC 2014, Zhou *et al.* JCTC 2014.

Stability of a Cylindrical Dielectric Boundary

(Cheng, Li, White, & Zhou. SIAP 2013)

$$F[\Gamma] = \gamma_0 \,\text{Area}\,(\Gamma) + \int_\Omega \frac{1}{2} f \psi_\Gamma \, dV$$

$$\begin{cases} \nabla \cdot \varepsilon_\Gamma \nabla \psi_\Gamma = -f & \text{in } \Omega \\ \psi_\Gamma = 0 & \text{on } r = R_\infty \end{cases}$$



$$\varepsilon_\Gamma = \begin{cases} \varepsilon_- & \text{in } \Omega_- \\ \varepsilon_+ & \text{in } \Omega_+ \end{cases}$$

Assume: $\varepsilon_- > \varepsilon_+$.

- Water molecules deep in a protein.
- Competition: surface energy vs. electrostatic energy.
- Stability of an equilibrium dielectric boundary.

Steepest descent: $V_n = -\delta_\Gamma F[\Gamma]$

$$\begin{cases} u_t = \gamma_0 \left(\dfrac{u_{zz}}{1+u_z^2} - \dfrac{1}{u} \right) - \dfrac{1}{2} \left(\dfrac{1}{\varepsilon_-} - \dfrac{1}{\varepsilon_+} \right) \dfrac{\left[\varepsilon_{\Gamma(t)} \left(\psi_r - u_z \psi_z \right) \right]^2}{\sqrt{1+u_z^2}} \\ \qquad - \dfrac{1}{2} \left(\varepsilon_+ - \varepsilon_- \right) \dfrac{\left(u_z \psi_r + \psi_z \right)^2}{\sqrt{1+u_z^2}} \qquad \forall (z,t) \in (-\infty, \infty) \times (0, T] \\ \quad u(z,t) \text{ is } L\text{-periodic in } z \text{ for each } t \in [0, T] \\ \quad u(z,0) \text{ is given for all } z \in (-\infty, \infty) \\ \nabla \cdot \varepsilon_{\Gamma(t)} \nabla \psi = -f \qquad \text{in } \Omega \\ \quad \psi(r,z,t) \text{ is } L\text{-periodic in } z \text{ for each } (r,t) \in [0, R_\infty) \times [0, T] \\ \quad \psi(R_\infty, z, t) = 0 \qquad \forall (z,t) \in (-\infty, \infty) \times [0, T] \end{cases}$$

Step 1. Steady-state solutions. $u = u_0$ and $\psi = \psi_0(r)$.

$$u_0 = \frac{1}{\eta_0}\left(\int_0^{u_0} sf(s)\,ds\right)^2$$

$$\psi_0(r) = \begin{cases} -\dfrac{1}{\varepsilon_-}\displaystyle\int_0^r \left[\frac{1}{s}\int_0^s \tau f(\tau)\,d\tau\right] ds + C_2 & \text{if } r < u_0 \\ -\dfrac{1}{\varepsilon_+}\displaystyle\int_{u_0}^r \left[\frac{1}{s}\int_{u_0}^s \tau f(\tau)\,d\tau\right] ds + C_3 \log r + C_4 & \text{if } r > u_0 \end{cases}$$

$$\begin{cases} C_2 - C_3 \log u_0 - C_4 = \dfrac{1}{\varepsilon_-}\displaystyle\int_0^{u_0} \left[\frac{1}{s}\int_0^s \tau f(\tau)\,d\tau\right] ds \\ C_3 = -\dfrac{1}{\varepsilon_+}\displaystyle\int_0^{u_0} sf(s)\,ds \\ C_3 \log R_\infty + C_4 = \dfrac{1}{\varepsilon_+}\displaystyle\int_{u_0}^{R_\infty} \left[\frac{1}{s}\int_{u_0}^s \tau f(\tau)\,d\tau\right] ds \end{cases}$$

$$\eta = 2\gamma_0\left(\frac{1}{\varepsilon_+} - \frac{1}{\varepsilon_-}\right)^{-1} > 0 \quad \text{and} \quad \eta R_\infty < \left(\int_0^{R_\infty} sf(s)\,ds\right)^2$$

Step 2. Linearization.

$$u = u(z,t,\delta) = u_0 + \delta u_1(z,t) + \cdots ,$$
$$\psi = \psi(r,z,t,\delta) = \psi_0(r) + \delta\psi_1(r,z,t) + \cdots .$$

$$\begin{cases} \partial_t u_1 = \gamma_0 \partial_z^2 u_1 + \left[\dfrac{\gamma_0}{u_0^2} - \left(\dfrac{1}{\varepsilon_-} - \dfrac{1}{\varepsilon_+}\right)\varepsilon_+^2 \psi_0'(u_0^+)\psi_0''(u_0^+)\right] u_1 \\ \qquad\qquad - \left(\dfrac{1}{\varepsilon_-} - \dfrac{1}{\varepsilon_+}\right)\varepsilon_+^2 \psi_0'(u_0^+)\partial_r\psi_1(u_0^+,z,t) \quad \forall z,t, \\ \Delta\psi_1 = 0 \qquad \text{if } 0 < r < u_0, \\ \Delta\psi_1 = 0 \qquad \text{if } u_0 < r < R_\infty, \\ \quad \psi_1(u_0^+,z,t) - \psi_1(u_0^-,z,t) = -u_1(z,t)\left[\psi_0'(u_0^+) - \psi_0'(u_0^-)\right] \quad \forall z,t, \\ \quad \varepsilon_-\partial_r\psi_1(u_0^-,z,t) = \varepsilon_+\partial_r\psi_1(u_0^+,z,t) \quad \forall z,t, \\ \quad \psi_1(R_\infty,z,t) = 0 \quad \forall z,t. \end{cases}$$

Step 3. Dispersion relations.

Assume

$$\begin{aligned} &u_1(z,t) = Ae^{\omega t}e^{ikz} \quad \text{with } k = 2\pi k'/L,\ k' \in \mathbb{Z}, \\ &\psi_1(r,z,t) = u_1(z,t)\phi_k(r). \end{aligned}$$

Then the dispersion relation $\omega = \omega(k)$ is given by

$$\omega(k) = -\gamma_0 k^2 + \frac{\gamma_0}{u_0^2} - \left(\frac{1}{\varepsilon_-} - \frac{1}{\varepsilon_+}\right)\varepsilon_+^2 \psi_0'(u_0^+)\left[\psi_0''(u_0^+) + \phi_k'(u_0^+)\right],$$

$$\begin{cases} \phi_k''(r) + \dfrac{1}{r}\phi_k'(r) - k^2\phi_k(r) = 0 & \text{if } 0 < r < u_0, \\ \phi_k''(r) + \dfrac{1}{r}\phi_k'(r) - k^2\phi_k(r) = 0 & \text{if } u_0 < r < R_\infty, \\ \quad \phi_k(u_0^+) - \phi_k(u_0^-) = -\left[\psi_0'(u_0^+) - \psi_0'(u_0^-)\right], \\ \quad \varepsilon_-\phi_k'(u_0^-) = \varepsilon_+\phi_k'(u_0^+), \\ \quad \phi_k(R_\infty) = 0. \end{cases}$$

The modified Bessel differential equation

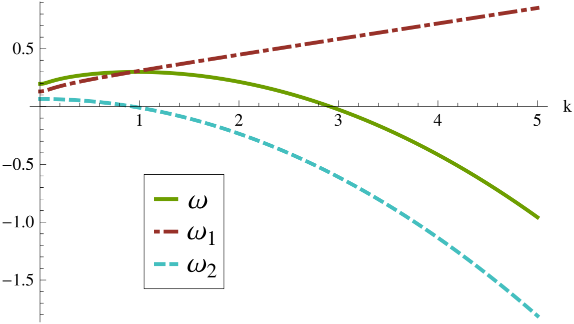
$$x^2 y''(x) + x y'(x) - x^2 y(x) = 0.$$

The modified Bessel functions

$$I_0(x) = \sum_{s=0}^{\infty} \frac{1}{(s!)^2} \left(\frac{x}{2}\right)^{2s} \quad \text{and} \quad K_0(x) = \int_0^{\infty} \frac{\cos(xs)}{\sqrt{1+s^2}}\, ds.$$

$$\phi_k(r) = \begin{cases} \mu\varepsilon_+ \left[\psi_0'(u_0^+) - \psi_0'(u_0^-)\right] I_0(kr) & \\ \qquad \left[K_0(kR_\infty) I_0'(ku_0) - I_0(kR_\infty) K_0'(ku_0)\right] & \text{if } 0 < r < u_0, \\ \mu\varepsilon_- \left[\psi_0'(u_0^+) - \psi_0'(u_0^-)\right] I_0'(ku_0) & \\ \qquad \left[K_0(kR_\infty) I_0(kr) - I_0(kR_\infty) K_0(kr)\right] & \text{if } u_0 < r < R_\infty, \end{cases}$$

$$\begin{aligned} \frac{1}{\mu} &= \varepsilon_- I_1(ku_0) \left[I_0(kR_\infty) K_0(ku_0) - I_0(ku_0) K_0(kR_\infty)\right] \\ &\quad + \varepsilon_+ I_0(ku_0) \left[I_1(ku_0) K_0(kR_\infty) + I_0(kR_\infty) K_1(ku_0)\right]. \end{aligned}$$



$$\omega(k) = \omega_1(k) + \omega_2(k)$$

$$\omega_1(k) = -\left(\frac{1}{\varepsilon_-} - \frac{1}{\varepsilon_+}\right) \varepsilon_+^2 \psi_0'(u_0^+) \left[\psi_0''(u_0^+) + \phi_k'(u_0^+)\right]$$

$$\omega_2(k) = -\gamma_0 k^2 + \frac{\gamma_0}{u_0^2}$$

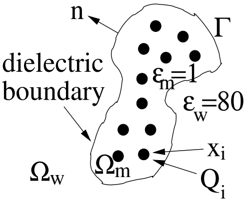
Conclusion: linearly stable if and only if $k > k_c$.

Possible implication in biology: Water molecules inside proteins are unstable—no hydrogen network.

(Rasaiah *et al.* JACS 2007 & JPCB 2010)

Dynamic Implicit-Solvent Model (DISM)

Li, Sun, & Zhou, SIAP 2015,
Sun, Zhou, Cheng, & Li, J. Comput. Phys. 2018,
Fan, Li, & White, SIAP 2021.



Interface motion $V_n = \mathbf{u}\cdot\mathbf{n}$ on $\Gamma(t)$,

Incompressibility $\nabla\cdot\mathbf{u} = 0$ in $\Omega_{\mathrm{w}}(t)$,

Stochastic Stokes eq. $\mu_{\mathrm{w}}\nabla^2\mathbf{u} = \nabla P_{\mathrm{w}}(t) + \nabla\cdot\mathbf{\Sigma}$ in $\Omega_{\mathrm{w}}(t)$,

Ideal-gas law $P_{\mathrm{m}}^{(i)}(t) = \dfrac{N_i(t)\,k_{\mathrm{B}}T}{\mathrm{Vol}(\Omega_{\mathrm{m}}^{(i)}(t))}$ in $\Omega_{\mathrm{m}}^{(i)}(t)$ $(i = 1,\dots,m(t))$,

PBE $\nabla\cdot\varepsilon_{\Gamma(t)}\nabla\psi - \chi_{\mathrm{w}}(t)B'(\psi) = -\sum_{j=1}^{N} Q_j\delta_{\mathbf{x}_j}$ in Ω,

Force balance $2\mu_{\mathrm{w}}\mathbf{D}(\mathbf{u})\mathbf{n} - \delta_\Gamma G[\Gamma]\mathbf{n} = \mathbf{0}$ on $\Gamma(t)$.

$\mathbf{\Sigma}$: Landau–Lifshitz stochastic stress tensor

$$\langle\mathbf{\Sigma}_{ij}(\mathbf{x},t)\mathbf{\Sigma}_{k\ell}(\mathbf{x}',t')\rangle = 2\,\mu_{\mathrm{w}}k_{\mathrm{B}}T\delta(\mathbf{x}-\mathbf{x}')\delta(t-t')\left(\delta_{ik}\delta_{j\ell}+\delta_{i\ell}\delta_{jk}\right).$$

Stability of a Cylindrical Dielectric Boundary, Again

(Li, Sun, & Zhou, SIAP 2015)

$$\begin{aligned}
\omega(k) &= \frac{\omega_{\mathrm{surf}}(k) + \omega_{\mathrm{vdW}}(k) + \omega_{\mathrm{ele}}(k)}{\omega_{\mathrm{hyd}}} \\
&= -\frac{\gamma_0}{2\mu_{\mathrm{w}}} k + O(1) \quad \text{as } k \to \infty.
\end{aligned}$$

$$\omega_{\mathrm{surf}}(k) = \gamma_0 \left(\frac{1}{R_0^2} - k^2 \right),$$

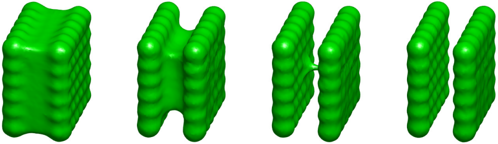
$$\omega_{\mathrm{vdW}}(k) = n_{\mathrm{w}} U'_{\mathrm{vdW}}(R_0),$$

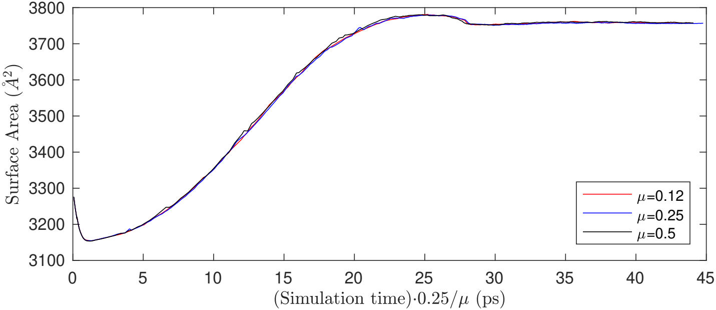
$$\omega_{\mathrm{ele}}(k) = \frac{(\varepsilon_{\mathrm{w}} - \varepsilon_{\mathrm{m}})^2}{\varepsilon_{\mathrm{w}}\varepsilon_{\mathrm{m}}(\varepsilon_{\mathrm{w}} + \varepsilon_{\mathrm{m}})} \left[\frac{1}{R_0} \int_0^{R_0} s\rho(s)\,\mathrm{d}s \right]^2 k + O(1),$$

$$\omega_{\mathrm{hyd}}(k) = 2\mu_{\mathrm{w}} k + O(1).$$

Numerical Simulations of a Two-Plate System

(Sun, Zhou, Cheng, & Li, J. Comput. Phys. 2018)

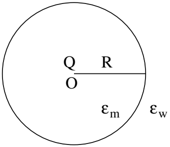




The area of the solute-solvent interface vs. the rescaled simulation time for three different values of solvent viscosity $\mu = \mu_{\mathrm{W}}$.

A Generalized Rayleigh–Plesset Equation for an Ion

(Fan, Li, & White, SIAP 2021)



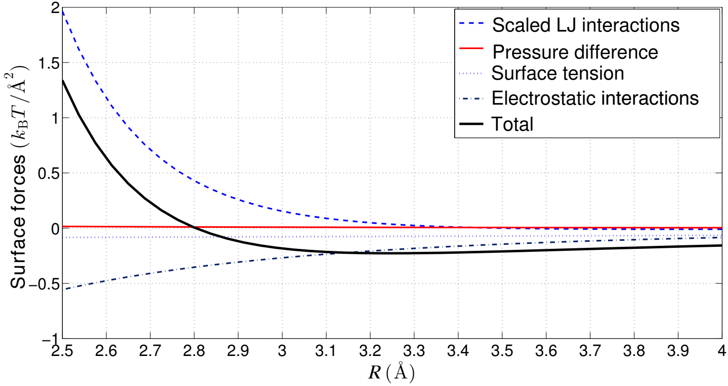
$$\frac{4\mu_w \dot{R}}{R} = F(R) + \xi \qquad (\xi : \text{ white noise })$$

$$\langle \xi(t)\xi(t') \rangle = \frac{4}{3}\mu_{\mathrm{w}} k_{\mathrm{B}} T \delta(t - t')$$

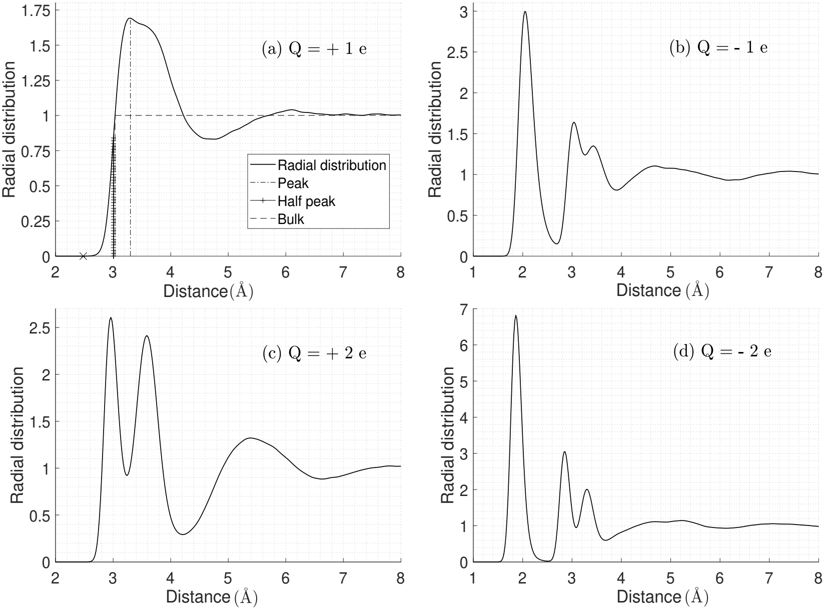
$$F(R) = P_{\mathrm{m}}(R) - P_\infty - 2\gamma_0 \left(\frac{1}{R} - \frac{\tau}{R^2} \right) + n_{\mathrm{w}} U_{\mathrm{LJ}}(R) + f_{\mathrm{ele}}(R)$$

$$P_{\mathrm{m}}(R) = \frac{3k_{\mathrm{B}}T}{4\pi R^3}$$

$$f_{\mathrm{ele}}(R) = \frac{Q^2}{32\pi^2} \left[\left(\frac{1}{\varepsilon_{\mathrm{w}}} - \frac{1}{\varepsilon_{\mathrm{m}}} \right) \frac{1}{R^4} - \frac{\kappa^2}{\varepsilon_{\mathrm{w}}(1 + \kappa R)^2 R^2} \right]$$



The total surface force density $F = F(R)$.



The radius of an ion (Fan, Li, & White, SIAP 2021)

Q (e)	Peak	Half-Peak	Bulk	First nonzero	RP
1	3.32	3.00	3.03	2.48	2.80
-1	2.04	1.90	1.86	1.56	2.80
2	2.96	2.83	2.81	2.32	2.46
-2	1.86	1.74	1.67	1.46	2.46

(Unit of length: Å.)

- With the same $|Q|$, the MD radius of a cation is larger than that of an anion But the RP radius remains the same. Charge asymmetry!
- The RP radius approximates well the averaged peak radius over those for the two ions with the same $|Q|$.
- For a cation, the RP radius is close to the average of the first nonzero and bulk radii.
- For an anion, an effective radius is the RP radius minus 0.5 Å.

Conclusions and Discussions

- The PB based DBF is crucial in qualitative descriptions of conformational dynamics of charged molecules.
- Dielectric boundary is sensitive in calculating the electrostatic energy and hence the DBF.
- Known problems of continuum electrostatics: charge asymmetry, ionic size effect, charge-charge correlations, etc.

Current Work

- Fast numerical method for minimizing the surface energy and electrostatic energy, using the Legendre transform.
- A sharp boundary is often too “rigid”, leading to high barriers in conformational changes. Relaxation?
- Including the solvent polarization.
- Coupling continuum and atomistic descriptions.

Thank You!