Biological Molecular Solvation with Stokes Flow and Poisson-Boltzmann Electrostatics

Bo Li

Department of Mathematics and qBio Ph.D. Program

UC San Diego

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Collaborators

Li-Tien Cheng – UCSD

Chao Fan – UCSD

Hui Sun – UCSD & Cal State Univ. Long Beach

Michael White – UCSD & U. Minnesota

Shenggao Zhou – UCSD & Shanghai Jiao Tong U. China

Joachim Dzubiella – Freiberg U. Germany

J. Andy McCammon - UCSD

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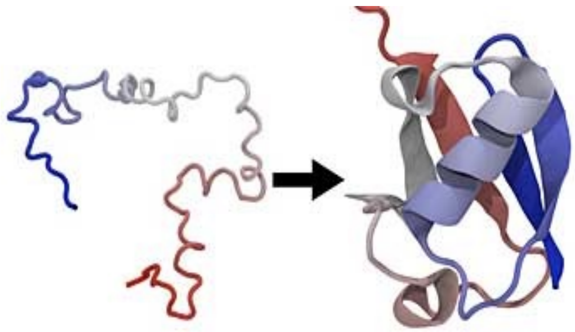
OUTLINE

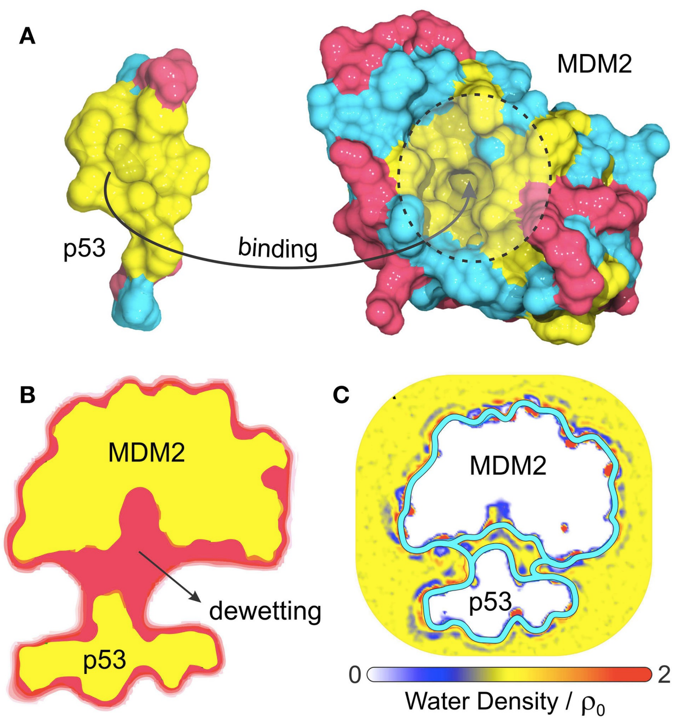
- **Biomolecular Solvation**
- **Variational Implicit-Solvent Model**
- **Dynamic Implicit-Solvent Model**
  - **Stability Analysis**
  - **Numerical Simulations**
- **A Generalized Rayleigh-Plesset Equation for Ions**
- **Conclusions**

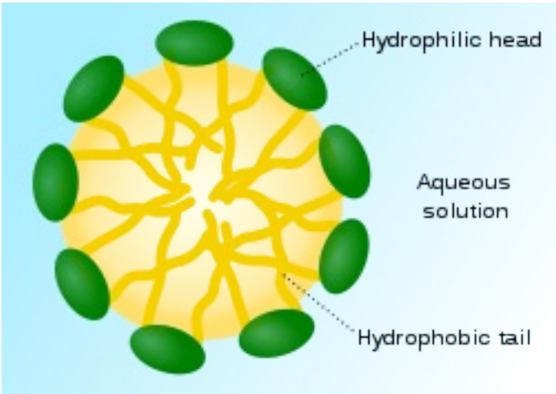
Biomolecular Solvation

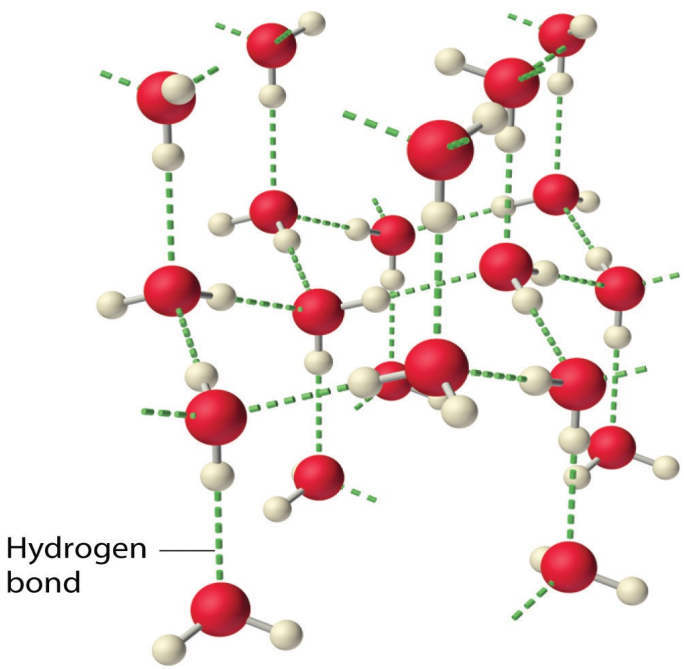
Biomolecular Processes

- Conformational changes
- Molecular recognition
- Molecular assembly



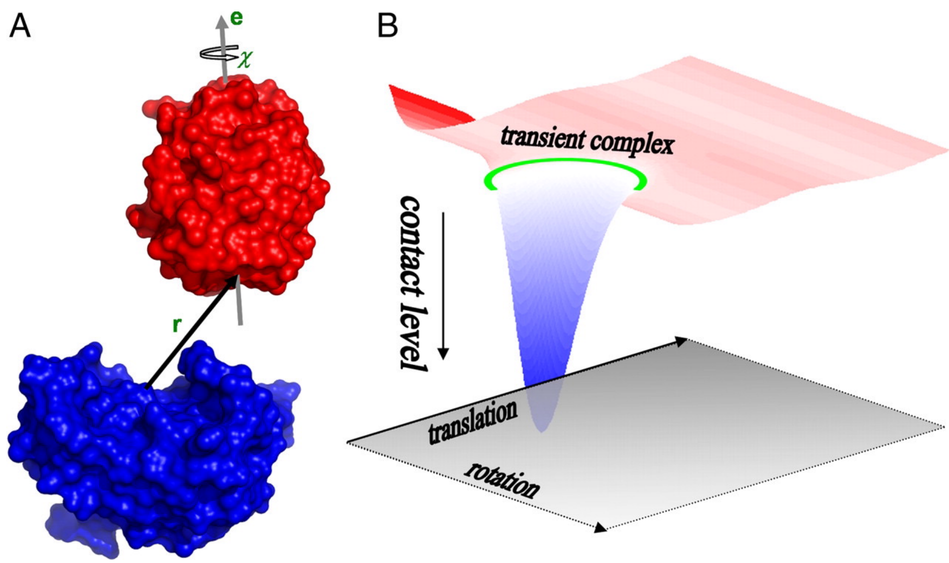






- **Electrostatic interactions**

  protein charges + ions + polarization of water



McCammon, PNAS 2009.

- **Hydrodynamic interactions**

  significant roles of solvent viscosity and shear flows in the protein dynamics.

Solute-solvent interface or dielectric boundary

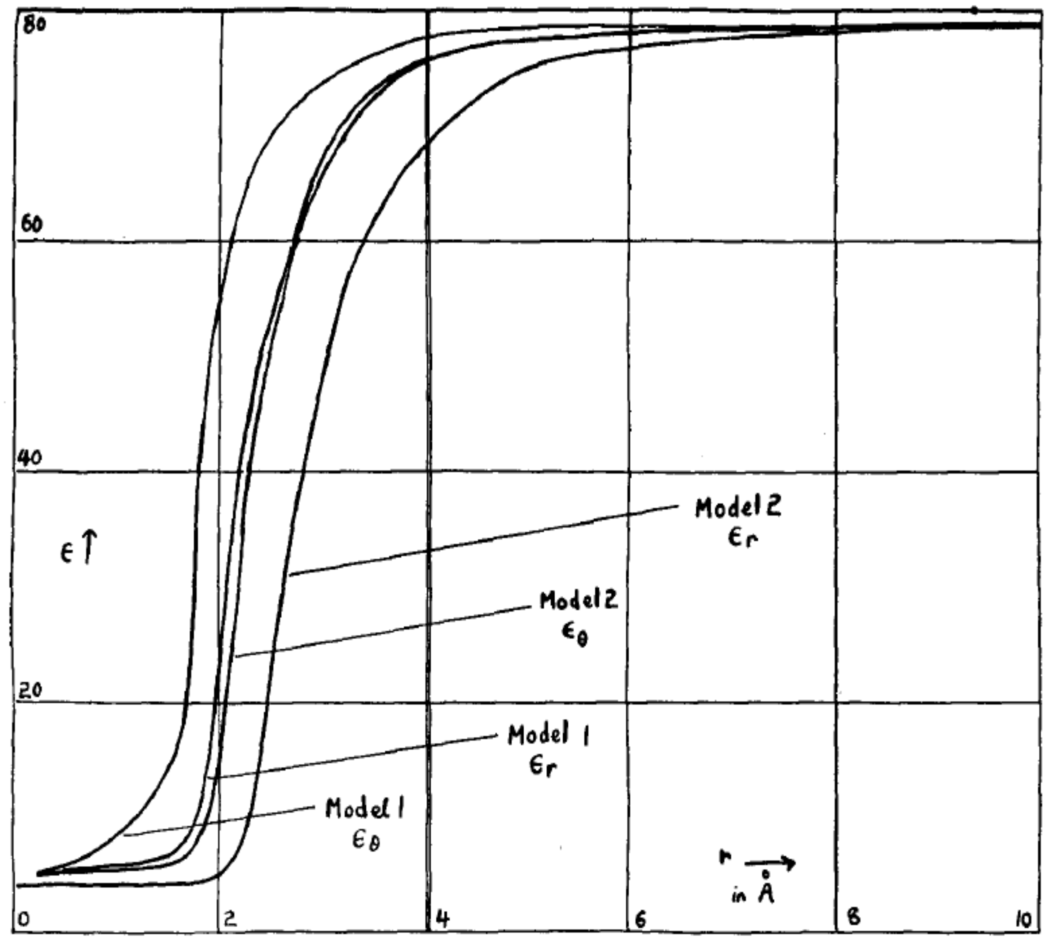
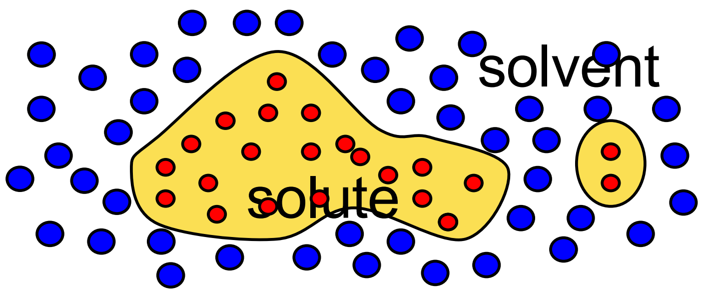
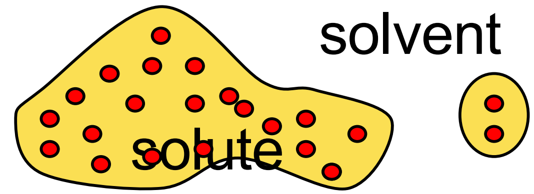


FIG. 1. Plot of dielectric constants ϵ_r, ϵ_θ against distance r in angstroms from an ion.

Hasted, Ritson, & Collie, JCP 1948.

Biomolecular Modeling: Explicit vs. Implicit



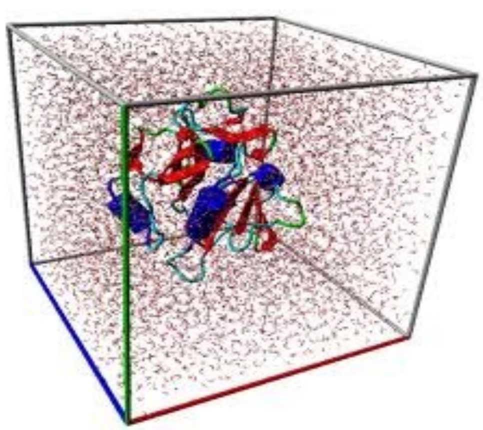


Molecular dynamics simulations

$$m_i \ddot{r}_i = -\nabla_{r_i} V(r_1, \ldots, r_N)$$

$$\langle A \rangle = \frac{1}{Z} \iint A(p,r) e^{-\beta H(p,r)} dp dr$$

$$= \langle A \rangle_{time} \text{ (ergodicity)}$$



Statistical mechanics

$$P(X,Y) = P_0 e^{-U(X,Y)/k_B T}$$

$$U(X,Y) = U_{uu}(X) + U_{vv}(Y) + U_{uv}(X,Y)$$

$$\overline{P}(X) = \int P(X,Y)\, dY = \overline{P}_0 e^{-W(X)/k_B T}$$

$W(X)$: **Potential of Mean Force**

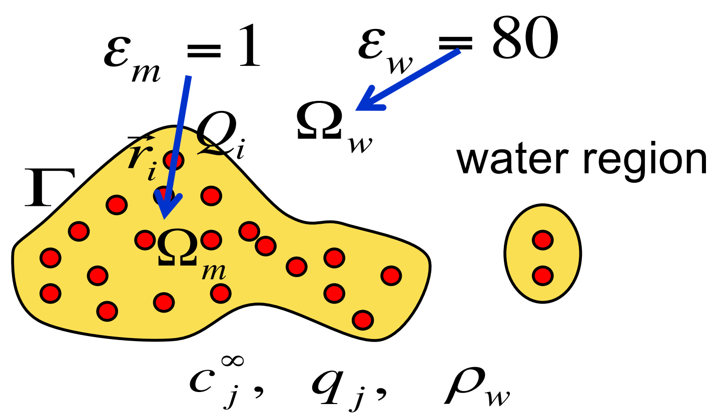
Roux & Simonson, Biophys. Chem. 1999.

Variational Implicit-Solvent Model (VISM)

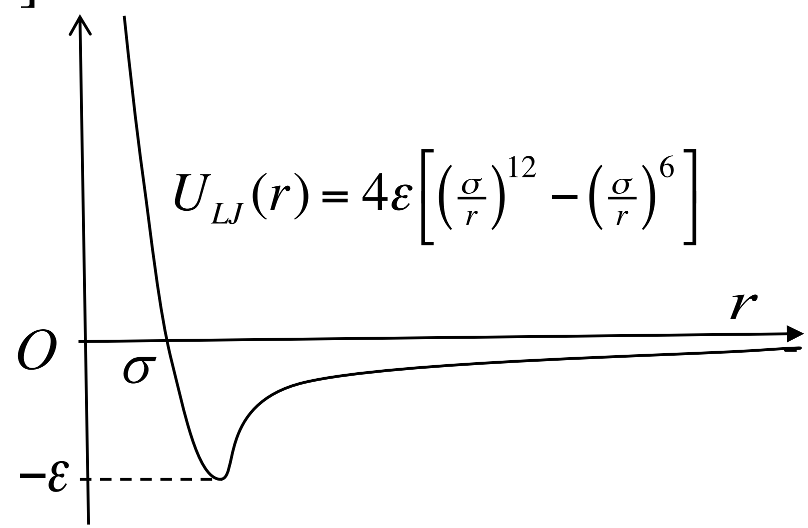
Dzubiella, Swanson, & McCammon, PRL and JCP, 2006.

Free energy of solute-solvent interface Γ

surface energy
\+ solute-solvent van der Waals interaction
\+ electrostatic energy



$$G[\Gamma] = P\,vol(\Omega_m) + \gamma_0 \int_\Gamma (1 - 2\tau H)\,dS$$
$$+\rho_w \int_{\Omega_w} \sum_i U_{LJ,i}(|\vec{r} - \vec{r}_i|)\,dV + G_{elec}[\Gamma]$$



Poisson-Boltzmann (PB) theory

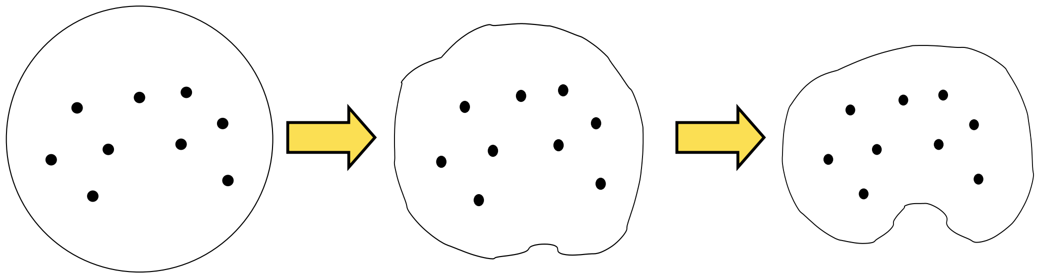
$$G_{elec}[\Gamma] = \int \left[-\frac{\varepsilon\varepsilon_0}{2} |\nabla\psi|^2 + \rho_f \psi - B(\psi) \right] dV$$

$$\nabla \cdot \varepsilon\varepsilon_0 \nabla\psi - B'(\psi) = -\rho_f \quad \text{(PBE)}$$

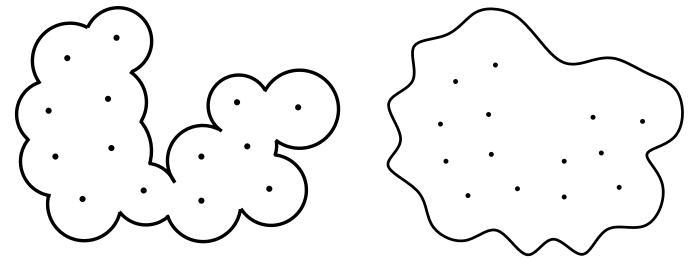
$$B(\psi) = \beta^{-1} \sum_{j=1}^{M} c_j^\infty \left(e^{-\beta q_j \psi} - 1 \right)$$

Level-set VISM simulations

JCP, JCTC, JCC, JPCB, PRL, PNAS, etc., 2007-2021



Relaxation



Tight initial Loose initial

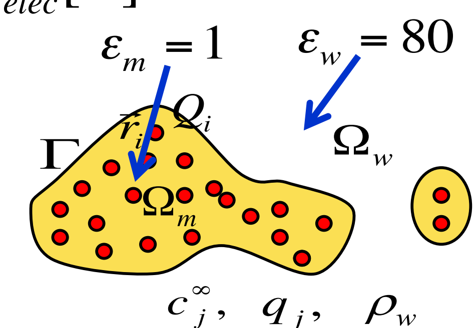
Normal velocity (i.e., boundary force)

Gaussian curvature

$$V_n = -\delta_\Gamma G[\Gamma](\vec{r}) = -P - 2\gamma_0[H(\vec{r}) - \tau K(\vec{r})] + \rho_w U(\vec{r}) - \delta_\Gamma G_{elec}[\Gamma]$$

$$G_{elec}[\Gamma] = \int \left[-\frac{\varepsilon\varepsilon_0}{2} |\nabla\psi|^2 + \rho_f \psi - B(\psi) \right] dV$$

$$\nabla \cdot \varepsilon\varepsilon_0 \nabla\psi - \chi_w \sum_{j=1}^{M} q_j c_j^\infty e^{-\beta q_j \psi} = -\rho_f$$

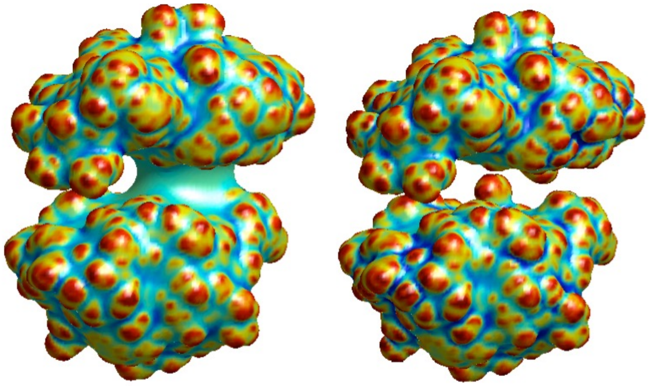


Γ_t ⟹ PBE: ψ_t ⟹ $G_{elec}[\Gamma_t]$ ⟹ $\delta_\Gamma G_{elec}[\Gamma] = \left(\frac{d}{dt}\right)_{t=0} G_{elec}[\Gamma_t]$

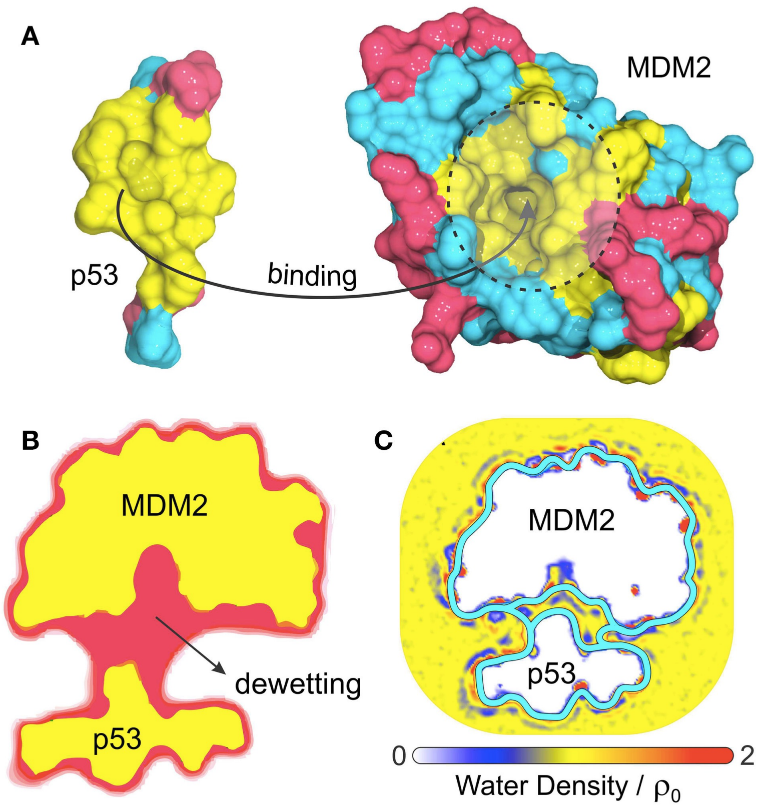
$$-\delta_\Gamma G_{elec}[\Gamma] = \frac{\varepsilon_0}{2}\left(\frac{1}{\varepsilon_w} - \frac{1}{\varepsilon_m}\right) |\varepsilon \partial_n \psi|^2 + \frac{\varepsilon_0}{2}(\varepsilon_m - \varepsilon_w)\left|(I - n \otimes n)\nabla\psi\right|^2 - B(\psi).$$

Li, Cheng, Zhang, SIAP 2011. Li, Zhang, Zhou, J. Nonlinear Sci. 2021.

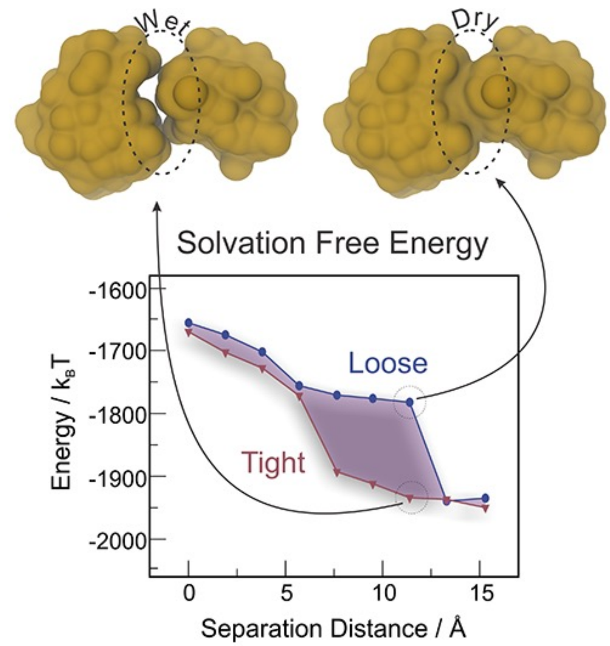
BphC



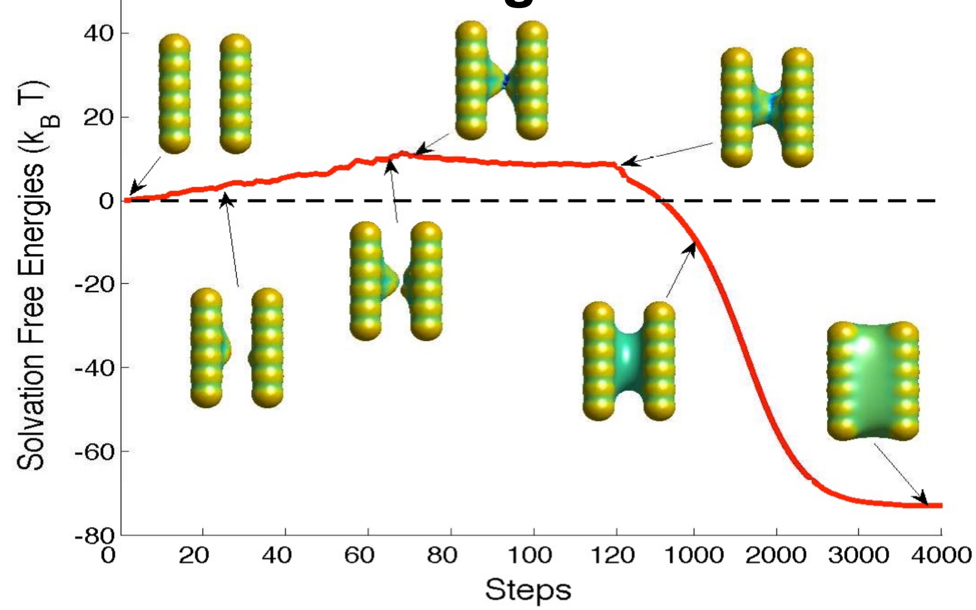
p53/MDM2



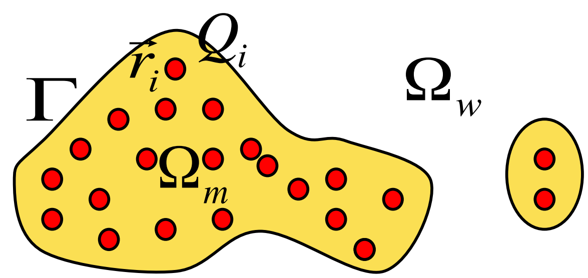
Barstar-barnase



Stochastic level-set VISM for dewetting transition



Dynamic Implicit-Solvent Model



Interface motion

$$V_n = u \cdot n$$

Fluctuating Stokes solvent fluid flow

$$\mu_w \nabla^2 u - \nabla p_w - n_w \nabla U_{ext} + \nabla \cdot \Sigma = 0 \qquad \text{in } \Omega_w(t)$$

$$\nabla \cdot u = 0 \qquad \text{in } \Omega_w(t)$$

$$p_{m,i}(t)\left|\Omega_{m,i}(t)\right| = N_i k_B T$$

$$\left\langle \Sigma_{ij}(x,t)\Sigma_{kl}(x',t')\right\rangle = 2\mu_w k_B T \delta(x-x')\delta(t-t')(\delta_{ik}\delta_{jl} + \delta_{il}\delta_{jk})$$

Electrostatics

$$\nabla \cdot \varepsilon\varepsilon_0 \nabla \psi - \chi_w B'(\psi) = -\rho_f \qquad \delta_\Gamma G[\Gamma]$$

Force balance

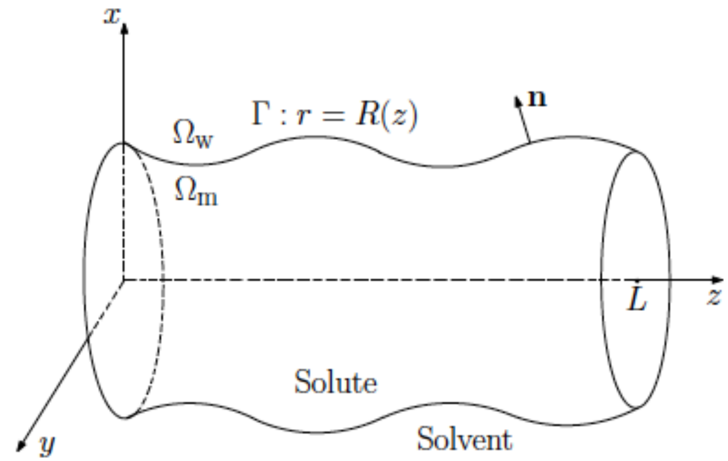
$$2\mu_w D(u)n + \delta_\Gamma G[\Gamma]n = 0 \qquad \text{at } \Gamma(t)$$

Parameter	Symbol	Value	Unit
temperature	T	298	K
solvent dynamic viscosity	μ_{w}	0.2	$\mathrm{k_B T \cdot ps/\AA^3}$
solvent number density	n_{w}	0.0333	$\mathrm{\AA^{-3}}$
solvent mass density	ρ_{w}	2.42×10^{-3}	$\mathrm{k_B T \cdot ps^2/\AA^5}$
bulk solvent pressure	P_{∞}	2.46×10^{-5}	$\mathrm{k_B T/\AA^3}$
surface tension	γ_0	0.175	$\mathrm{k_B T/\AA^2}$
Tolman length	τ	1	Å
LJ length parameter	σ	3.5	Å
LJ energy parameter	ε	0.3	$\mathrm{k_B T}$
vacuum permittivity	ε_0	1.4372×10^{-4}	$\mathrm{e^2/(k_B T \cdot \AA)}$
solute dielectric constant	ε_{p}	1	
solvent dielectric constant	ε_{w}	78	
inverse Debye length	κ	0.025	$\mathrm{\AA^{-1}}$
point charge	Q	1	e

Stability Analysis

A cylindrical solute-solvent interface

Li, Sun, and Zhou, SIAP 2015



$$\partial_t R(z,t) = u(R(z,t),z,t) - w(R(z,t),z,t)\partial_z R(z,t) \quad \forall z \in \mathbb{R},$$

$R(z,t)$ is L-periodic in z.

$$\mu_{\mathrm{w}} \left(\partial^2_{rr} u + \frac{1}{r}\partial_r u - \frac{1}{r^2} u + \partial^2_{zz} u \right) - \partial_r p_{\mathrm{w}} = 0 \quad \text{if } r > R(z,t),$$

$$\mu_{\mathrm{w}} \left(\partial^2_{rr} w + \frac{1}{r}\partial_r w + \partial^2_{zz} w \right) - \partial_z p_{\mathrm{w}} = 0 \quad \text{if } r > R(z,t),$$

$$\partial_r u + \frac{1}{r} u + \partial_z w = 0 \quad \text{if } r > R(z,t),$$

$u(r,z,t)$, $w(r,z,t)$, and $p_{\mathrm{w}}(r,z,t)$ are L-periodic in z,

$$u(\infty,z,t) = w(\infty,z,t) = 0 \;\text{ and }\; p_{\mathrm{w}}(\infty,z,t) = p_\infty \quad \forall z \in \mathbb{R}.$$

$$\varepsilon_{\mathrm{m}}\left(\partial^2_{rr}\phi + \frac{1}{r}\partial_r\phi + \partial^2_{zz}\phi\right) = -\rho \qquad \text{in } \Omega_{\mathrm{m}}(t),$$

$$\varepsilon_{\mathrm{w}}\left(\partial^2_{rr}\phi + \frac{1}{r}\partial_r\phi + \partial^2_{zz}\phi\right) = -\rho \qquad \text{in } \Omega_{\mathrm{w}}(t),$$

$$\phi(R(z,t)^-, z, t) = \phi(R(z,t)^+, z, t) \qquad \forall z \in \mathbb{R},$$

$$\varepsilon_{\mathrm{m}}\left[\partial_r\phi(R(z,t)^-, z, t) - \partial_z R(z,t)\partial_z\phi(R(z,t)^-, z, t)\right]$$
$$= \varepsilon_{\mathrm{w}}\left[\partial_r\phi(R(z,t)^+, z, t) - \partial_z R(z,t)\partial_z\phi(R(z,t)^+, z, t)\right] \qquad \forall z \in \mathbb{R},$$

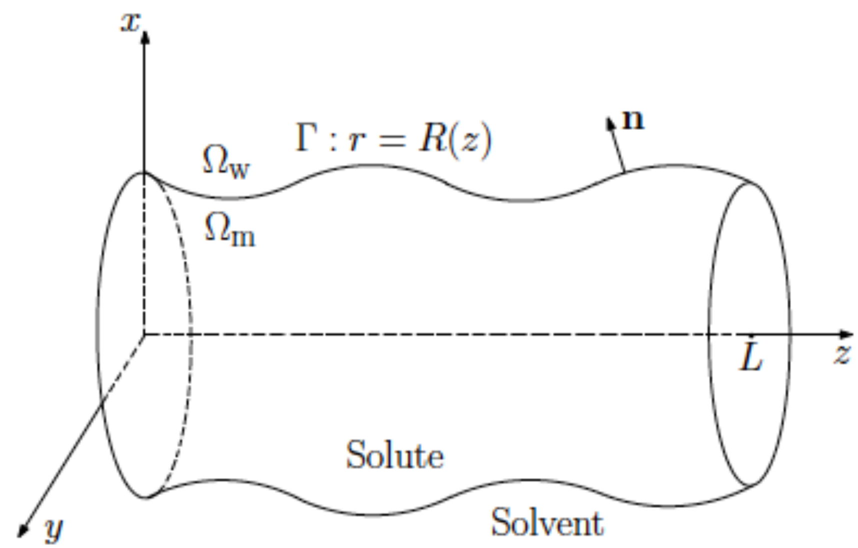
$$\phi = \phi(r,z,t) \text{ is } L\text{-periodic in } z,$$

$$\phi(\infty, z, t) = 0 \qquad \forall z \in \mathbb{R},$$

$$\frac{2\mu_{\mathrm{w}}}{1+(\partial_z R)^2}\left[\partial_r u - \partial_z R(\partial_z u + \partial_r w) + (\partial_z R)^2\partial_z w\right]$$
$$+ \frac{C_{\mathrm{m}}}{\pi}\left[\int_0^L R(s,t)^2\, ds\right]^{-1} - p_{\mathrm{w}}$$
$$- \gamma_0\left\{\frac{1}{R\left[1+(\partial_z R)^2\right]^{1/2}} - \frac{\partial^2_{zz}R}{\left[1+(\partial_z R)^2\right]^{3/2}}\right\} + n_{\mathrm{w}}U_{\mathrm{vdW}}(R)$$
$$+ \frac{1}{2}\left(\frac{1}{\varepsilon_{\mathrm{w}}} - \frac{1}{\varepsilon_{\mathrm{m}}}\right)\frac{\left[\varepsilon_{\Gamma(t)}\left(\partial_r\phi - \partial_z R\partial_z\phi\right)\right]^2}{1+(\partial_z R)^2}$$
$$+ \frac{1}{2}\left(\varepsilon_{\mathrm{m}} - \varepsilon_{\mathrm{w}}\right)\frac{\left(\partial_z R\partial_r\phi + \partial_z\phi\right)^2}{1+(\partial_r R)^2} = 0 \qquad \forall z \in \mathbb{R},$$

$$\partial_z R\left(\partial_r u - \partial_z w\right) + \frac{1}{2}\left[1-(\partial_z R)^2\right]\left(\partial_z u + \partial_r w\right) = 0 \quad \forall z \in \mathbb{R}.$$

Dispersion relations



$$\omega_{\mathrm{air}}(k) = -\frac{2C_m}{\pi L R_0^3}\chi_{\{k=0\}}(k),$$

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

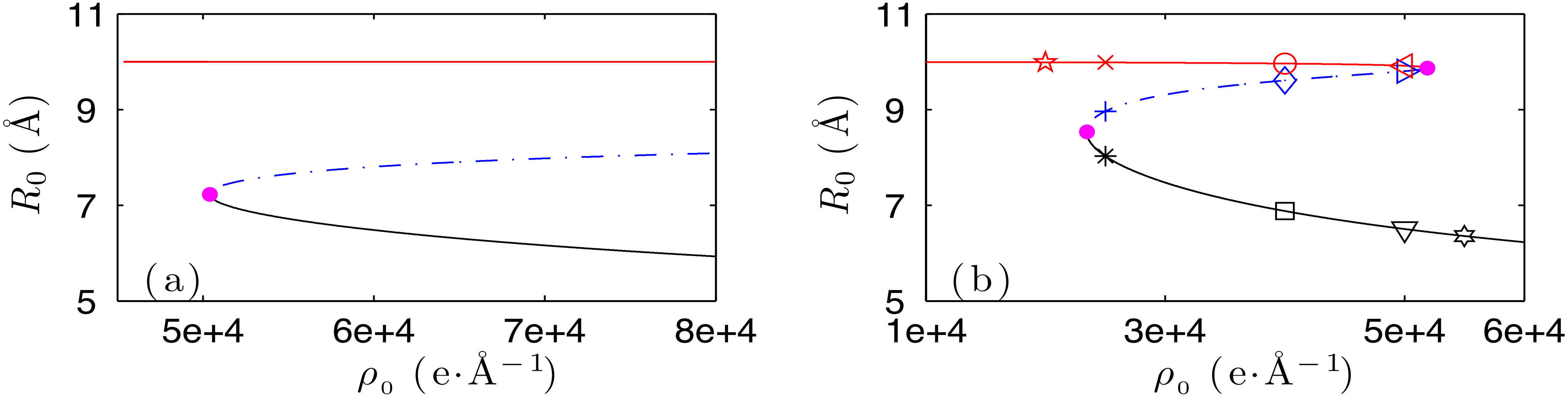
$$\omega_{\mathrm{vdW}}(k) = n_\mathrm{w} U'_{\mathrm{vdW}}(R_0),$$

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

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

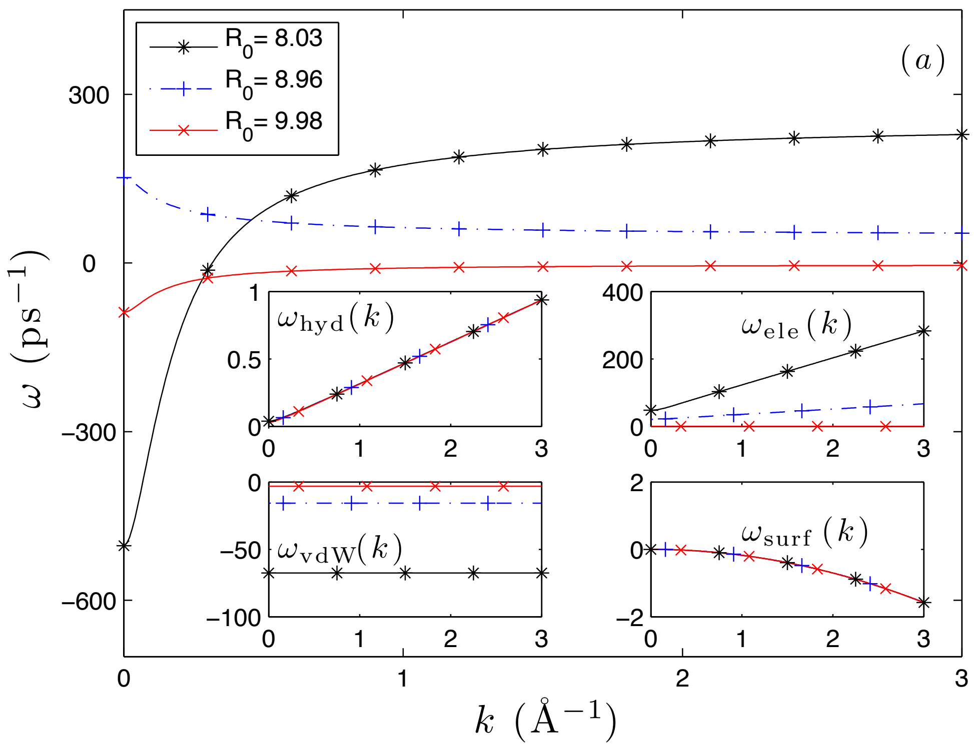
$$\omega(k) = \frac{\omega_{\mathrm{air}}(k) + \omega_{\mathrm{surf}}(k) + \omega_{\mathrm{vdW}}(k) + \omega_{\mathrm{ele}}(k)}{\omega_{\mathrm{hyd}}} = -\frac{\gamma_0}{2\mu_\mathrm{w}}k + O(1)$$

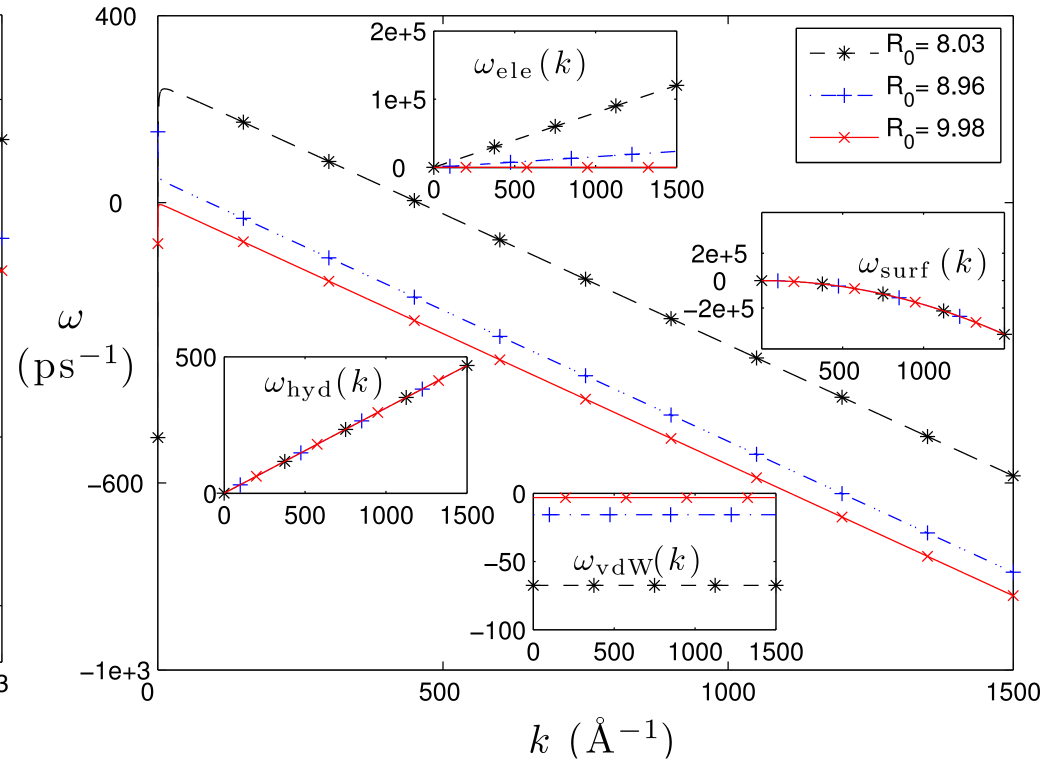
$$\rho(r) = \rho_0 \frac{R_c^4(2r - R_c)}{8r^4(r - R_c)^3} \exp\left(-\frac{R_c^4}{16r^2(r - R_c)^2}\right) \chi_{\{0\le r\le R_c\}}(r)$$



Multiple steady state solutions and their stabilities.

$$\rho(r) = \rho_0 \frac{R_c^4(2r - R_c)}{8r^4(r - R_c)^3} \exp\left(-\frac{R_c^4}{16r^2(r - R_c)^2}\right) \chi_{\{0\le r\le R_c\}}(r)$$





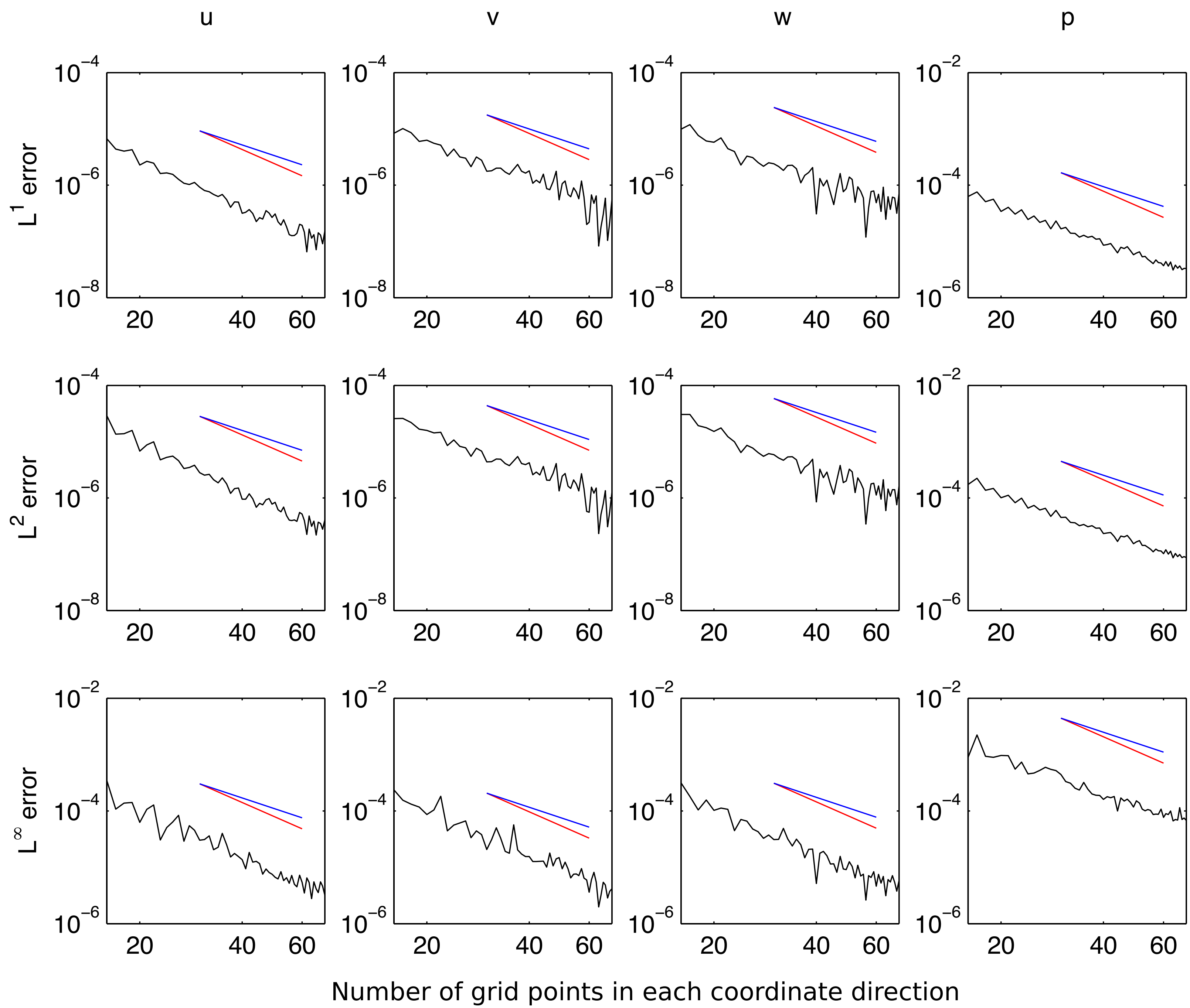
Numerical simulations

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

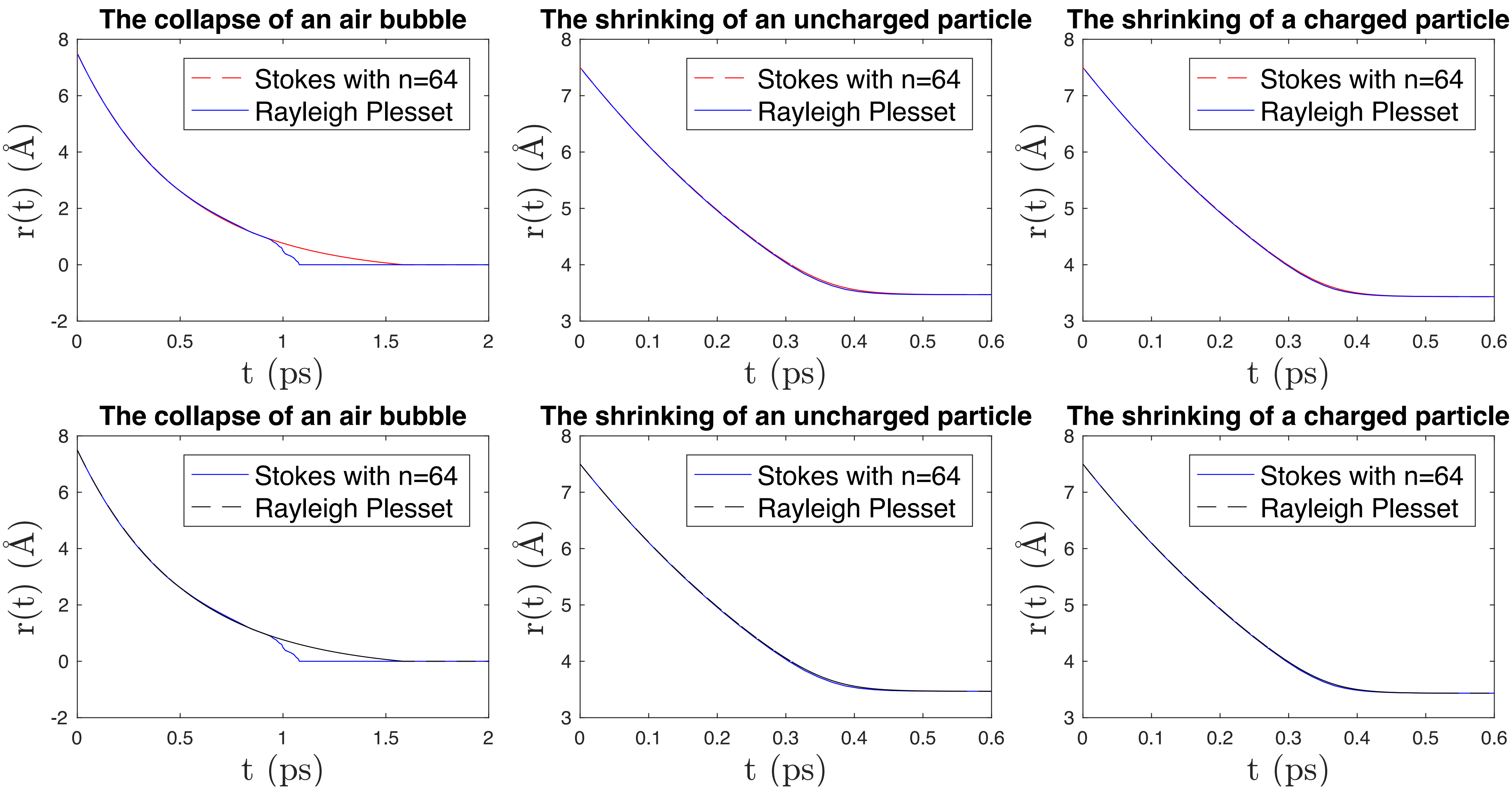
- Level-set method for the moving dielectric boundary
- Numerical boundary conditions to allow the change of solute volume

$$(I - \mathbf{n} \otimes \mathbf{n})\mathbf{u} = \mathbf{u}_0 \qquad \text{and} \qquad p_{\mathrm{w}} = p_{\mathrm{w}0} \qquad \text{on } \partial\Omega$$

- Reformulation: Poisson equation for pressure
- MAC scheme for discretization
- Schur complement and the least-squares method
- GMRES, algebraic multigrid method, and additive Schwarz method for solving the linear system



Slope: -2 for blue lines and -2.5 for red lines


The collapse of an air bubble
The shrinking of an uncharged particle
The shrinking of a charged particle
Stokes with n=64
Rayleigh Plesset
r(t) (Å)
t (ps)
The collapse of an air bubble
The shrinking of an uncharged particle
The shrinking of a charged particle
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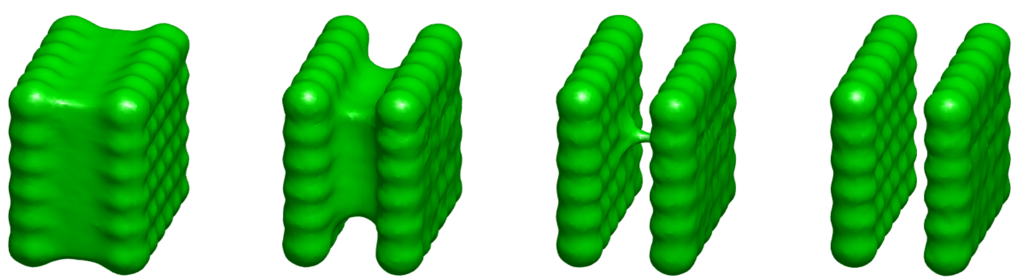
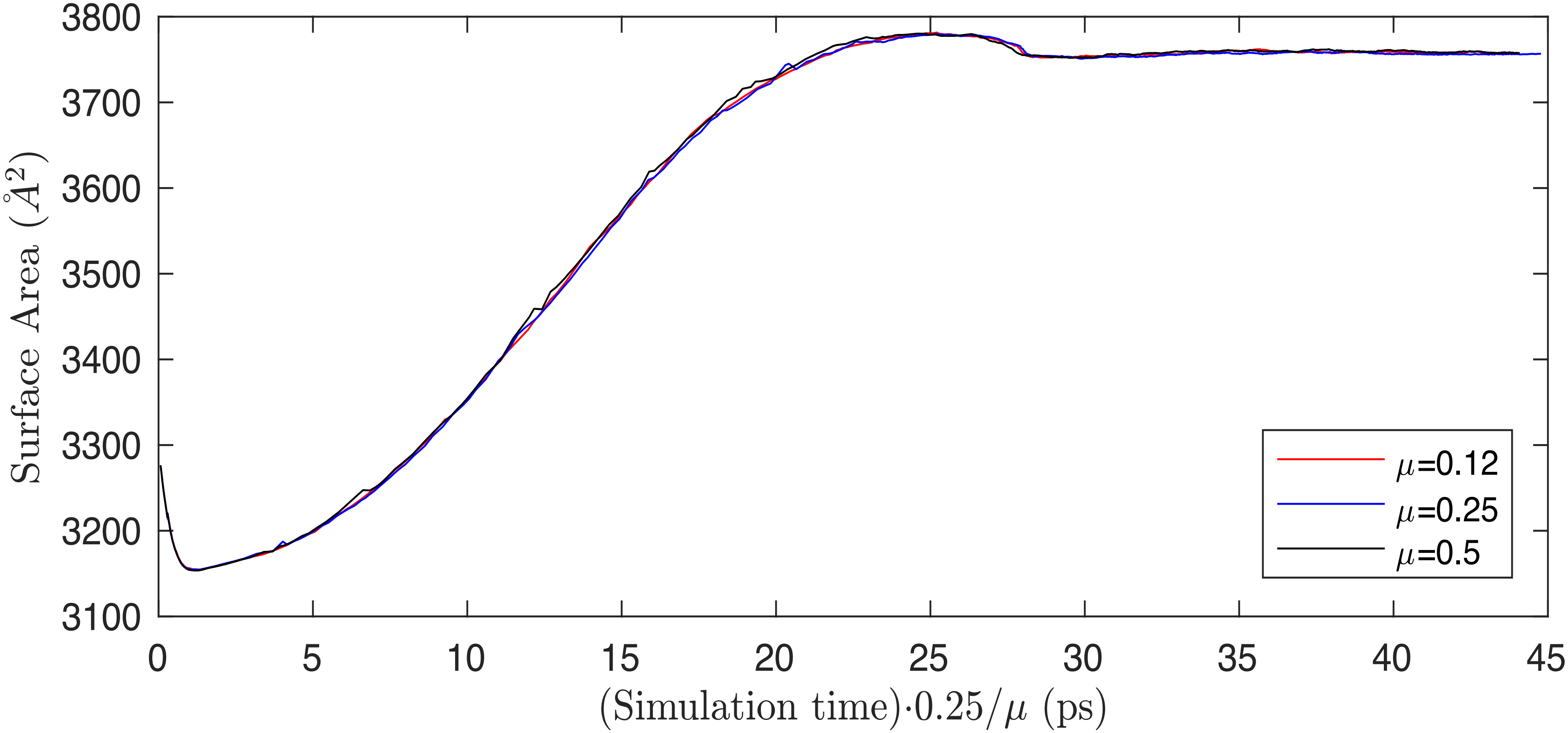
r(t) (Å)
t (ps)



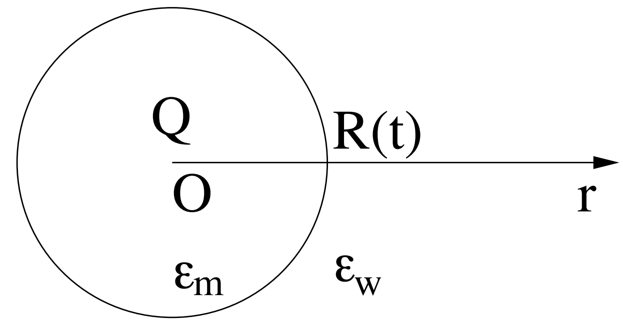
A scaling law: $\text{Area}(\Gamma(t)) = f(t/\mu)$



A Generalized Rayleigh-Plesset equation for Ions

$$\frac{4\mu_{\mathrm{w}}\dot{R}}{R} = F(R) + \xi$$

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

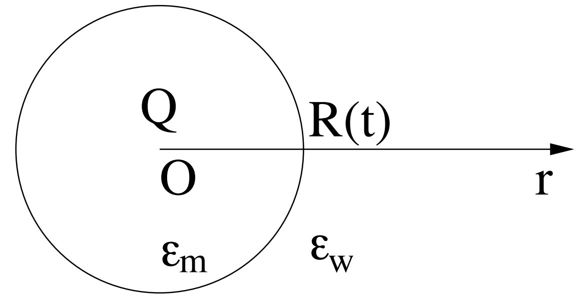


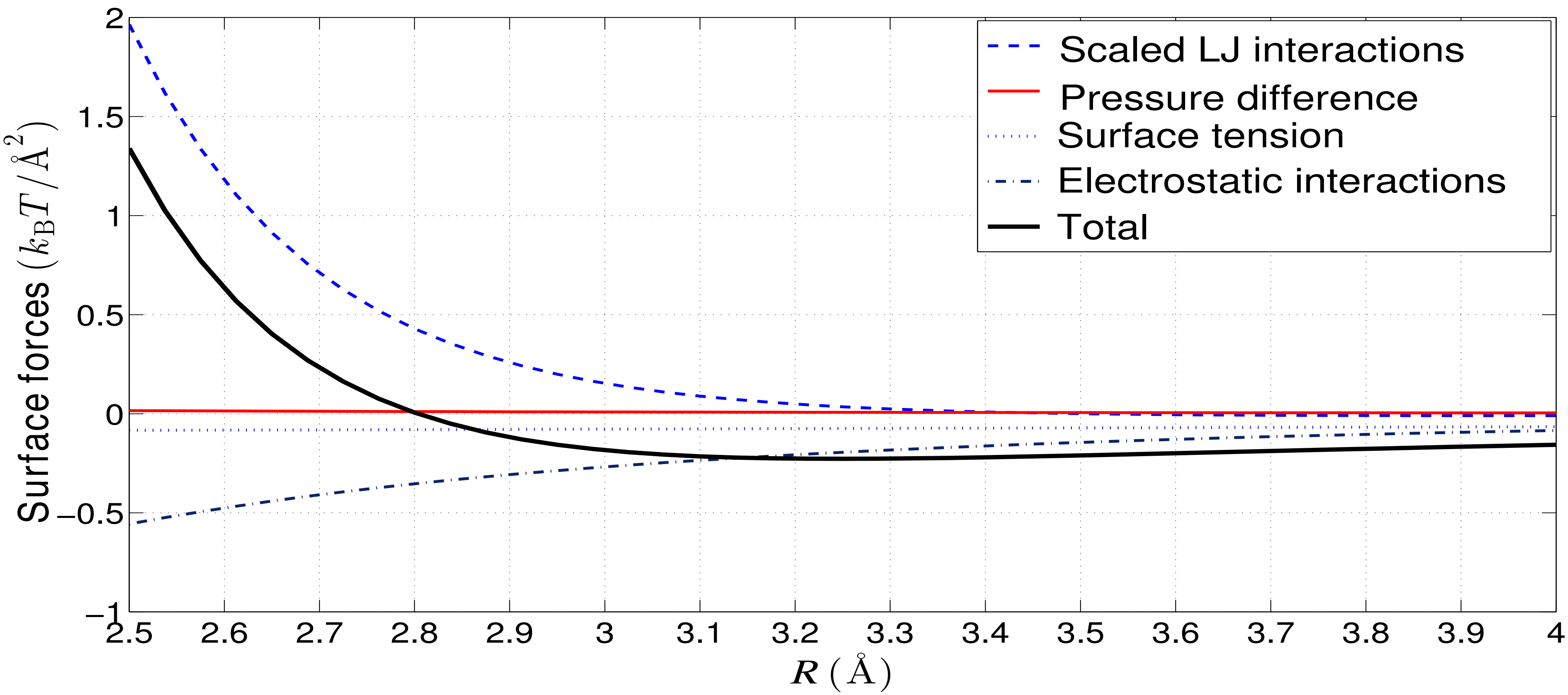
$$F(R) = P_{\mathrm{p}}(R) - P_{\infty} - 2\gamma_0 \left(\frac{1}{R} - \frac{\tau}{R^2}\right) + n_{\mathrm{w}}\left[U_{\mathrm{LJ}}(R) + U_{\mathrm{ext}}(R)\right] + f_{\mathrm{elec}}(R)$$

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

$$f_{\mathrm{elec}}(R) = \frac{Q^2}{32\pi^2\varepsilon_0}\left[\left(\frac{1}{\varepsilon_{\mathrm{w}}} - \frac{1}{\varepsilon_{\mathrm{p}}}\right)\frac{1}{R^4} - \frac{\kappa^2}{\varepsilon_{\mathrm{w}}(1+\kappa R)^2 R^2}\right]$$

Surface force
total and individual components





Simulation with the Euler-Maruyama method

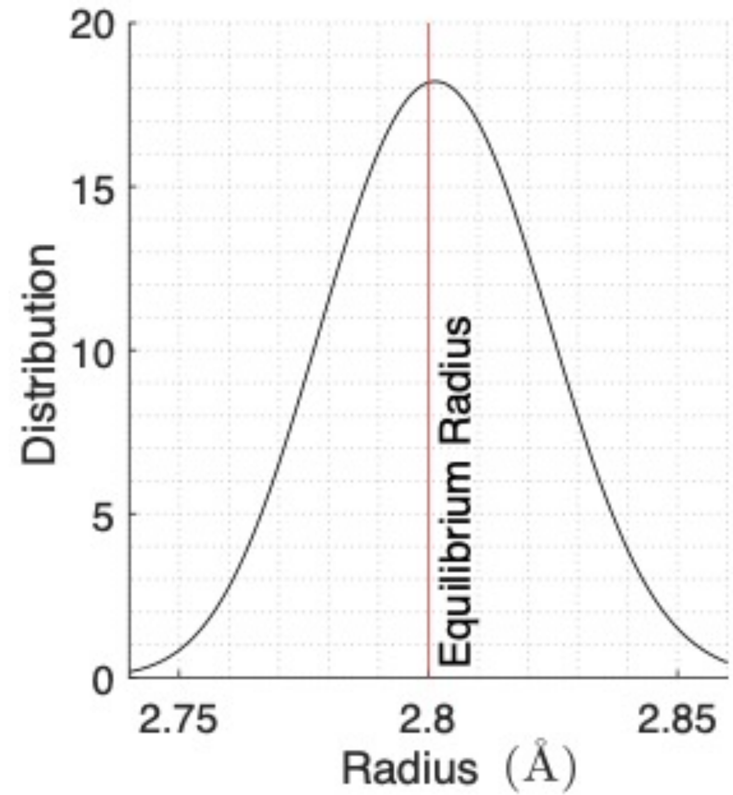
$$dR_t = a(R_t)\,dt + b(R_t)\,dw_t$$

$$a(R_t) = \frac{RF(R)}{4\mu_{\mathrm{w}}}$$

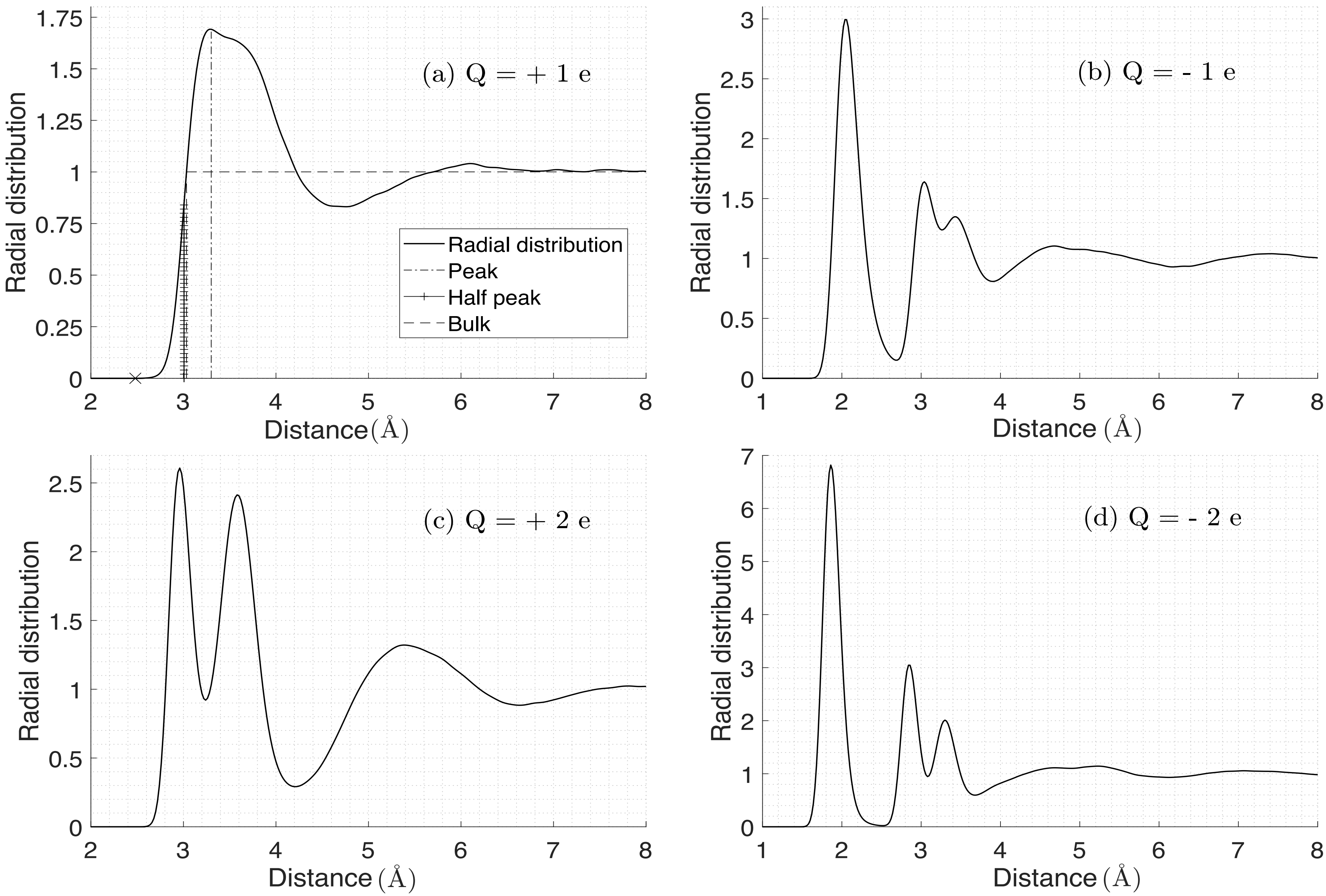
$$b(R_t) = \sqrt{\frac{k_{\mathrm{B}}T}{12\mu_{\mathrm{w}}}}\,R.$$

$$R^{(n+1)} = R^n + a(R^n)\Delta t + b(R^n)\Delta w^n$$

Δw^n: iid Gaussian $\mathcal{N}(0, \Delta t)$



Molecular dynamics simulations with GROMACS



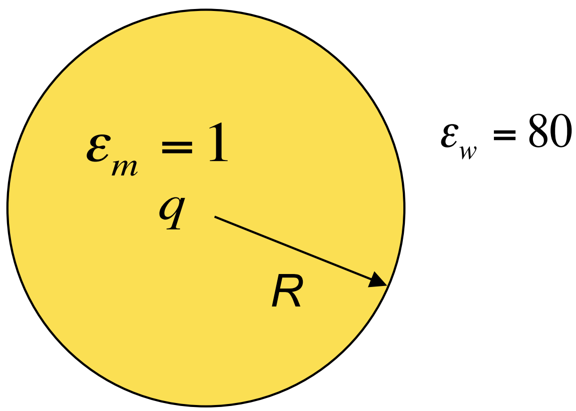
Generalized RPE vs. MD simulations

Ion	Q (e)	First nonzero (Å)	Peak (Å)	Half-Peak (Å)	Bulk (Å)	RP (Å)
1	1	2.48	3.32	3.00	3.03	2.80
2	−1	1.56	2.04	1.90	1.86	2.80
3	2	2.32	2.96	2.83	2.81	2.46
4	−2	1.46	1.86	1.74	1.67	2.46

Cation: RPE value is close to the average of first nonzero and peak values
Anion: RPE value – 0.5 A is a good approximation

Born's model (1920)

$$\Delta G = -\frac{q^2}{8\pi\varepsilon_0 R}\left(\frac{1}{\varepsilon_m} - \frac{1}{\varepsilon_w}\right)$$



Charge asymmetry!

Conclusions

Dynamic implicit-solvent model

- Dielectric boundary and fluctuating Stokes flow
- Linear stability analysis. Key parameter: surface tension / viscosity
- Numerical simulations: level-set, numerical boundary conditions, etc. Predict: area = f (time / viscosity)
- A generalized Rayleigh-Plesset equation for ionic radius: derivation and simulation. Good agreement MD simulations.

No tracking of individual water molecules!

Further studies

- Solute atomic mechanical interactions coupled with implicit solvent.
- Extension: stochastic dynamics for many collective variables.
- Hybrid and multiscale modeling and simulations.
- One of the bottlenecks: force calculations. New theory and simulations techniques?

Thank You!