Dielectric Boundary in Biomolecular Solvation

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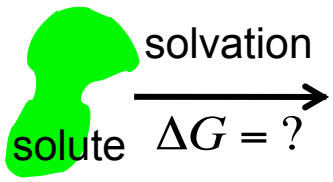
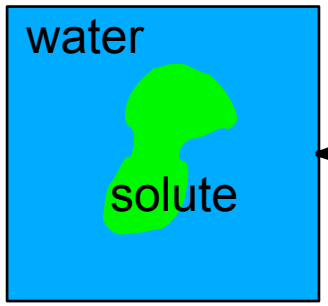
Solvation

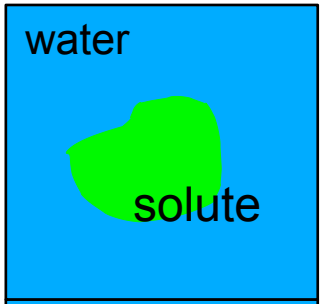


solvation

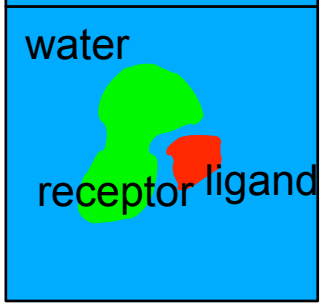
$\Delta G = ?$

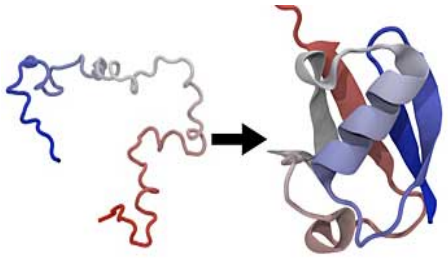


conformational change



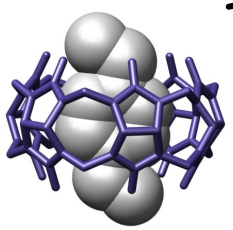
binding



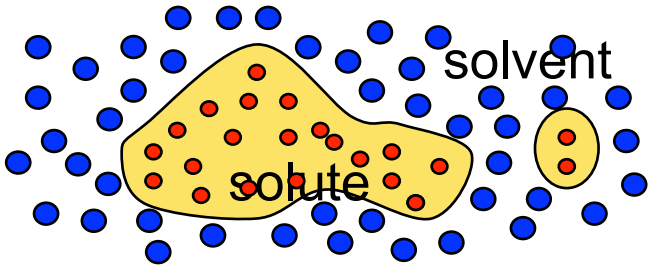


protein folding

molecular recognition



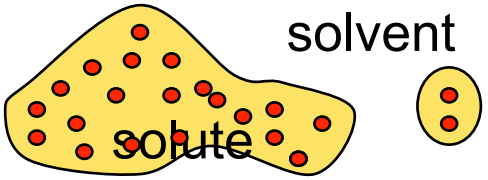
Biomolecular Modeling: Explicit vs. Implicit



MD simulations

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

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



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**

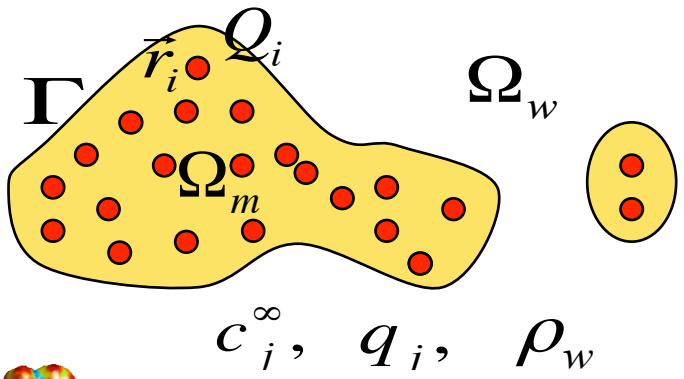
Variational Implicit-Solvent Model (VISM)

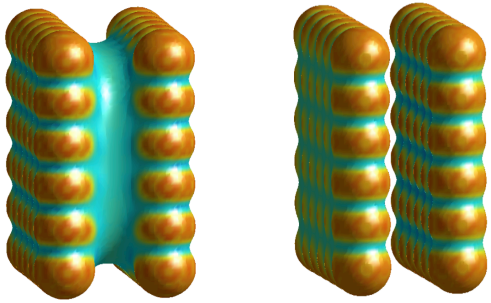
Dzubiella, Swanson, & McCammon: PRL, 2006; JCP, 2006.

Free-energy functional

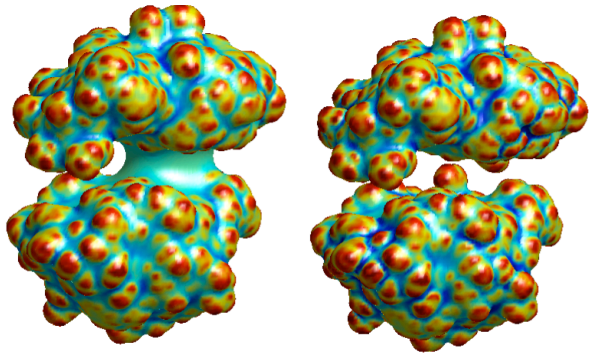
$$G[\Gamma] = Pvol(\Omega_m) + \gamma_0 \int_\Gamma (1 - 2\tau H) dS$$

$$+\rho_w \int_{\Omega_w} \sum_i U_{LJ,i}(|\vec{r} - \vec{r}_i|) dV + G_{elec}[\Gamma]$$

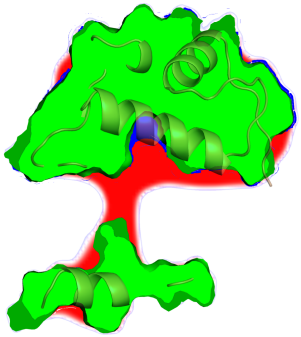




Two paraffin plates



BphC



p53/MDM2

This talk focuses on:

1. **The Poisson-Boltzmann (PB) Theory and Dielectric Boundary Force;**
2. **Stability of a Cylindrical Solute-Solvent Interface.**

Main Collaborators

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Piotr Setny (Munich & Warsaw)
Jianwei Che (GNF)
Zuojun Guo (GNF)
Yang Xie (Georgia Tech)

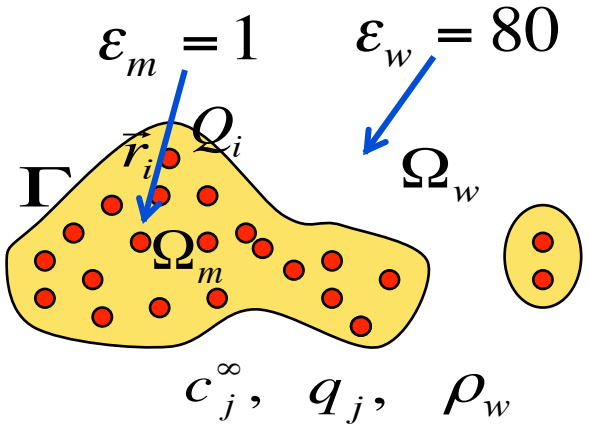
Funding: NIH, NSF, and CTBP

The Poisson-Boltzmann (PB) Theory

$$\nabla \cdot \varepsilon\varepsilon_0 \nabla\psi - B'(\psi) = -\rho_f$$

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

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



Poisson equation $\nabla \cdot \varepsilon\varepsilon_0 \nabla\psi = -\rho$

Charge density $\rho = \rho_f + \rho_i = \sum_{i=1}^{N} Q_i \delta_{r_i} + \sum_{i=1}^{M} q_j c_j$

Boltzmann distributions $c_j = c_j^{\infty} e^{-\beta q_j \psi}$

- Linearized PBE: $\nabla \cdot \varepsilon\varepsilon_0 \nabla\psi - \kappa^2\psi = -\rho_f$
- Sinh PBE $\nabla \cdot \varepsilon\varepsilon_0 \nabla\psi - 2c^{\infty} \sinh(\beta\psi) = -\rho_f$

Theorem. $G_{elec}[\Gamma, \bullet]$ has a unique maximizer, uniformly bouded in H^1 and L^{∞}. It is the unique solution to the PBE.

Proof. Direct methods in the calculus of variations.

- Uniform bounds by comparison.
- Regularity theory and routine calculations. **Q.E.D.**

Li,, SIMA, 2009 & 2011; Nonlinearity, 2009; Li, Cheng, & Zhang, SIAP, 2011.

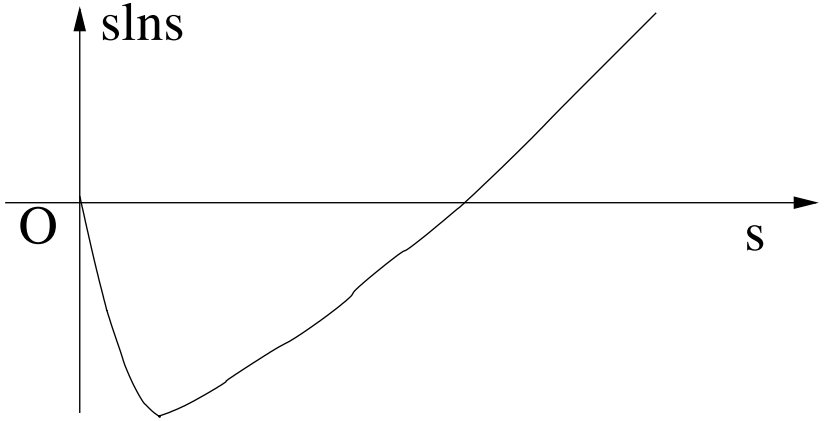
Electrostatic Free-energy functional

$$F[c] = \int \left[\frac{1}{2}\rho\psi + \beta^{-1} \sum_{i=1}^{M} c_i \ln(\Lambda^3 c_i) - \sum_{i=1}^{M} \mu_i c_i \right] dV$$

$$\rho = \rho_f + \sum_i^M q_i c_i$$

$$\nabla \cdot \varepsilon\varepsilon_0 \nabla\psi = -\rho$$

$$\delta_i F[c] = 0 \quad \Rightarrow \quad c_j = c_j^{\infty} e^{-\beta q_j \psi}$$

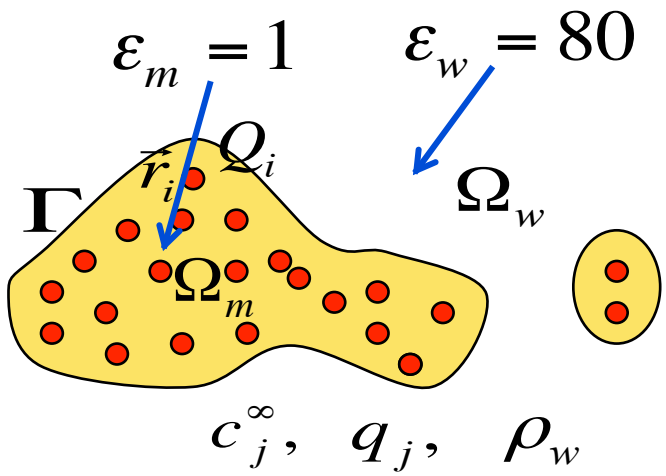


Theorem (B.L. SIMA 2009)

- $F[c]$ has a unique minimizer $c = (c_1, \ldots, c_M)$ satisfying the Boltzmann distributions.
- There exist $\theta_1, \theta_2 > 0$ such that $\theta_1 \le c_j \le \theta_2$ for all $j = 1, \ldots, M$.
- The corresponding ψ is the unique solution to PBE.

Dielectric boundary force (DBF) : $F_n = -\delta_\Gamma G_{elec}[\Gamma]$

A shape derivative approach



Perturbation defined by $V : R^3 \to R^3$:

$$\begin{cases} \dot{x} = V(x) \\ x(0) = X \end{cases} \Rightarrow \quad x = x(X,t) = T_t(X)$$

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

Structure Theorem There exists $w : \Gamma \to \mathbb{R}$ such that

$$\delta_{\Gamma,V} G_{ele}[\Gamma] = \int_\Gamma w(X)[V(X) \cdot n(X)]\, dS_X \quad \forall V \in C_c^\infty(\mathbb{R}^3, \mathbb{R}^3).$$

Shape derivative $\delta_\Gamma G_{elel}[\Gamma](X) = w(X) \qquad \forall X \in \Gamma$

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

$$\nabla \cdot \varepsilon\varepsilon_0 \nabla\psi - \chi_w B'(\psi) = -\rho_f$$

Theorem. Let n point from Ω_m to Ω_w. Then

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

Li, Cheng, & Zhang, SIAP, 2011. Luo *et al.,* PCCP 2012 & JCP 2013.

Consequence: Since $\varepsilon_w > \varepsilon_m$, the force $-\delta_\Gamma G_{elec}[\Gamma] > 0.$

Chu, Molecular Forces, based on Debye's lectures, Wiley, 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."

Proof of Theorem. Let $V \in C_c^\infty(\mathbb{R}^3, \mathbb{R}^3)$ be local, $\Gamma_0 = \Gamma$, and

$$G[\Gamma_t] = G[\Gamma_t, \psi_t] = \max_{\phi \in H_g^1(\Omega)} G[\Gamma_t, \phi].$$

Note $\psi_0 = \psi$. Define $z(t, \phi) = G[\Gamma_t, \phi \circ T_t^{-1}]$. We have

$$G[\Gamma_t] = \max_{\phi \in H_g^1(\Omega)} z(t, \phi).$$

Step 1. Easy to verify that

$$\frac{z(t, \psi_0) - z(0, \psi_0)}{t} \leq \frac{G[\Gamma_t] - G[\Gamma]}{t} \leq \frac{z(t, \psi_t \circ T_t) - z(0, \psi_t \circ T_t)}{t}.$$

Hence

$$\partial_t z(\xi, \psi_0) \leq \frac{G[\Gamma_t] - G[\Gamma]}{t} \leq \partial_t z(\eta, \psi_t \circ T_t), \quad \xi, \eta \in [0, t].$$

Step 2. Direct calculations lead to

$$\partial_t z(t,\phi) = \int_\Omega \Big[-\frac{\varepsilon_\Gamma}{2} A'(t) \nabla\phi \cdot \nabla\phi + ((\nabla \cdot (fV)) \circ T_t)\phi J_t - \chi_w B(\phi)((\nabla \cdot V) \circ T_t) J_t \Big] dV.$$

Replacing t by η and ϕ by $\psi_t \circ T_t$, respectively, we obtain

$$\lim_{t\to 0} \partial_t z(\eta, \psi_t \circ T_t) = \partial_t z(0, \psi_0)$$

and hence

$$\delta_{\Gamma,V} G[\Gamma] = \partial_t z(0, \psi_0),$$

provided that

$$\lim_{t\to 0} \|\psi_t \circ T_t - \psi_0\|_{H^1(\Omega)} = 0.$$

Step 3. The limit

$$\lim_{t \to 0} \|\psi_t \circ T_t - \psi_0\|_{H^1(\Omega)} = 0$$

follows from:

- Weak form of the Euler–Lagrange equation for the maximization of $z(t, \cdot)$ by $\psi_t \circ T_t$ for $t > 0$ and by ψ_0 for $t = 0$, respectively;
- Subtract one from the other;
- Use the properties of $T_t(X)$ and the convexity of B.

Step 4. We now have

$$\delta_{\Gamma, V} G[\Gamma] = \partial_t z(0, \psi_0).$$

Direct calculations complete the proof. **Q.E.D.**

Surface energy vs. electrostatic energy

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

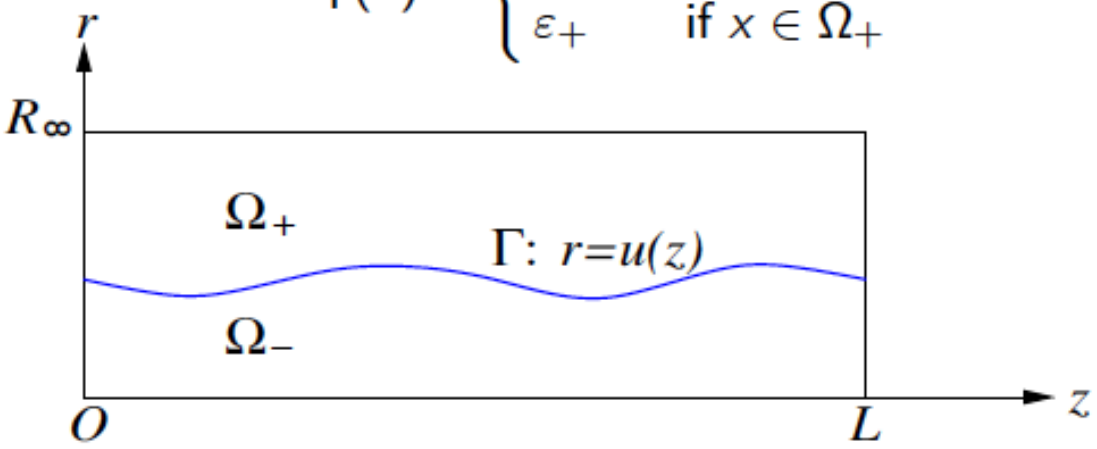
Free-energy functional

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

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

- $\gamma_0 > 0$: a given constant
- $f = f(r,z) : \Omega \to \mathbb{R}$: a given function, L-periodic in z
- dielectric coefficient

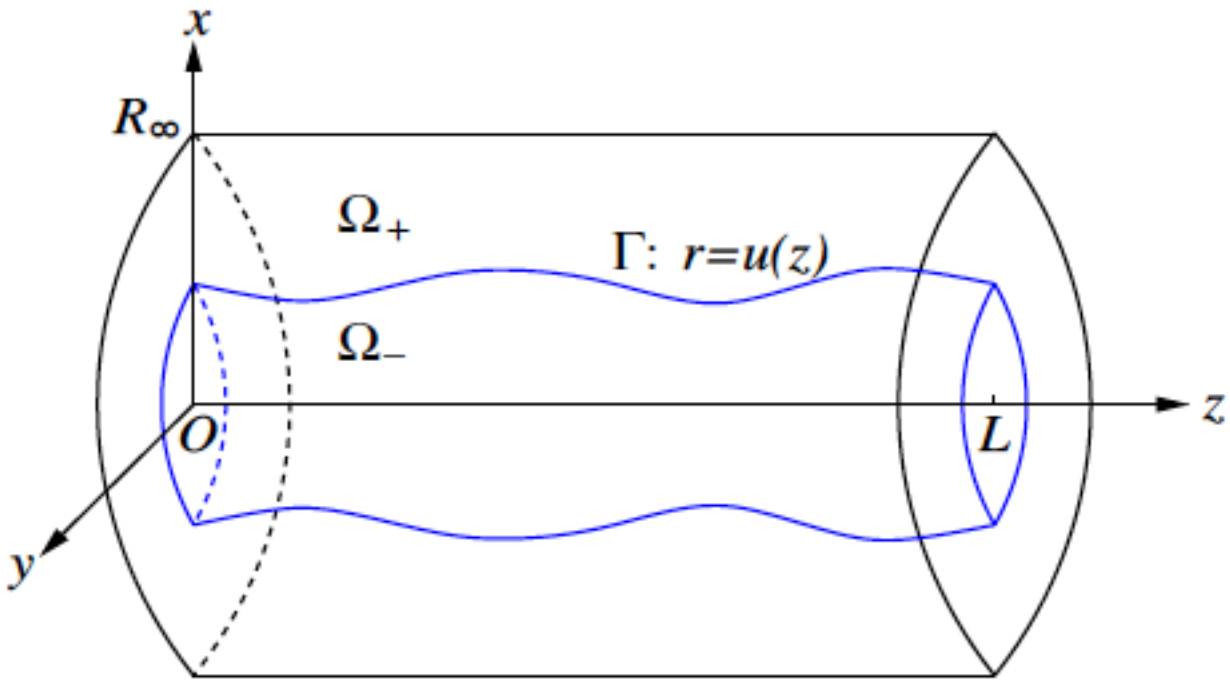
$$\varepsilon_\Gamma(x) = \begin{cases} \varepsilon_- & \text{if } x \in \Omega_- \\ \varepsilon_+ & \text{if } x \in \Omega_+ \end{cases}$$



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

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

Linear Stability Analysis for the Case $\varepsilon_- > \varepsilon_+$



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

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.

$$
\begin{aligned}
u &= u(z,t,\tau) = u_0 + \tau u_1(z,t) + \cdots, \\
\psi &= \psi(r,z,t,\tau) = \psi_0(r) + \tau \psi_1(r,z,t) + \cdots, \\
u(z,0,\tau) &= u_0 + \tau u_1(z,0).
\end{aligned}
$$

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

Step 3. Dispersion relations.

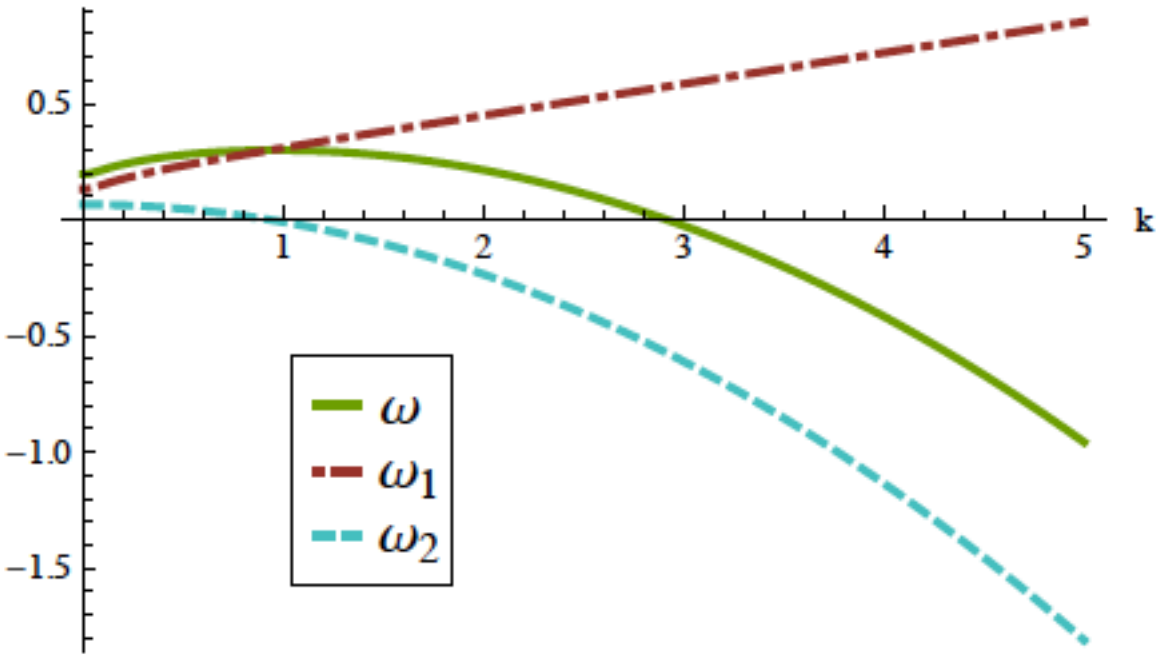
Assume

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

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

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

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



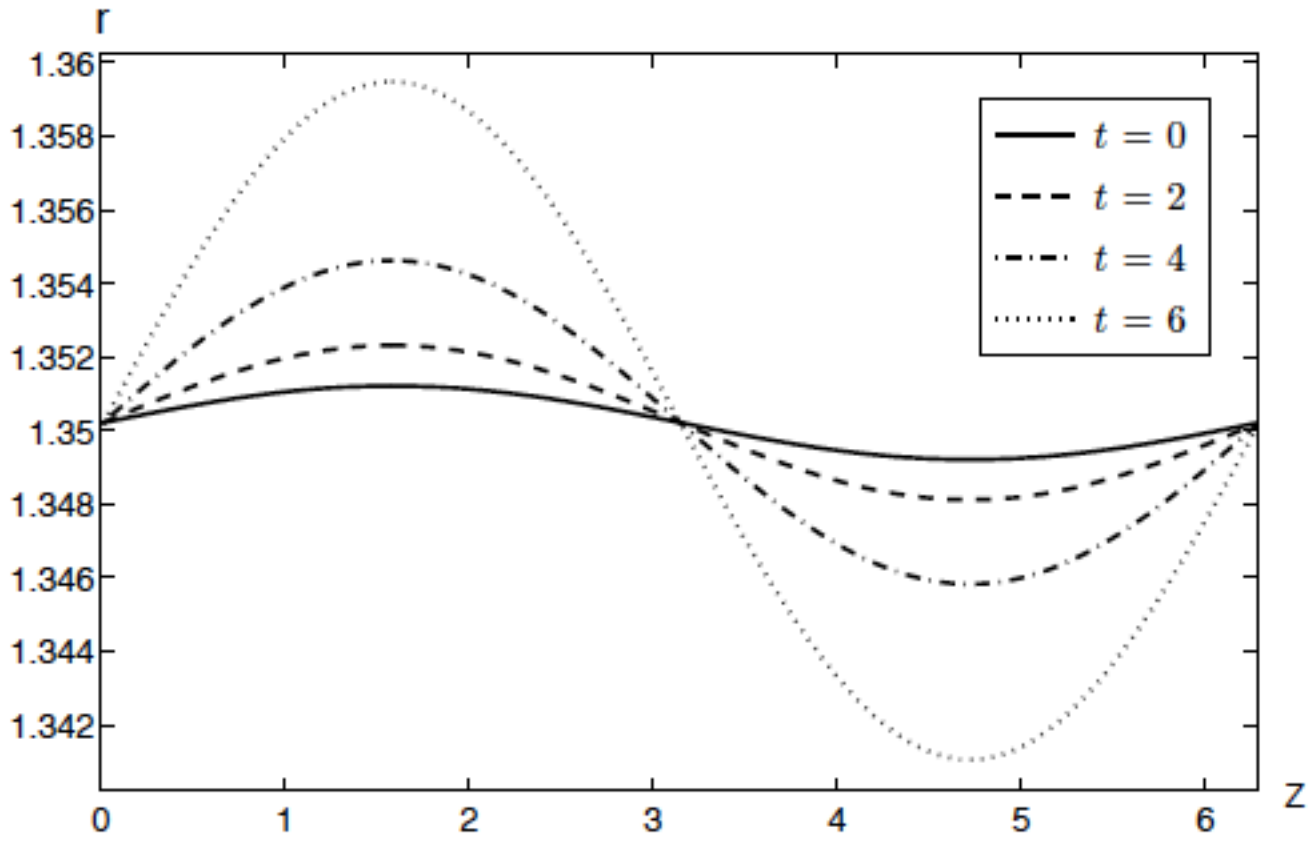
$$\omega(k) = \omega_1(k) + \omega_2(k)$$

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

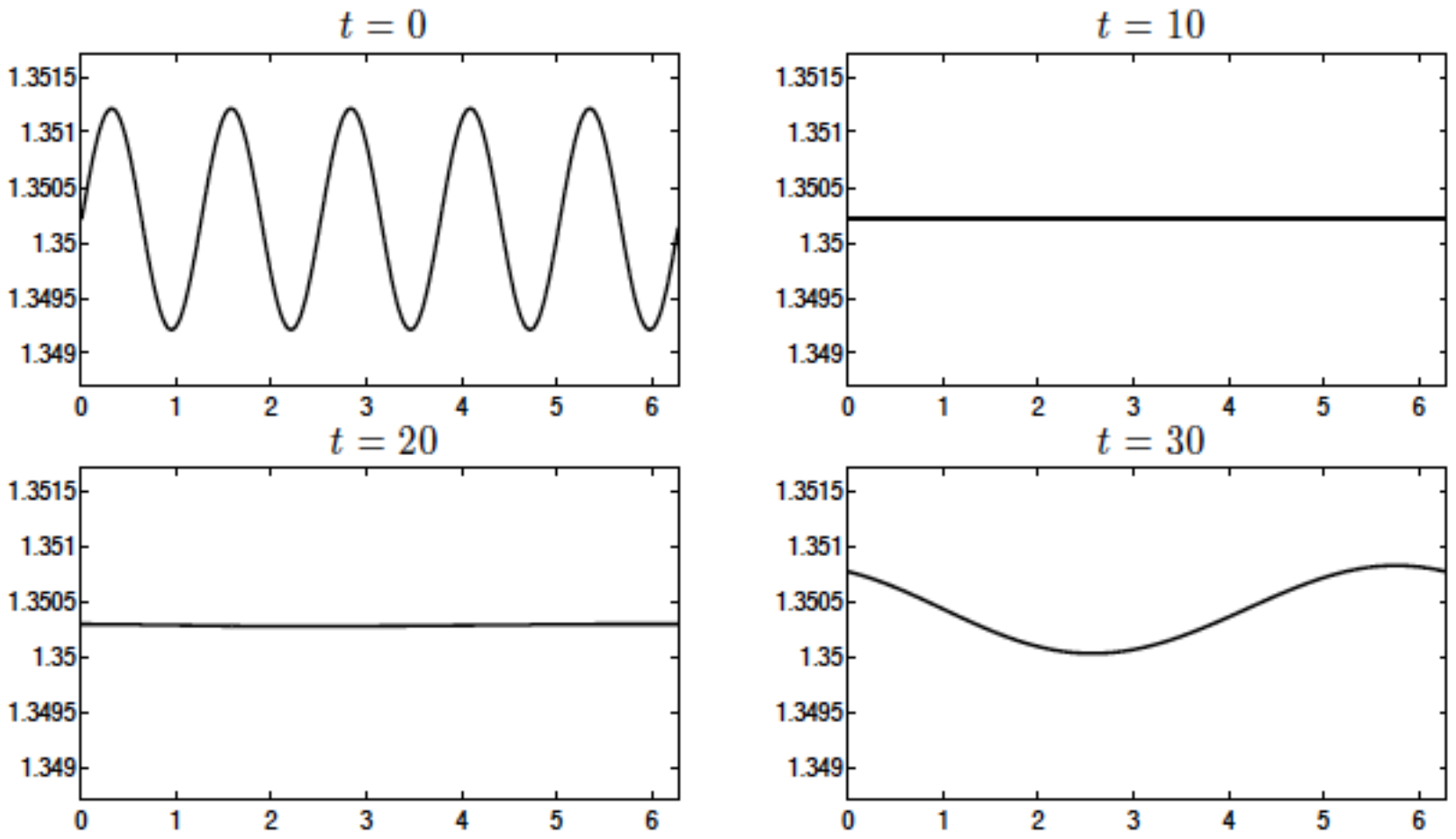
$$\omega_2(k) = -\gamma_0 k^2 + \frac{\gamma_0}{u_0^2}$$

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

Numerical results: The case $\varepsilon_- > \varepsilon_+$



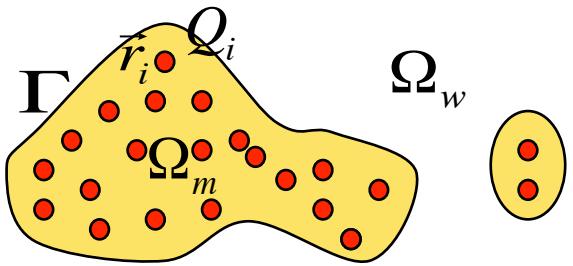
$\varepsilon_- = 80$, $\varepsilon_+ = 2$, $u_0 \approx 1.35$,, $u(z,0) = u_0 + 10^{-3} \sin z$, $k = 1$ and $\omega(k) > 0$.



$u(z,0) = u_0 + 10^{-3}\sin(5z)$, $k = 5$ and $\omega(k) < 0$.

Solvent Fluid Dynamics and Fluctuations

Interface motion



$$V_n = u \cdot n$$

Fluctuating solvent fluid:

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

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

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

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

Electrostatics

$$\nabla \cdot \varepsilon\varepsilon_0 \nabla\psi - \chi_w B'(\psi) = -\rho_f$$

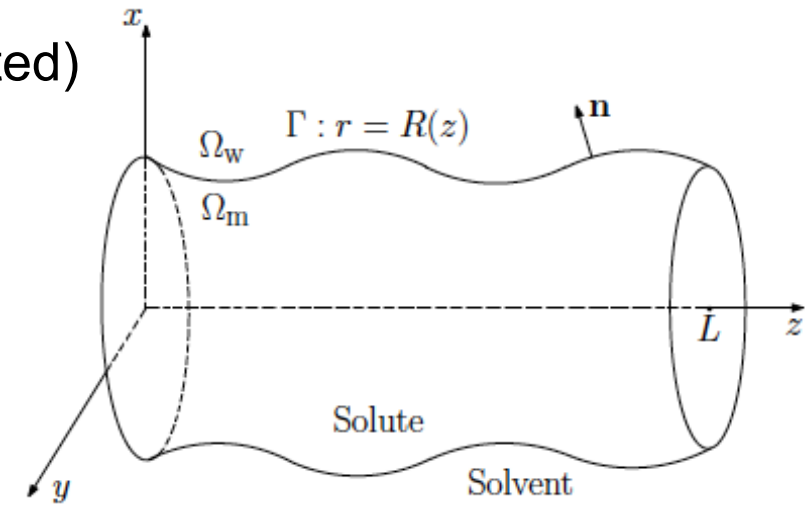
$$-f_{ele} = \frac{\varepsilon_0}{2}\left(\frac{1}{\varepsilon_m} - \frac{1}{\varepsilon_w}\right)\left|\varepsilon \partial_n \psi\right|^2 + \frac{\varepsilon_0}{2}\left(\varepsilon_w - \varepsilon_m\right)\left|(I - n \otimes n)\nabla\psi\right|^2 + B(\psi)$$

Force balance

$$2\mu_w D(u)n + (p_m - p_w - 2\gamma_0 H + n_w U_{vdW} + f_{ele})n = 0 \qquad \text{at} \quad \Gamma(t)$$

Stability of a cylindrical solute-solvent interface

Li, Sun, and Zhou, SIAP, 2014 (submitted)



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

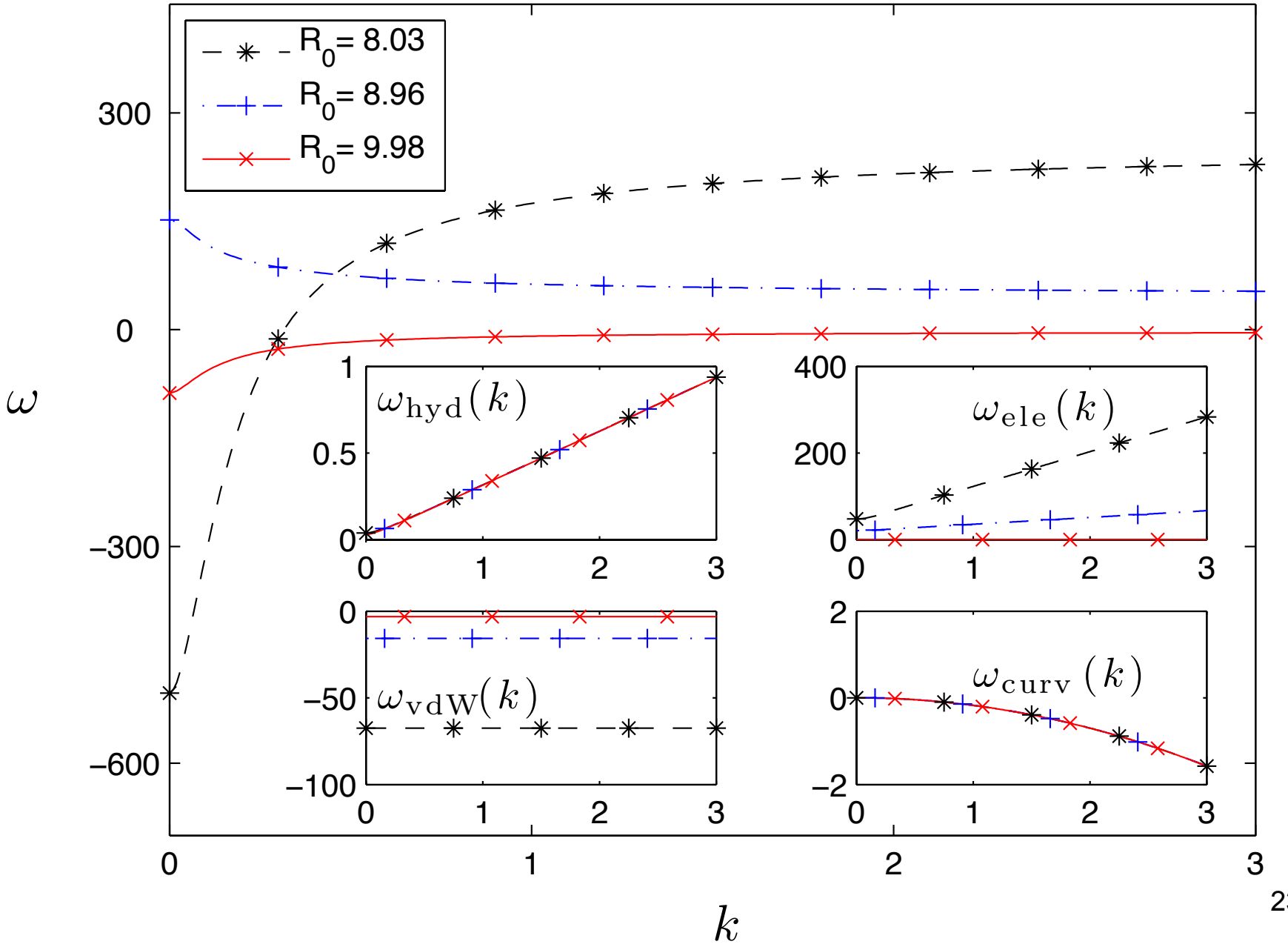
$$\omega_{\mathrm{surf}}(k) = \gamma_0\left(\frac{1}{R_0^2} - k^2\right),$$

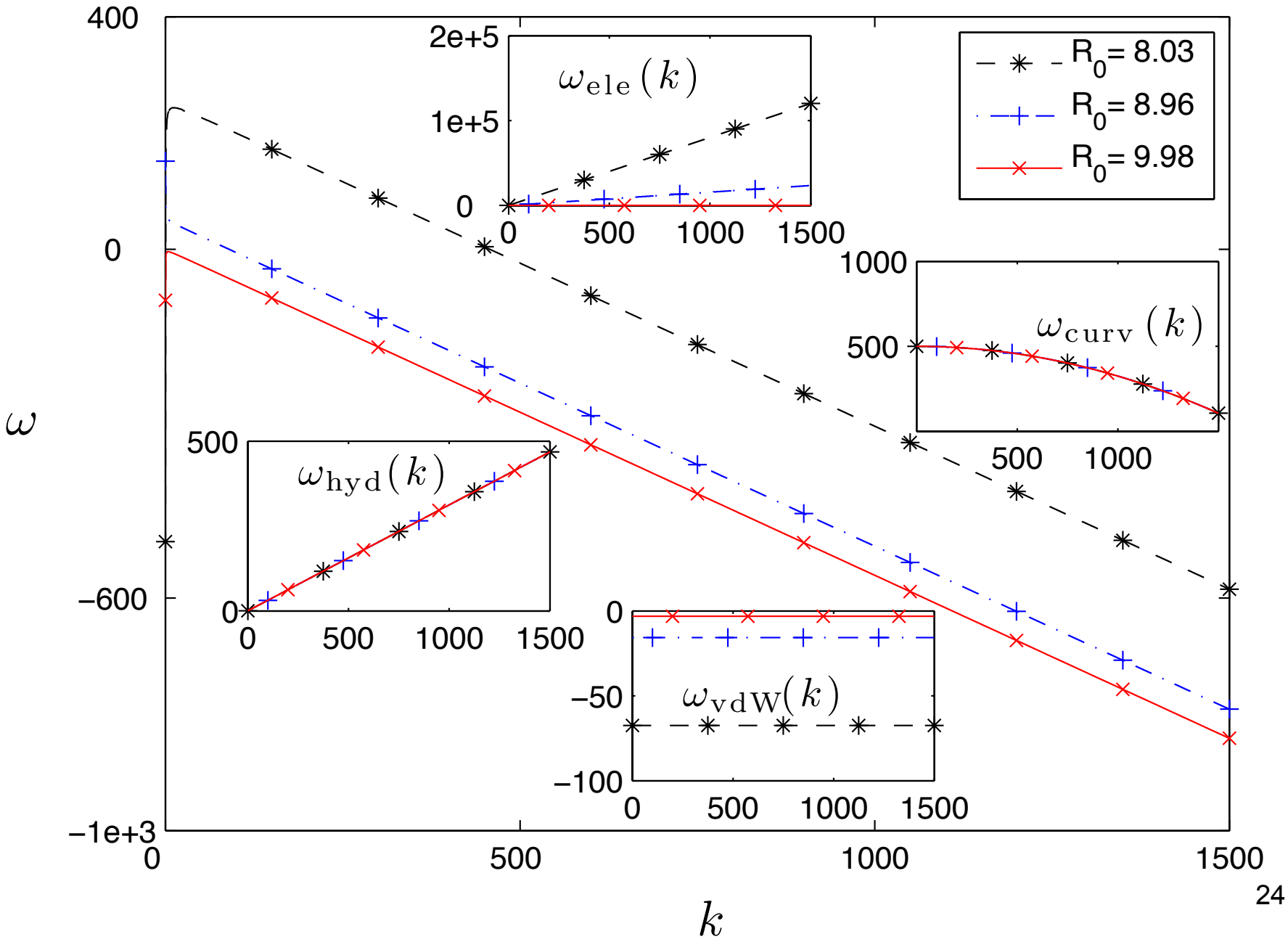
$$\omega_{\mathrm{vdW}}(k) = n_{\mathrm{w}}U'_{\mathrm{vdW}}(R_0),$$

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

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

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


R0= 8.03
R0= 8.96
R0= 9.98
300
0
−300
−600
ω
0
1
2
3
k
ωhyd(k)
ωele(k)
ωvdW(k)
ωcurv(k)
1
0.5
0
400
200
−50
−100
2
−2

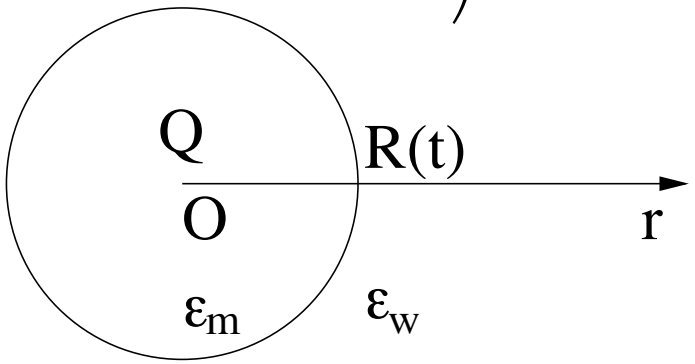

400
0
−600
−1e+3
0
500
1000
1500
ω
k
R0= 8.03
R0= 8.96
R0= 9.98
2e+5
1e+5
0
ω_ele(k)
1000
500
ω_curv(k)
500
0
ω_hyd(k)
0
−50
−100
ω_vdW(k)

A generalized Rayleigh-Plesset equation for a charged sphere

$$dR = \frac{R}{4\mu_w}\left(p_0(R) - p_\infty - \frac{2\gamma_0}{R} + n_w U(R) + f_{ele}(R) + d\eta \right)$$

$$\left\langle \eta(t)\eta(t') \right\rangle = \frac{4}{3} k_B T \delta(t - t')$$

$$p_0(R) = \frac{3k_B T}{4\pi R^3}$$



$$U(r) = U_{vdW}(r) + U_{ext}(r) = 4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6} \right] + U_{ext}(r)$$

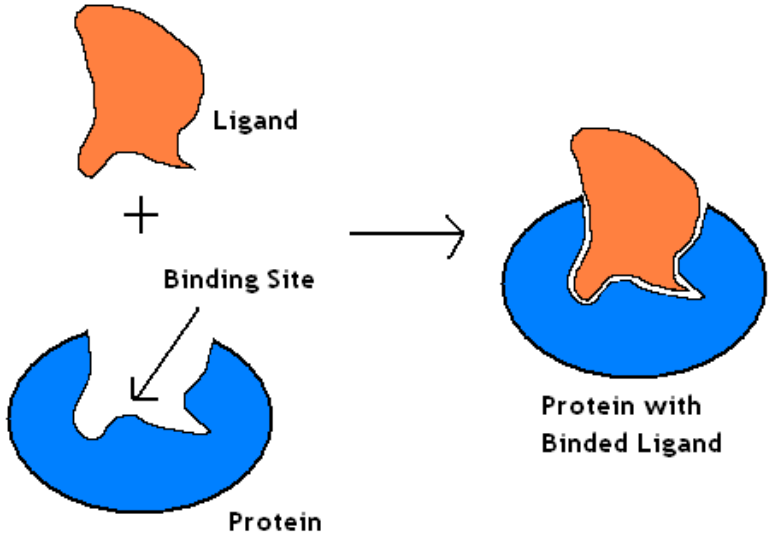
$$f_{ele}(R) = \frac{Q^2}{32\pi^2\varepsilon_0}\left[\left(\frac{1}{\varepsilon_w} - \frac{1}{\varepsilon_m} \right)\frac{1}{R^4} - \frac{\kappa^2}{\varepsilon_w (1+\kappa R)^2 R^2} \right]$$

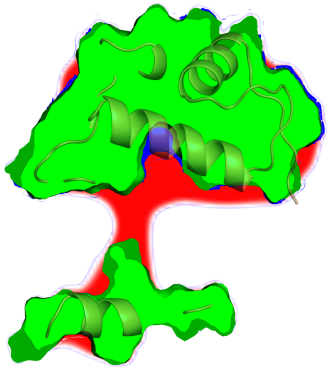
Concluding remarks

- Dielectric boundary force: pointing to charged molecules.
- Electrostatics and hydrodynamics: instability.

- Mathematical analysis

- Modeling: solute-solvent interfacial fluctuations.
- Hybrid approach: solute MD + implicit solvent.
- Application: protein-ligand binding, rational drug design.





Green: molecular surface.
Red: VISM surface.

Thank you!