Level-Set Variational Solvation Coupling Solute Molecular Mechanics with Continuum Solvent

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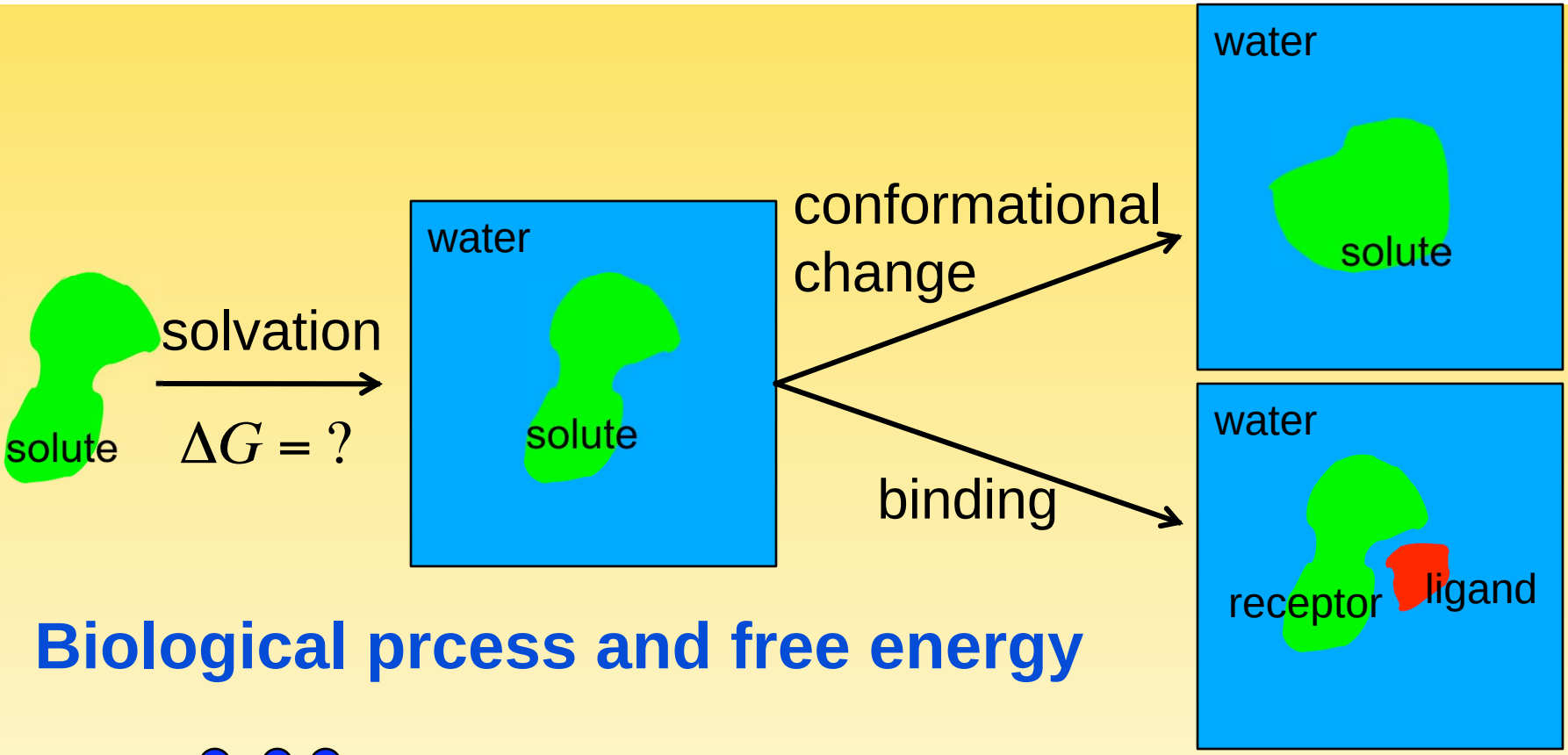
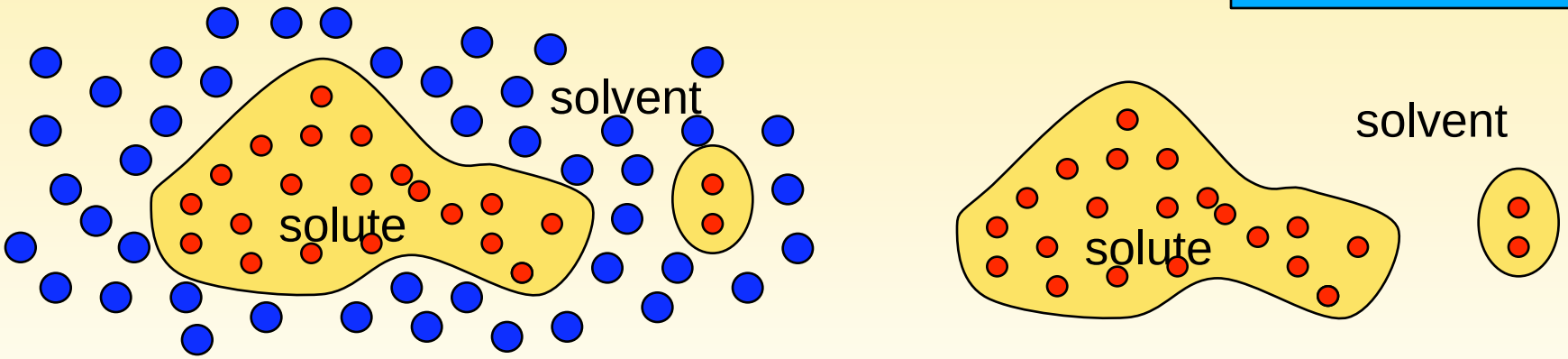
OUTLINE

1. Introduction
2. A variational model of solvation
3. The level-set method
4. Numerical results
5. Electrostatic free energy
6. Conclusions

1. Introduction

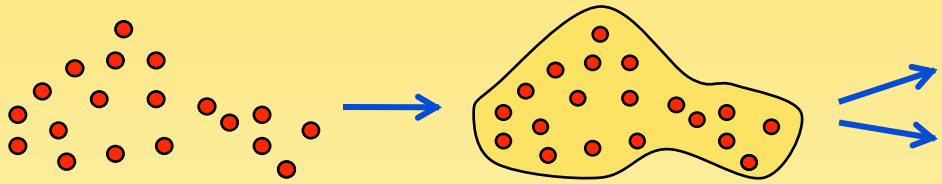


Biological prcess and free energy



Explicit solvent vs. implicit solvent

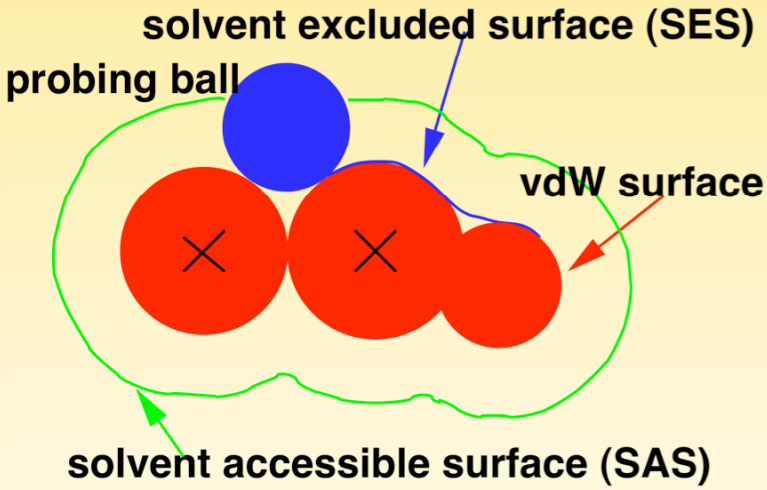
Established implicit-solvent models



Surface energy

PB/GB calculations

- Get data of biomolecules.
- Generate solute-solvent interface.
- Calculate surface energy.
- Calculate the electrostatic free energy using PB/GB with the surface as dielectric boundary.

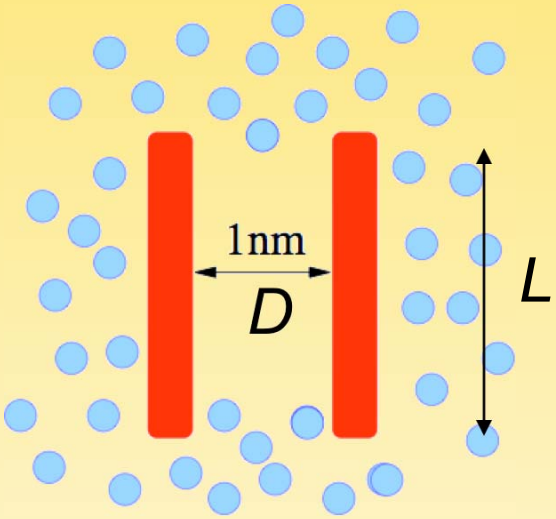


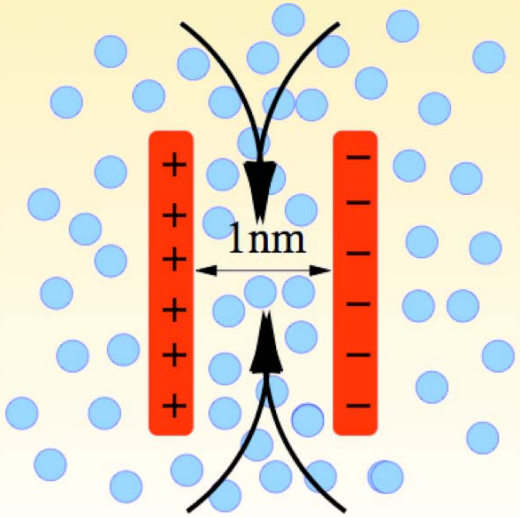
$$G = G_{np} + G_p$$

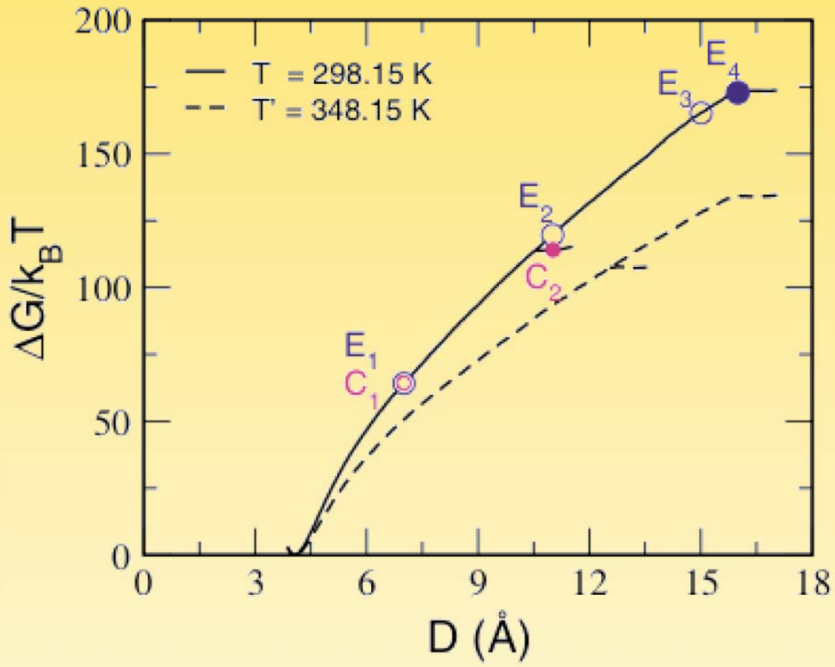
$$G_{np} = \sum_{i}^{\text{solute atoms}} a_i S_i + b_i + PV + G_{\text{vdw}}$$

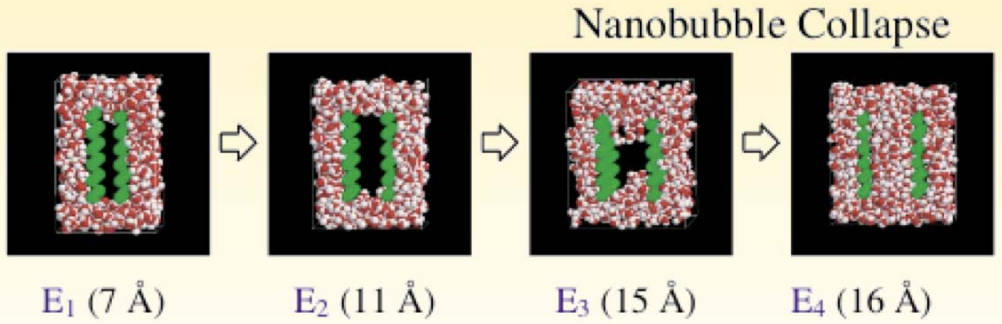
(S_i: Surface area)

Example 1. Capillary evaporation in hydrophobic confinement.





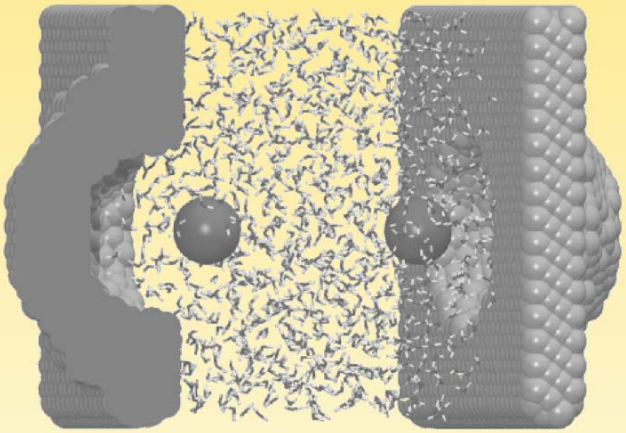




Koishi *et al.,* Phys. Rev. Lett., 93, 185791, 2004.

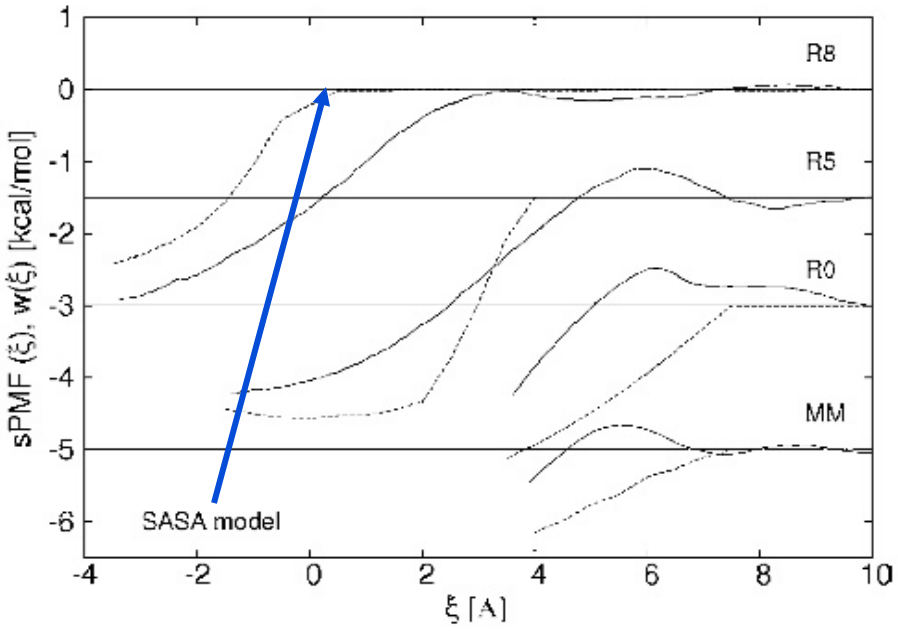
Example 2. A receptor-ligand (pocket wall-methane atom) system.

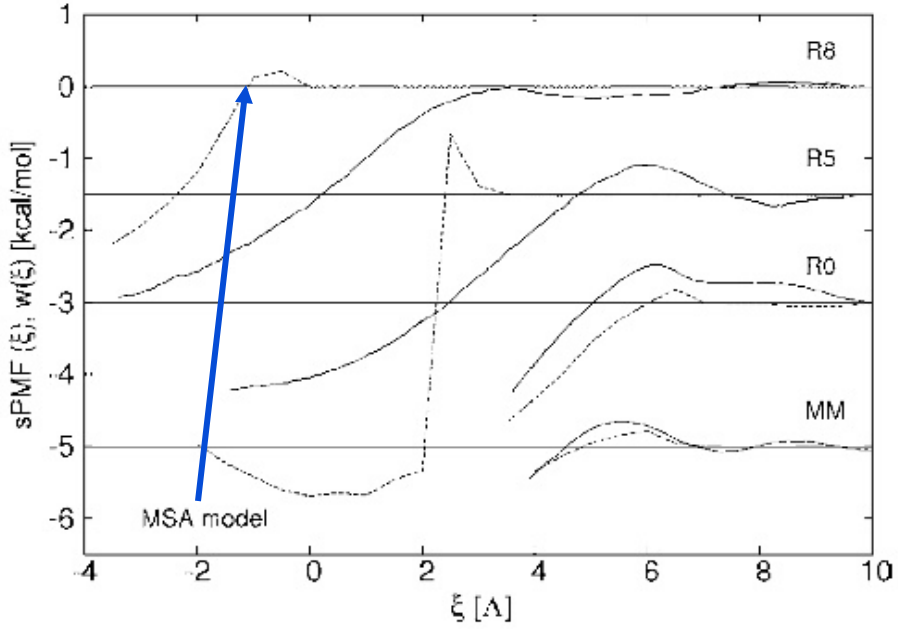
Setny, J. Chem. Phys., 127, 054505, 2007.



MD: weakly solvated pocket, strong hydrophobic attraction.

<u>SASA/MSA: Onset of attraction is wrong by 2-4 Angstroms!</u>





Example 3. Evaporation in proteins.

MD simulations of the melittin protein tetramer

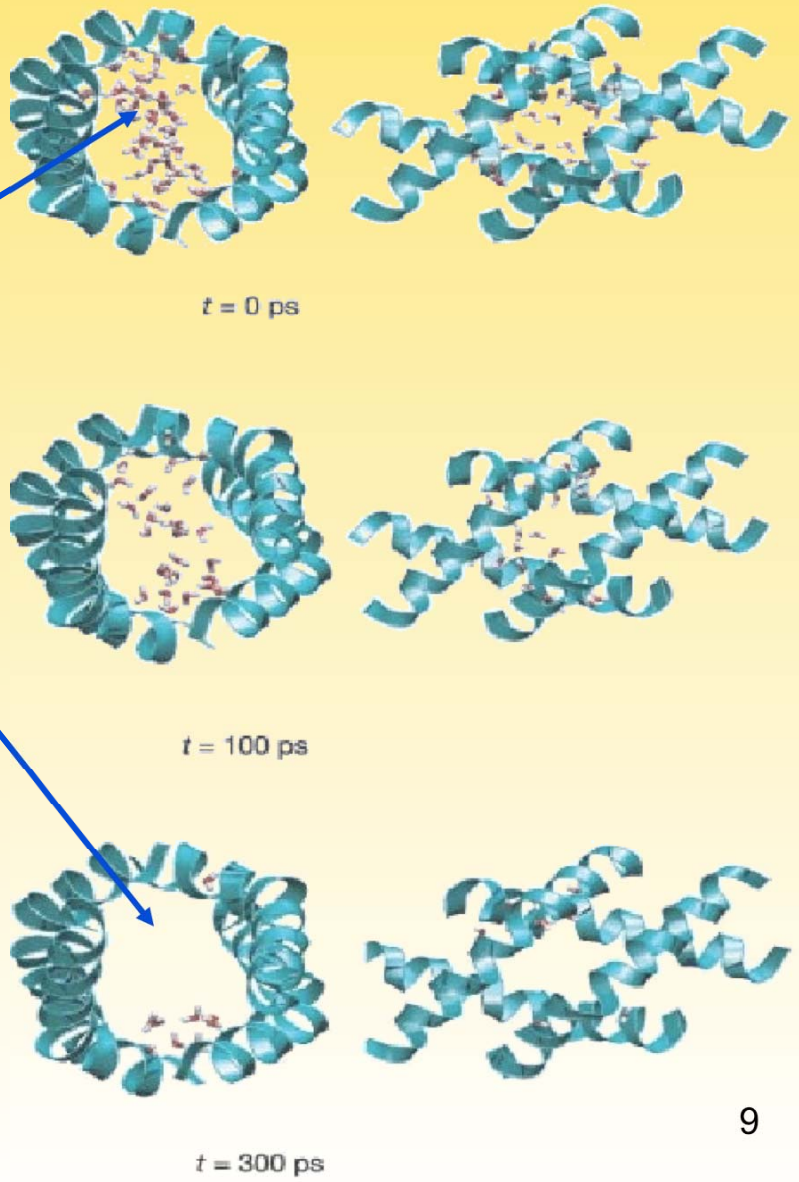
- Water in hydrophobic core
- Stable nanobubble

Liu *et al*., Nature, 437, 159, 2005.

More MD simulations

- Electrostatics
- Curvature

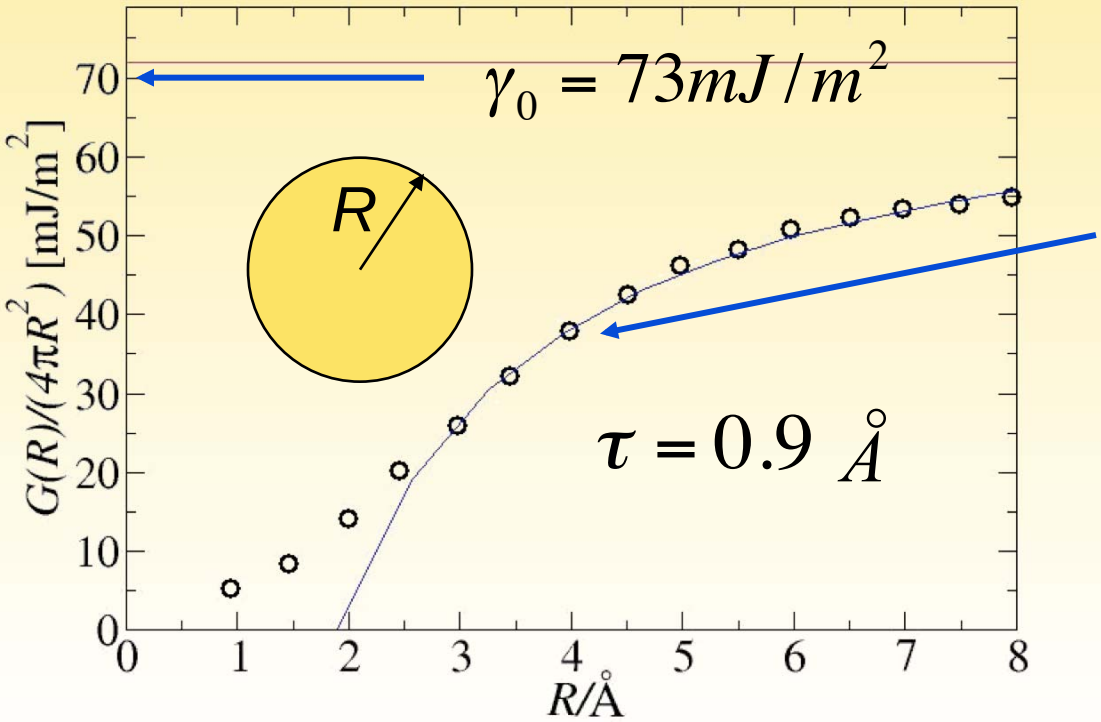
Giovambattista *et al.,* PNAS, 105, 2274, 2008.



Possible issues of fixed-surface models

- Hydrophobic cavities
- Curvature correction
- Decoupling of polar and nonpolar contributions

Strong curvature effects at small scales



Symbols: MD, SPC/E water, *P*=1bar, *T*=300K.

$$\gamma = \gamma_0\left(1 - 2\tau H\right)$$

τ : the Tolman length

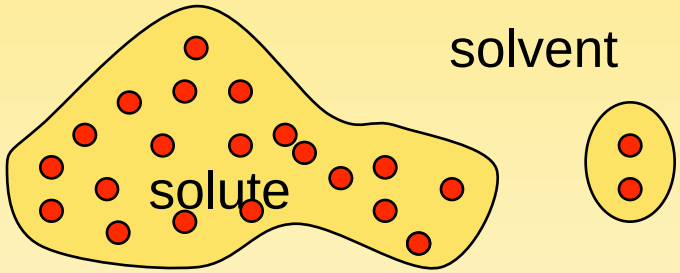
H : mean curvature

Huang, Geissler, & Chandler, J. Phys. Chem. B, 105, 6704, 2001.

2. A Variational Model of Solvation

A variational implicit-solvent model (VISM)

- Dzubiella, Swanson, & McCammon, Phys. Rev. Lett., 96, 087802, 2006.
- Dzubiella, Swanson, & McCammon, J. Chem. Phys., 124, 084905, 2006.

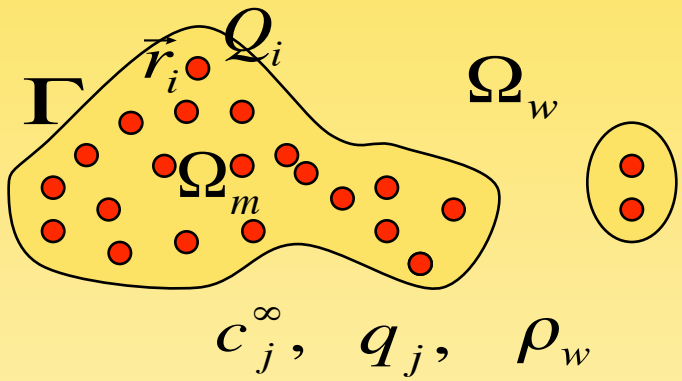


Guiding principles

- Solvation structure
  = Solute atomic positions + Solute-solvent interface.
- Free-energy minimization determines solute-solvent interfaces.
- Free energy couples different interactions: polar, nonpolar, dispersive, etc.

A free-energy functional

$$G[\Gamma] = G_{geom}[\Gamma] + G_{vdW}[\Gamma] + G_{elec}[\Gamma]$$



- $G_{geom}[\Gamma] = Pvol(\Omega) + \int_\Gamma \gamma(\vec{r})dS$

$Pvol(\Omega)$: Creation of a cavity in the solvent

P= Liquid-vapor pressure difference

$\int_\Gamma \gamma(\vec{r})dS$: Molecular rearrangement near the interface

$\gamma = \gamma(\vec{r})$: Surface tension

$\gamma(\vec{r}) = \gamma_0\left[1 - 2\tau H(\vec{r})\right]$ (Scaled Particle Theory)

γ_0: the (planar) surface tension

τ: the Tolman length, a fitting parameter

$H = H(\vec{r})$: mean curvature

$$G_{geom}[\Gamma] = Pvol(\Omega) + \gamma_0 area(\Gamma) - 2\gamma_0\tau\int_\Gamma HdS \quad \left(+c_K\int_\Gamma KdS\right)$$

Hadwiger's Theorem

Let C = the set of all convex bodies,

M = the set of finite union of convex bodies.

If $F : M \to R$ is

- rotationally and translationally invariant,
- additive:

$$F(U \cup V) = F(U) + F(V) - F(U \cap V) \qquad \forall U, V \in M,$$

- conditionally continuous:

$$U_j, U \in C, U_j \to U \Rightarrow F(U_j) \to F(U),$$

then

$$F(U) = aVol(U) + bArea(\partial U) + c\int_{\partial U} H dS + d\int_{\partial U} K dS \quad \forall U \in M.$$

Application to nonpolar solvation

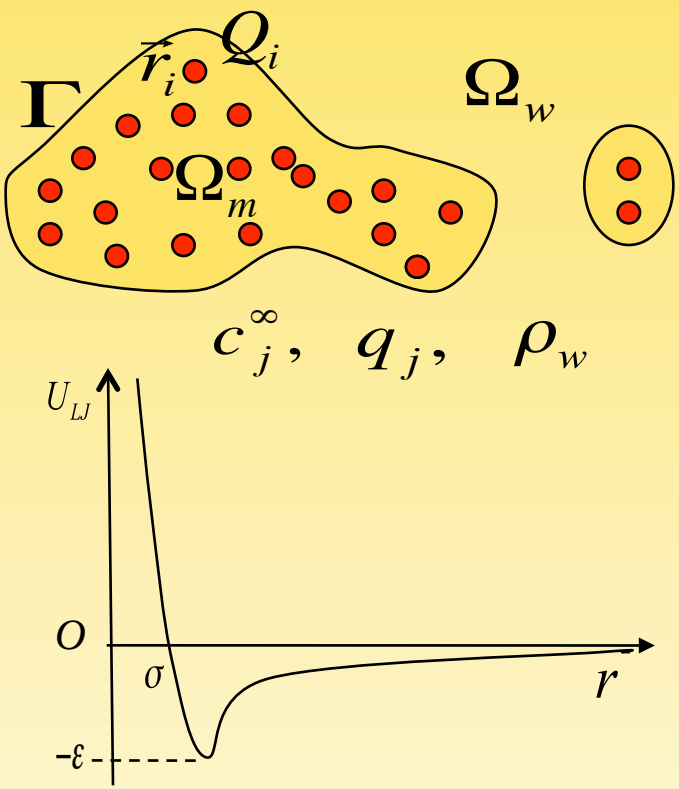
Roth, Harano, & Kinoshita, Phys. Rev. Lett., 97, 078101, 2006.
Harano, Roth, & Kinoshita, Chem. Phys. Lett., 432, 275, 2006.

- $G_{vdW}[\Gamma] = \rho_w \int_{\Omega_w} U(\vec{r}) dV$

  solute-solvent van der Waals interaction

$$U(\vec{r}) = \sum_i U_i(|\vec{r} - \vec{r}_i|)$$

$$U_i(r) = U_{LJ,i}(r) = 4\varepsilon_i \left[\left(\frac{\sigma_i}{r} \right)^{12} - \left(\frac{\sigma_i}{r} \right)^{6} \right]$$



- $G_{elec}[\Gamma]$ - Electrostatic free energy
  - The Poisson-Boltzmann (PB) theory
  - The generalized Born (GB) model

Coupling solute molecular mechanics with implicit solvent

Molecular mechanical interactions of solute atoms

$$V[\vec{r}_1,\ldots,\vec{r}_N] = \sum_{i,j} W_{bond}(\vec{r}_i,\vec{r}_j) + \sum_{i,j,k} W_{bend}(\vec{r}_i,\vec{r}_j,\vec{r}_k)$$
$$+ \sum_{i,j,k,l} W_{torsion}(\vec{r}_i,\vec{r}_j,\vec{r}_k,\vec{r}_l) + \sum_{i,j} W_{LJ}(\vec{r}_i,\vec{r}_j)$$
$$+ \sum_{i,j} W_{Coulomb}(\vec{r}_i,Q_i;\vec{r}_j,Q_j)$$

An effective total Hamiltonian

$$H[\Gamma;\vec{r}_1,\ldots,\vec{r}_N] = V[\vec{r}_1,\ldots,\vec{r}_N] + G[\Gamma;\vec{r}_1,\ldots,\vec{r}_N],$$

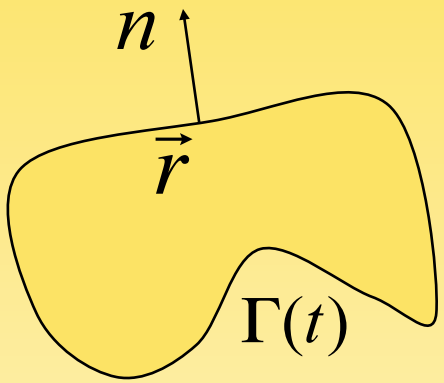
$$\min H[\Gamma;\vec{r}_1,\ldots,\vec{r}_N] \Rightarrow \text{Equilibrium conformations}$$

3. The Level-Set Method

The level-set method

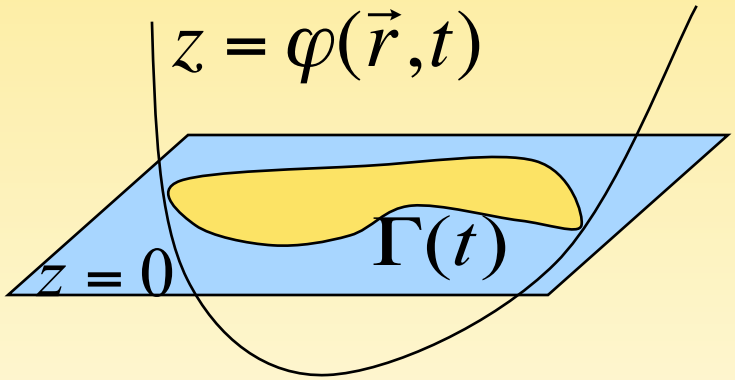
- Interface motion

$$V_n = V_n(\vec{r},t) \quad \text{for } \vec{r} \in \Gamma(t)$$



- Level-set representation

$$\Gamma(t) = \{\vec{r} \in \Omega : \varphi(\vec{r},t) = 0\}$$



- The level-set equation

$$\varphi_t + V_n \,|\nabla\varphi| = 0$$

$$\left[\begin{array}{c} \varphi(\vec{r}(t),t) = 0 \quad \Longrightarrow \quad \varphi_t + \nabla\varphi\cdot\vec{r}_t = 0 \\ \nabla\varphi\cdot\vec{r}_t = \left(\frac{\nabla\varphi}{|\nabla\varphi|}\cdot\vec{r}_t\right)|\nabla\varphi| = (\vec{n}\cdot\vec{r}_t)\,|\nabla\varphi| = V_n\,|\nabla\varphi| \end{array}\right]$$

Examples of normal velocity

- Geometrically based motion
  - Motion by mean curvature

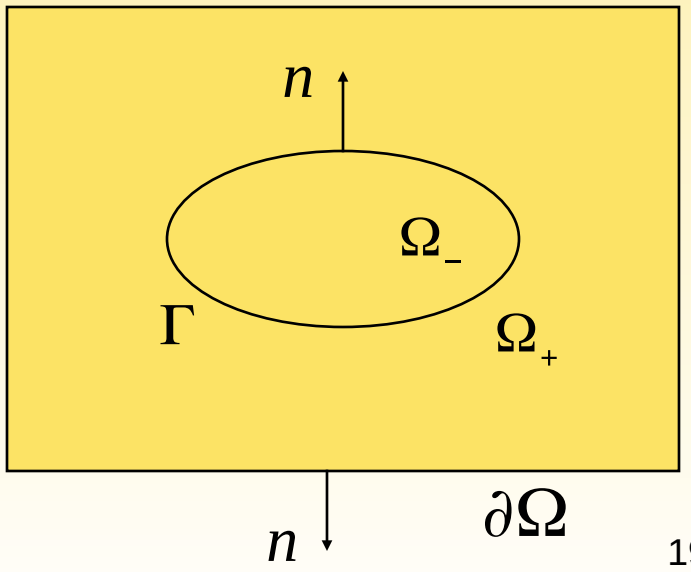
$$V_n = -H$$

  - Motion by the surface Laplacian of mean curvature

$$V_n = \Delta_s H$$

- External field

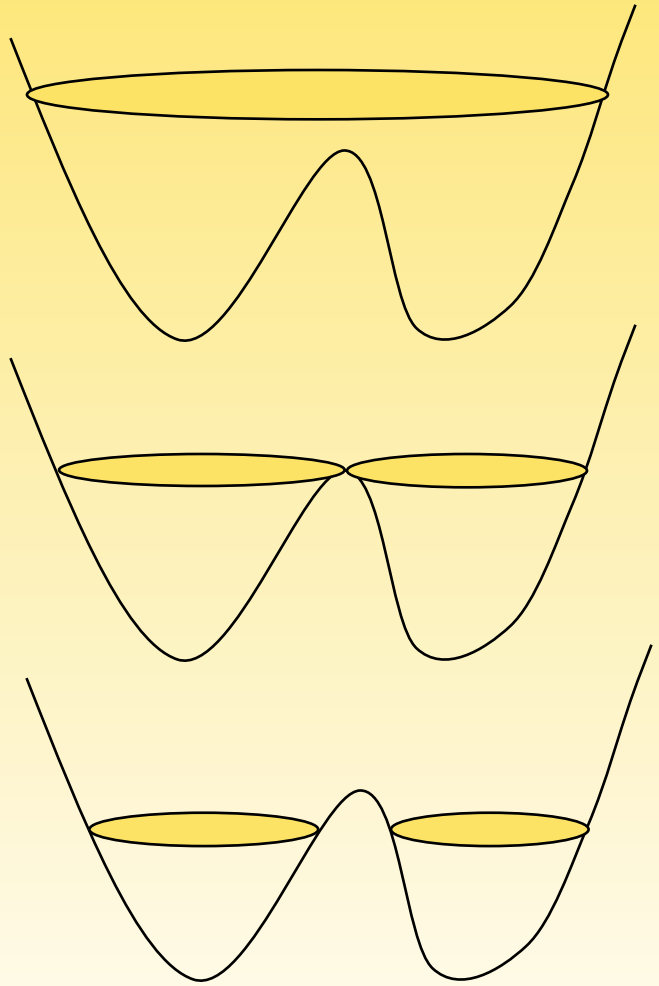
$$\begin{cases} u_t - \Delta u = 0 & \text{in } \Omega_- \cup \Omega_+ \\ u = -H & \text{on } \Gamma \\ \frac{\partial u}{\partial n} = 0 & \text{on } \partial\Omega \\ V_n = \left[\frac{\partial u}{\partial n}\right] & \text{on } \Gamma \end{cases}$$



Level-set formulas of geometrical quantities

- Unit normal $\vec{n} = \frac{\nabla\varphi}{|\nabla\varphi|}$
- Mean curvature $H = \frac{1}{2}\nabla \cdot \vec{n}$
- Gaussian curvature $K = \vec{n} \cdot adj(He(\varphi))\vec{n}$
- Surface integral $\int_{\Gamma} f(\vec{r})dS = \int_{R^3} f(\vec{r})\delta(\varphi)dV$
- Volume integral $\int_{\Omega} f(\vec{r})dV = \int_{R^3} f(\vec{r})[1 - H(\varphi)]dV$

- Topological changes
  - Merging
  - Break-up
  - Disappearing
  - Nucleation?
- Accuracy issues
  - Interface approximation
  - Conservation of mass
  - Rigorous analysis



Application to variational solvation

- Cheng, Dzubiella, McCammon, & Li, J. Chem. Phys. 127, 084503, 2007.
- Cheng, Xie, Dzubiella, McCammon, Che, & Li, J. Chem. Theory Comput., 5, 257, 2009.
- Cheng, Wang, Setny, Dzubiella, Li, & McCammon, J. Chem. Phys., 2009.

Relaxation

$$\varphi_t + V_n \left| \nabla \varphi \right| = 0$$

$$\frac{d\vec{r}_i}{dt} = -\nabla_{\vec{r}_i} H[\Gamma;\vec{r}_1,\ldots,\vec{r}_N] = -\nabla_{\vec{r}_i} V[\vec{r}_1,\ldots,\vec{r}_N] - \nabla_{\vec{r}_i} G[\Gamma]$$

$$V_n = -\delta_\Gamma H[\Gamma;,\vec{r}_1,\ldots,\vec{r}_N] = -\delta_\Gamma G[\Gamma]$$

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

$$\delta_\Gamma \int_\Omega dV = 1 \qquad \delta_\Gamma \int_\Gamma dS = -2H \qquad \delta_\Gamma \int_\Gamma H dS = -K$$

Algorithm

Step 1. Input parameters and initialize level-set function

Step 2. Calculate the normal and curvatures

Step 3. Calculate and extend the normal velocity

Step 4. Solve the level-set equation

Step 5. Reinitialize the level-set function

Step 6. Solve ODEs for the motion of solute particles

Step 7. Set $t := t + \Delta t$ and go to Step 2

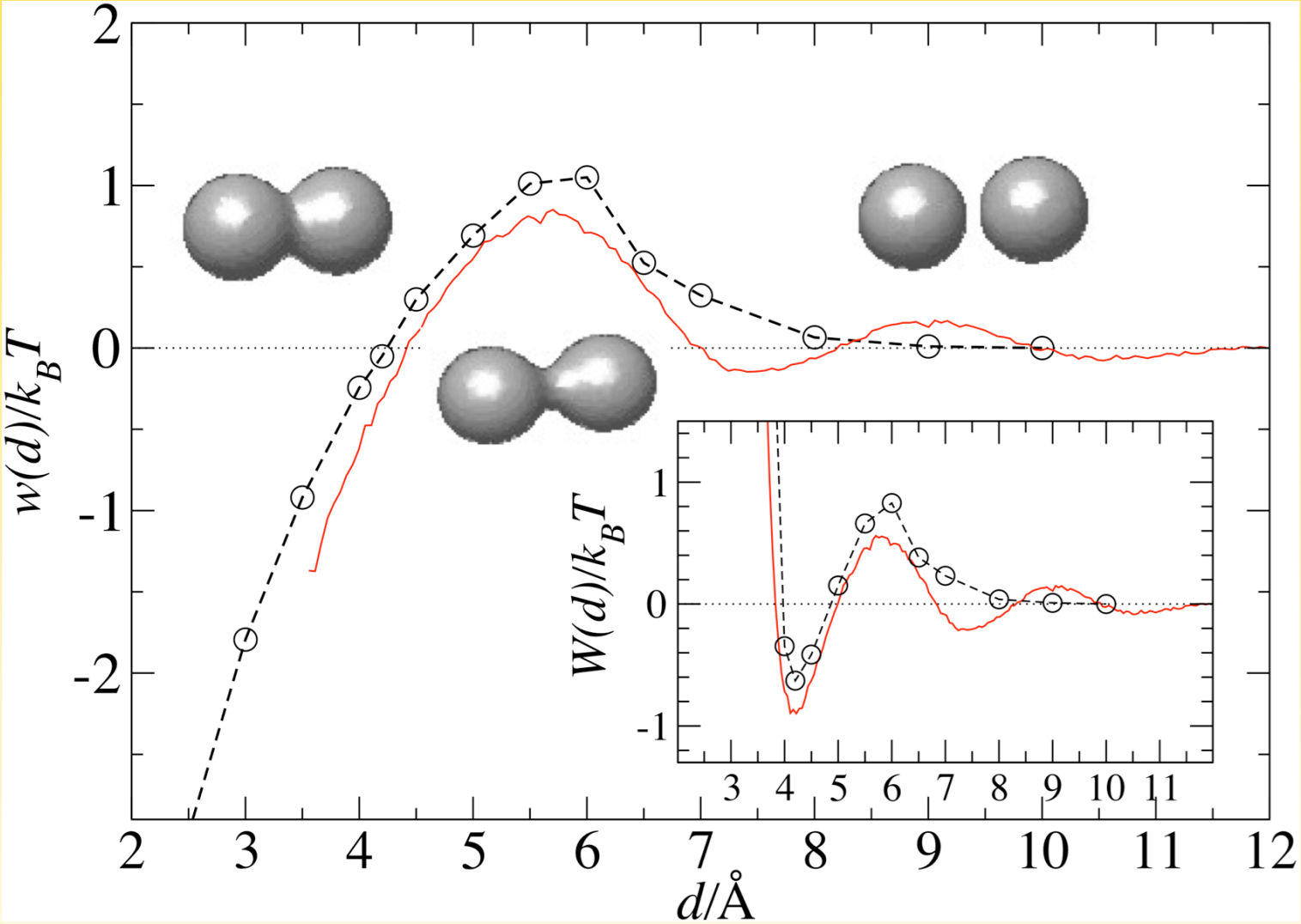
New level-set techniques

- Pre-computation of the potential
- Numerical regularization
- Fast numerical integration
- Local level-set method

Efficiency

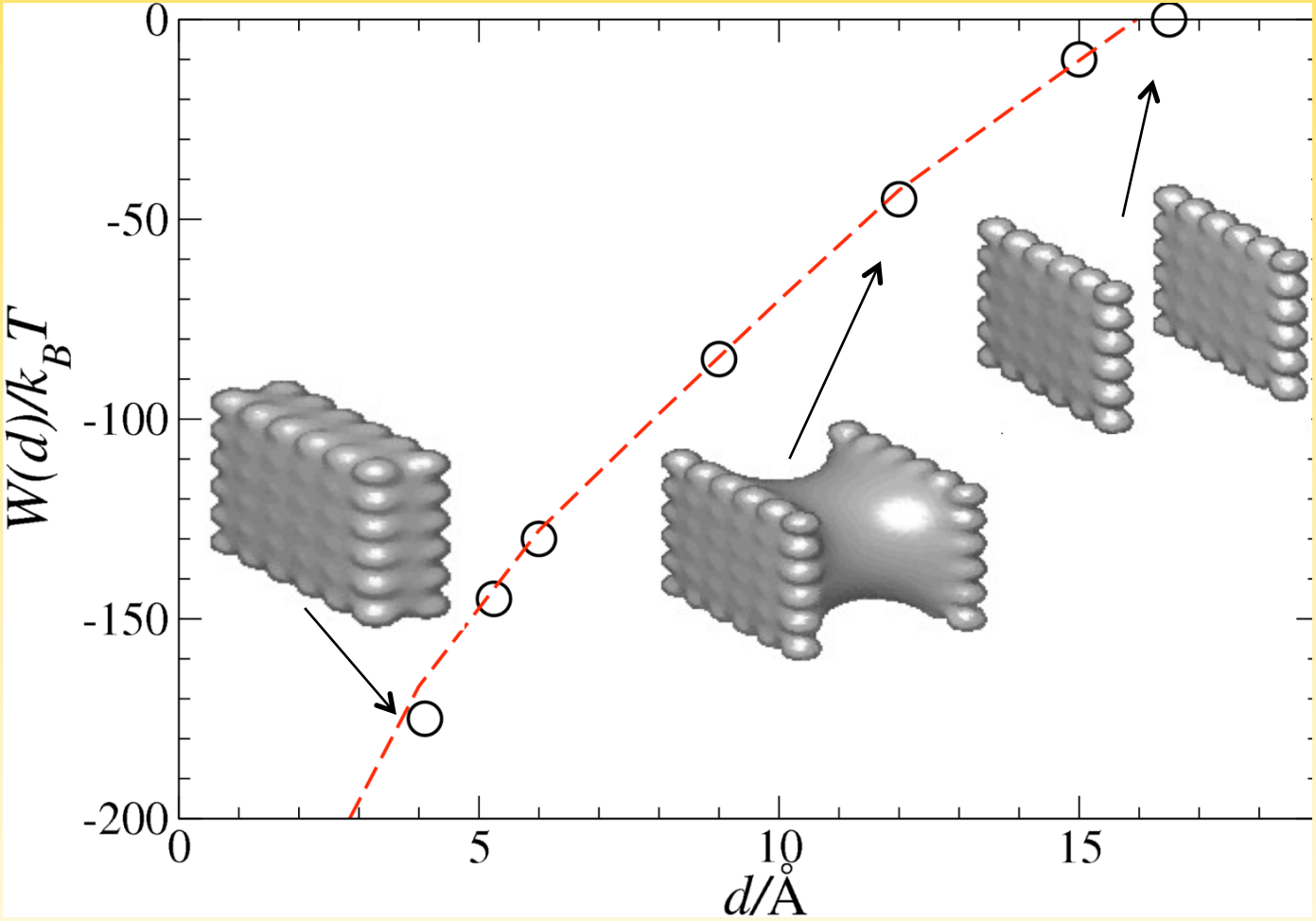
- 4,000 solute atoms, 50x50x50 grid size, a good initial guess ⇨ 5 minutes
- 4,000 solute atoms, high resolution, a bad initial guess ⇨ about 2 – 4 hours
- Dynamics: a different situation

4. Numerical Results



Comparison of PMF by the level-set (circles) and MD (solid line) calculations.

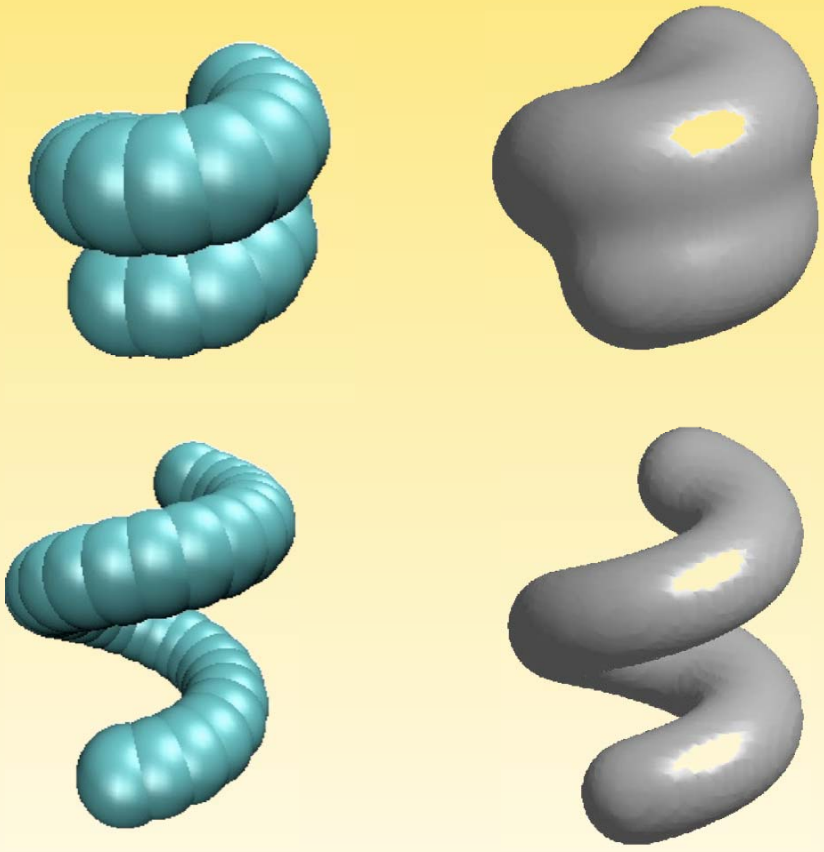
Paschek, J. Chem. Phys., 120, 6674, 2004.



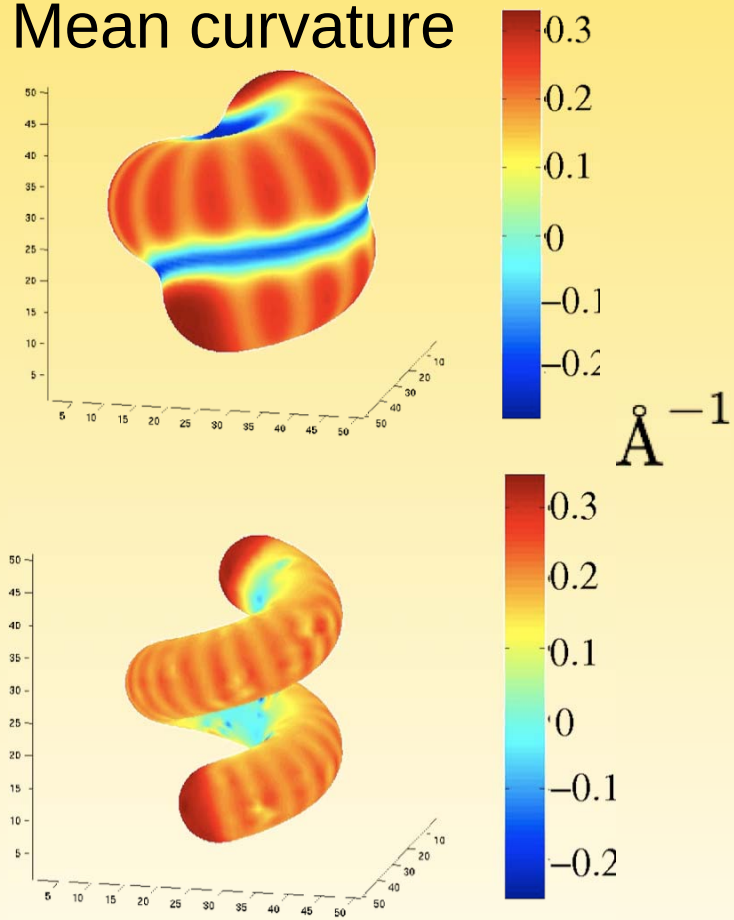
Comparison of the level-set and MD calculations for the two paraffin plates.

MD: Koishi *et al.* Phys. Rev. Lett., 93, 185701, 2004;
J. Chem. Phys., 123, 204707, 2005.

Two helical alkanes (~30 atoms)



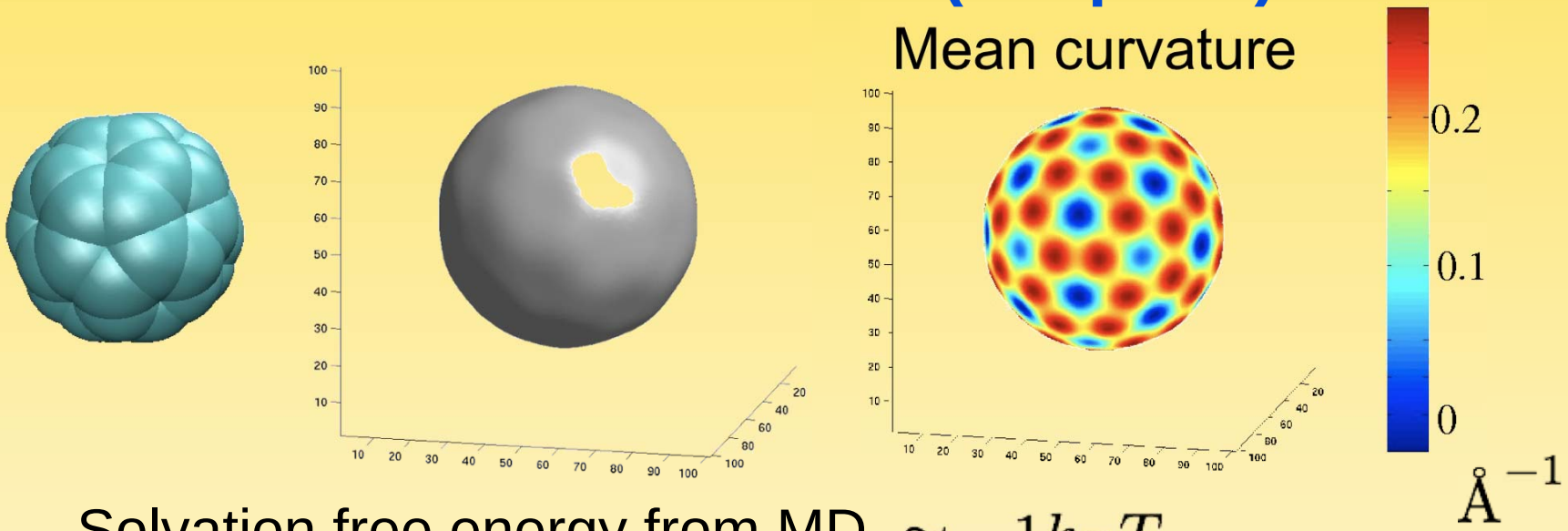
Mean curvature



Parameters: $P = 0, \quad \gamma_0 = 0.176, \quad \tau = 1.2,$

$\rho_w = 0.033, \quad \sigma = 3.538, \quad \varepsilon = 0.2654.$

Solvation of C60 fullerene (nonpolar)



Solvation free energy from MD $\simeq -1 k_B T$

Best fit Tolman length $\tau = 1.2\ \mathring{A}$

<u>Side note: enthalpy-entropy compensation in solvation:</u>

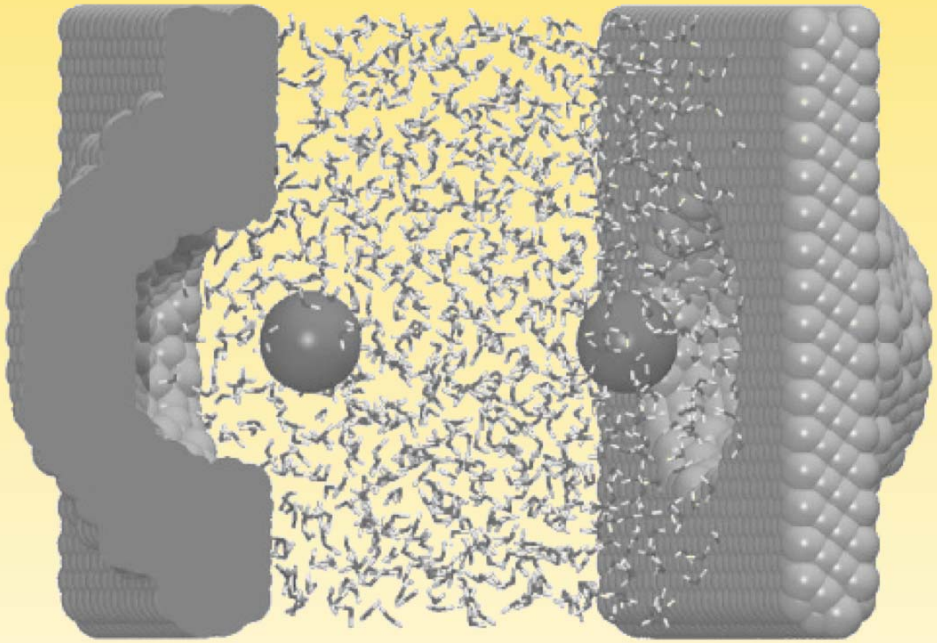
Solvation free energy is a difference of big numbers:

Solvation entropy $\simeq 49 k_B T$

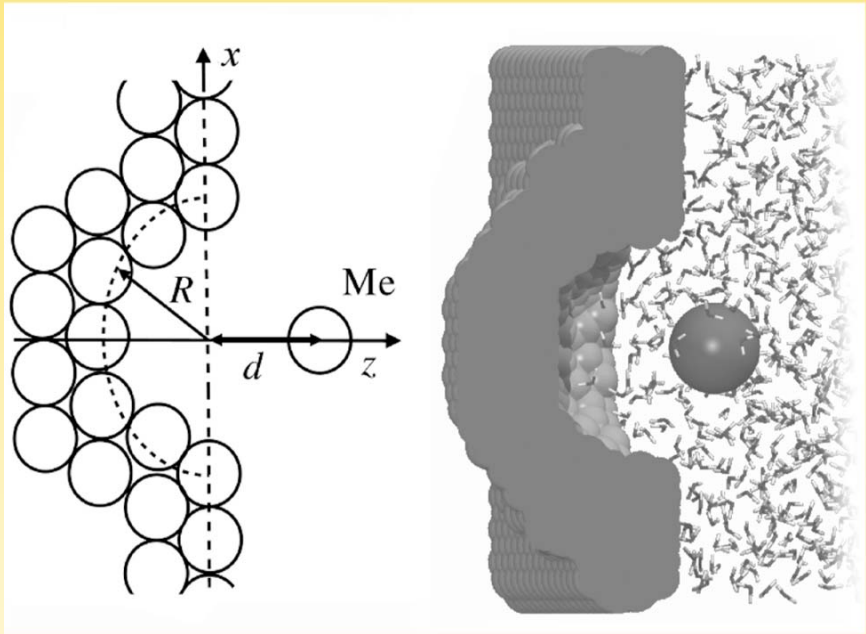
Solvation enthalpy $\simeq -50 k_B T$

A big problem for solvation free-energy calculations!

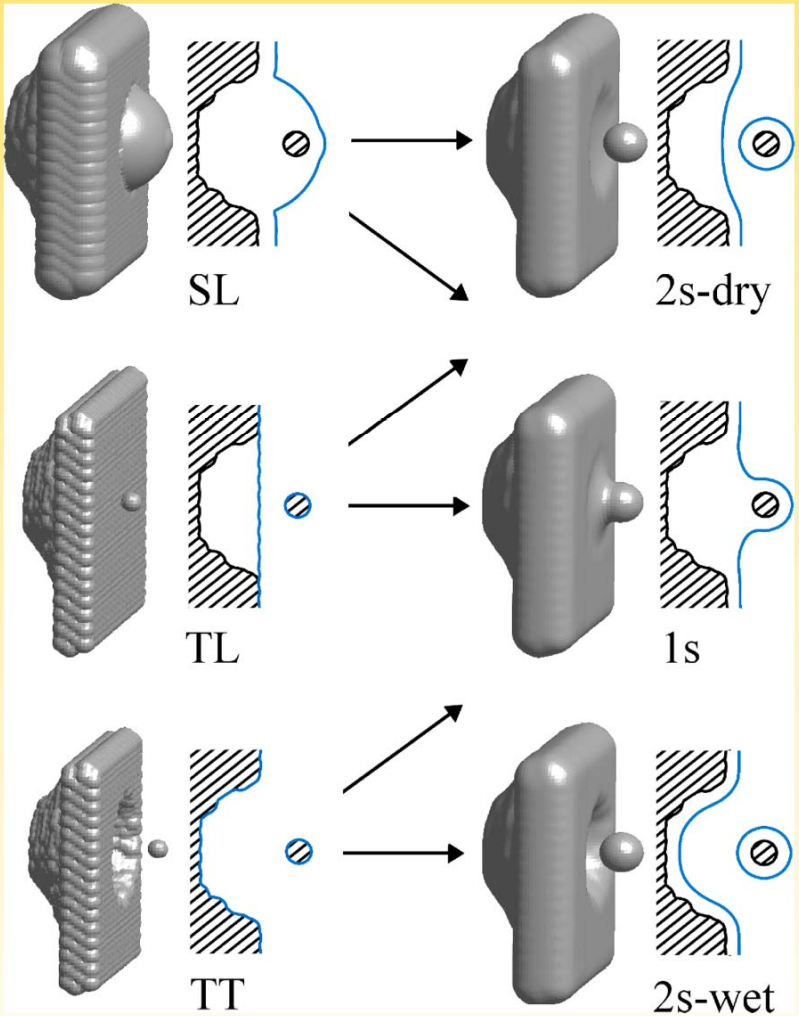
A Hydrophobic receptor-ligand system

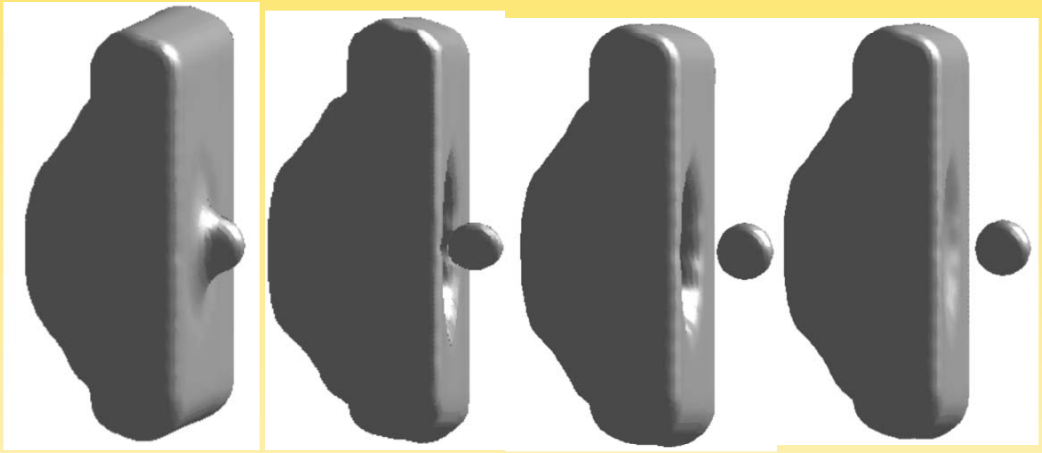


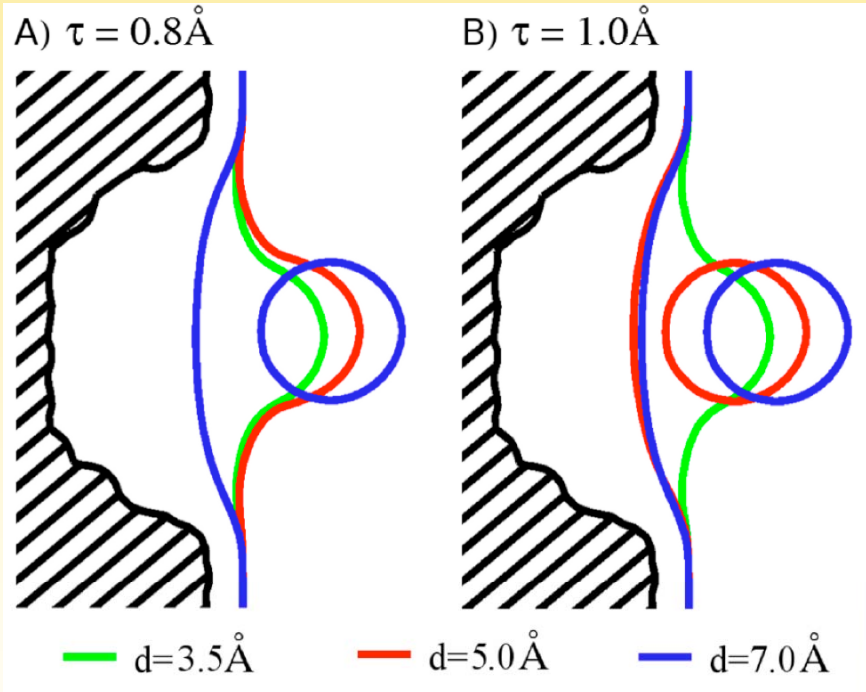
Each wall consists of 4,242 atoms.

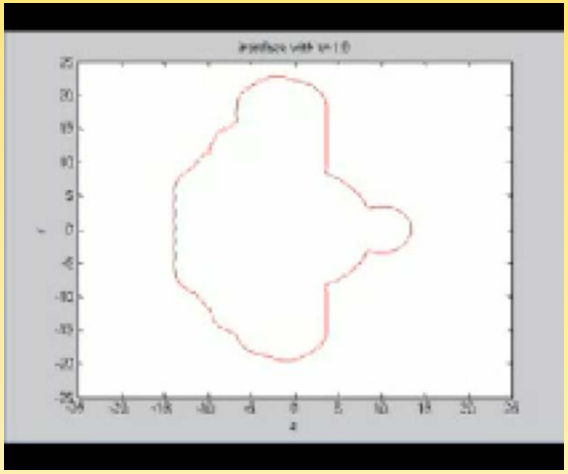


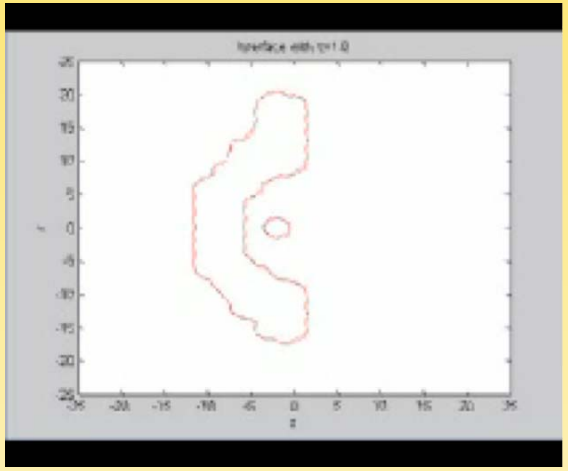
System setup for the level-set VISM calculation.

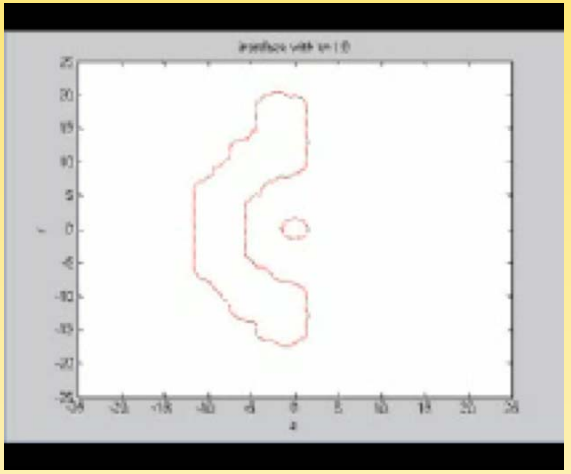

SL
2s-dry
TL
1s
TT
2s-wet

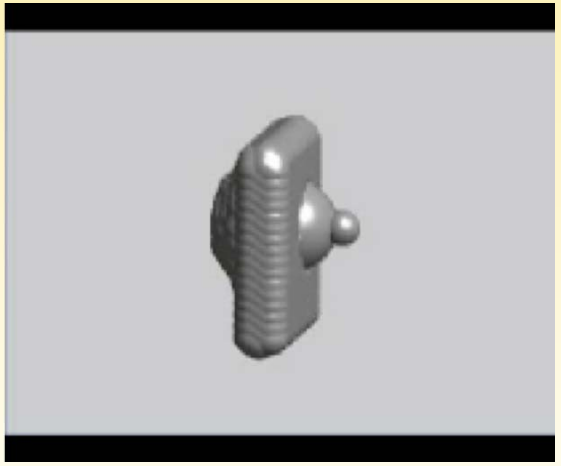


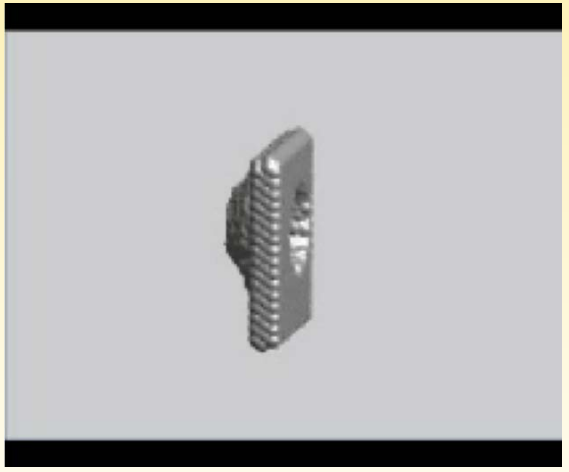

A) τ = 0.8Å
B) τ = 1.0Å
d=3.5Å
d=5.0Å
d=7.0Å

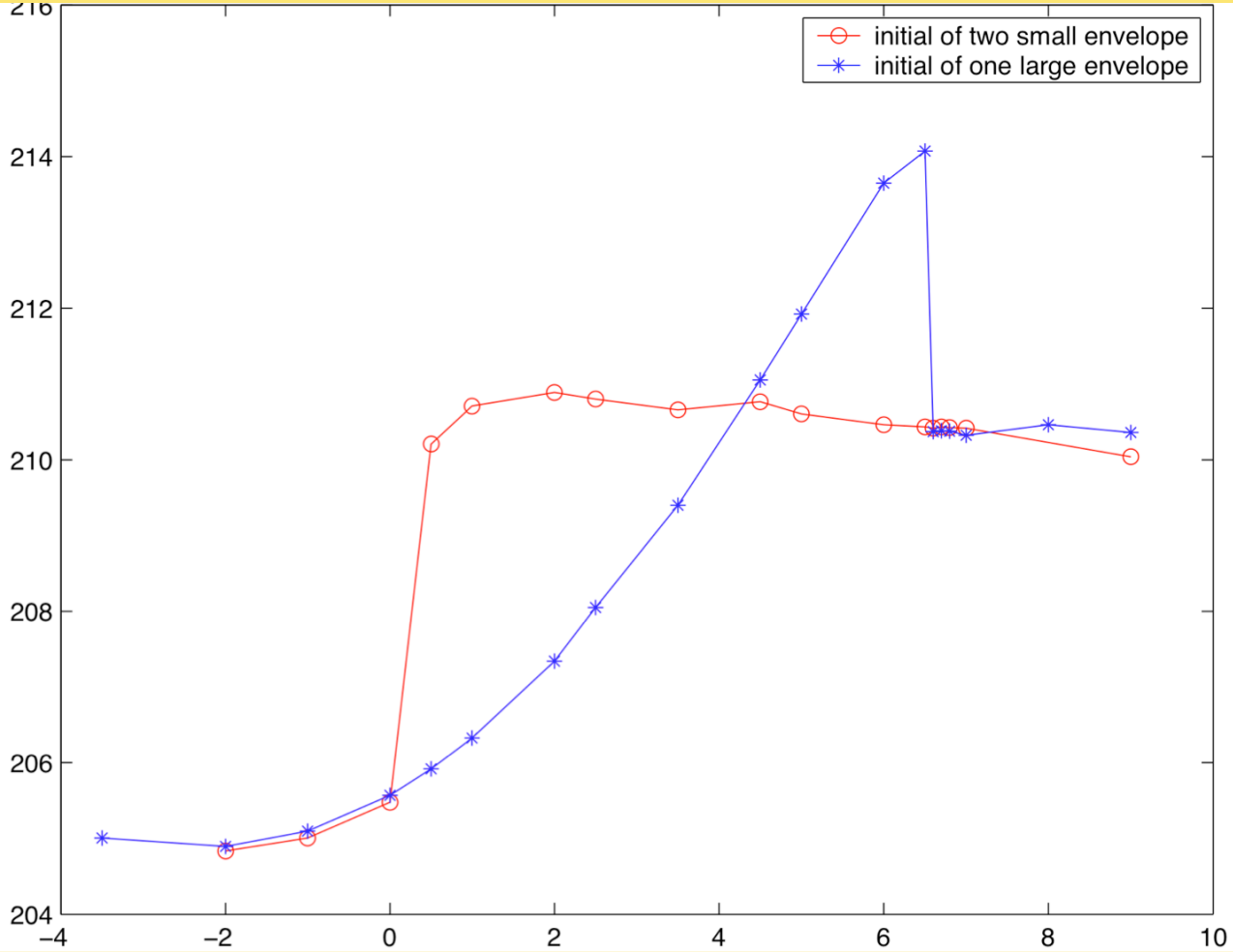






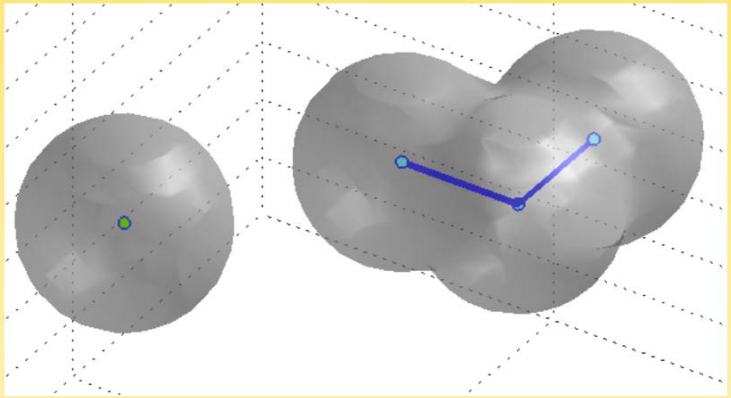


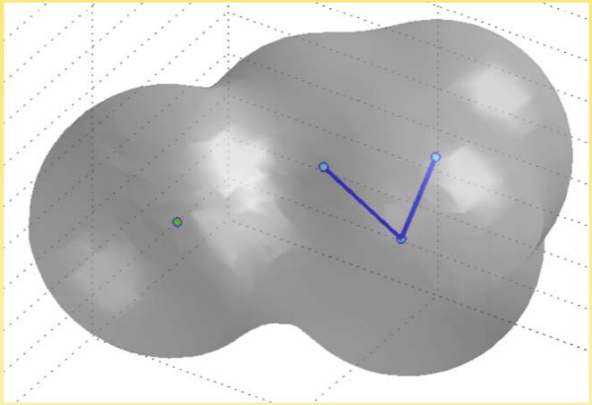




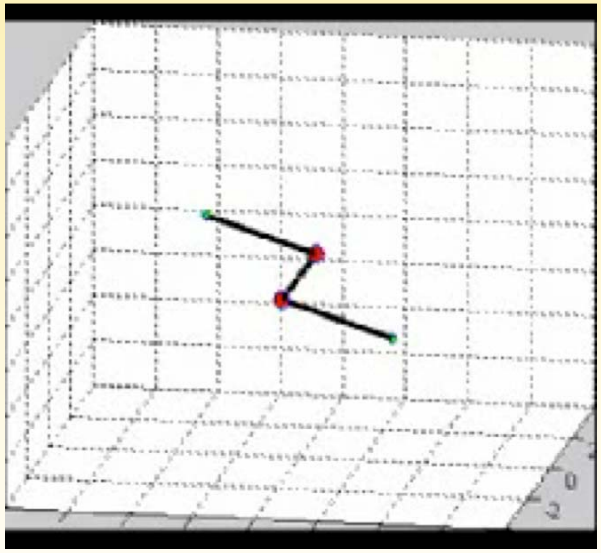
Free energy vs. the distance between ligand and wall: a bimodal behavior.

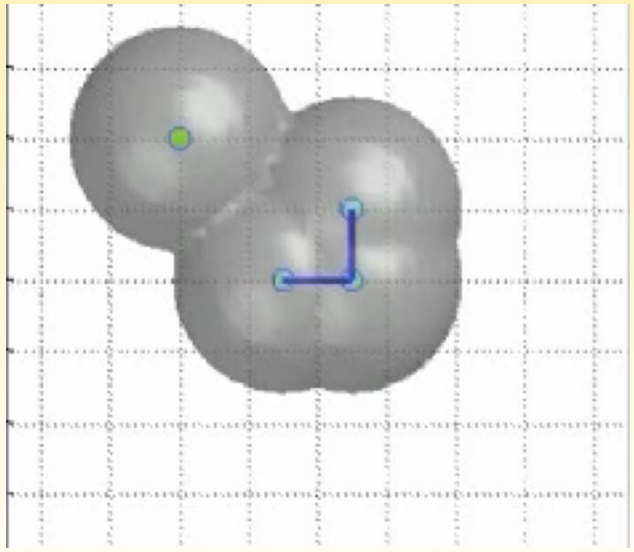
A model system of 4 atoms

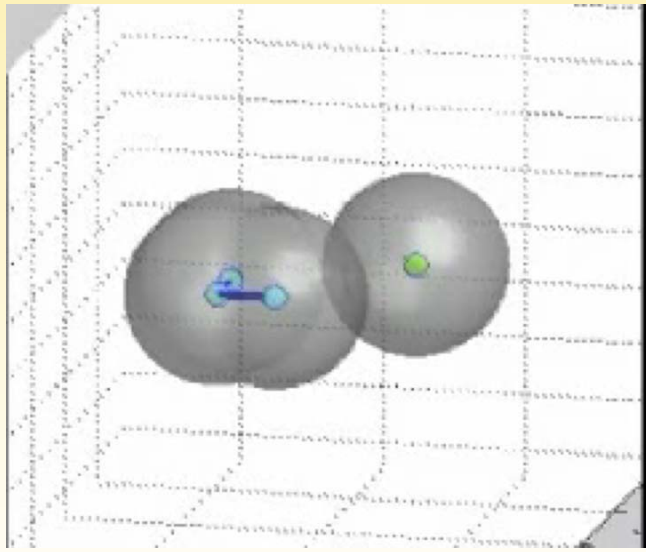




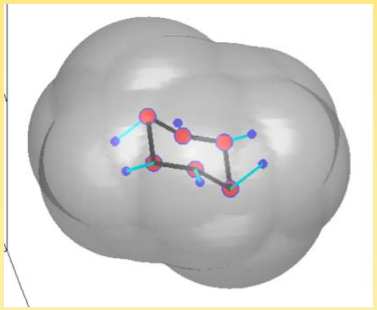
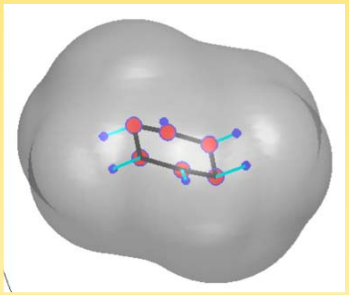
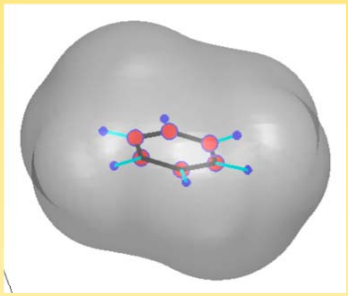
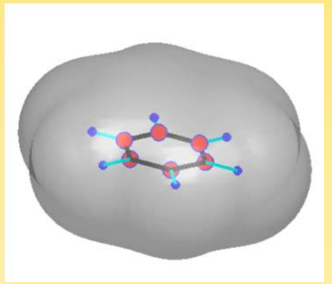
Left: initial positions. Right: final positions.

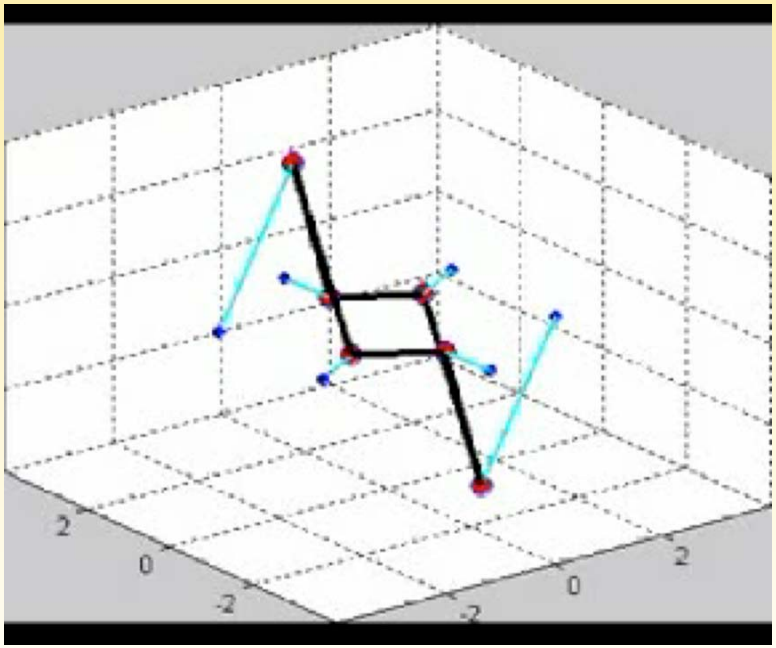


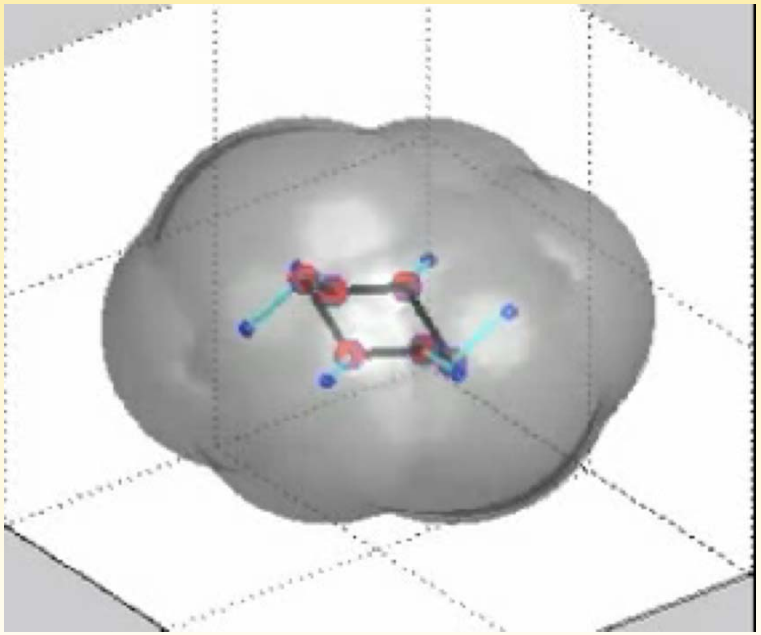




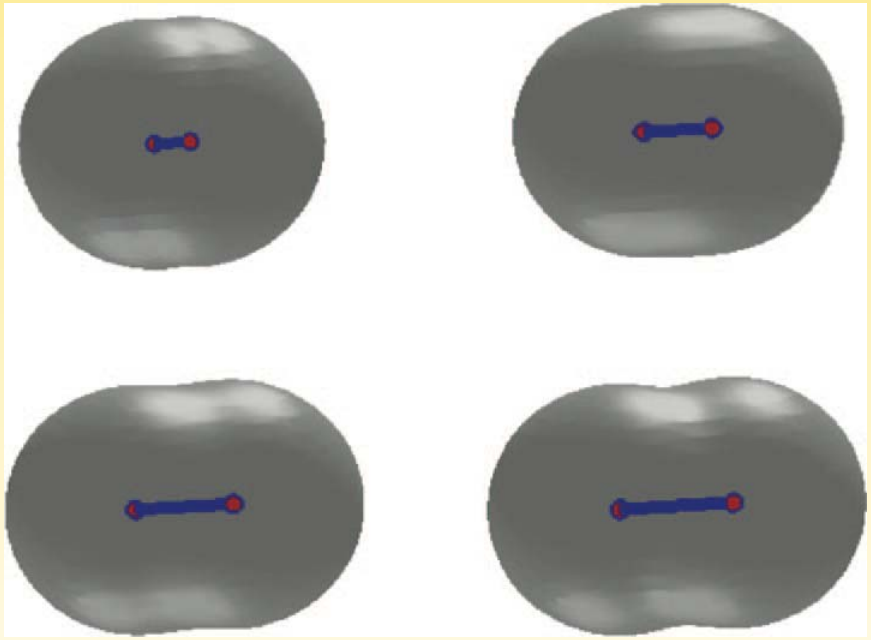
A benzene molecule

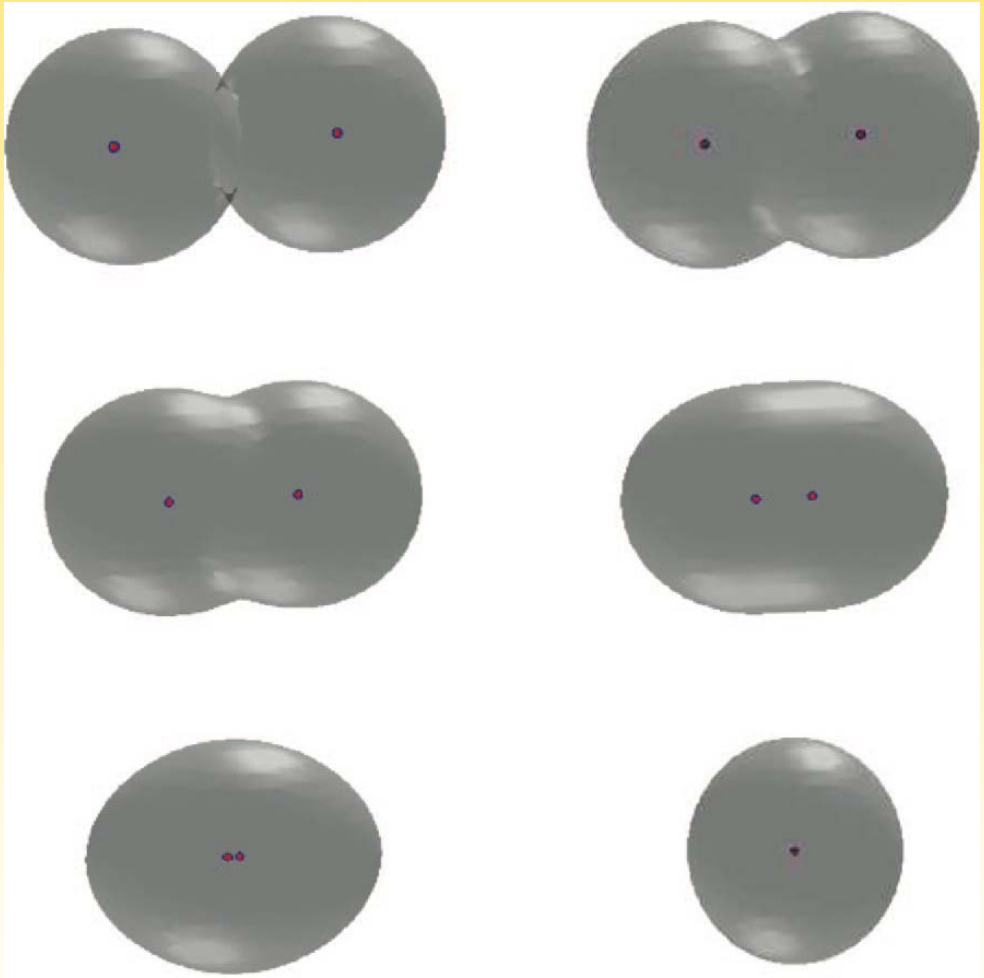









A two-particle system: the surface motion influences the particle motion



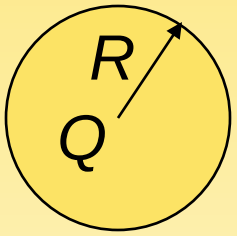


5. Electrostatic Free Energy

The Coulomb-field approximation

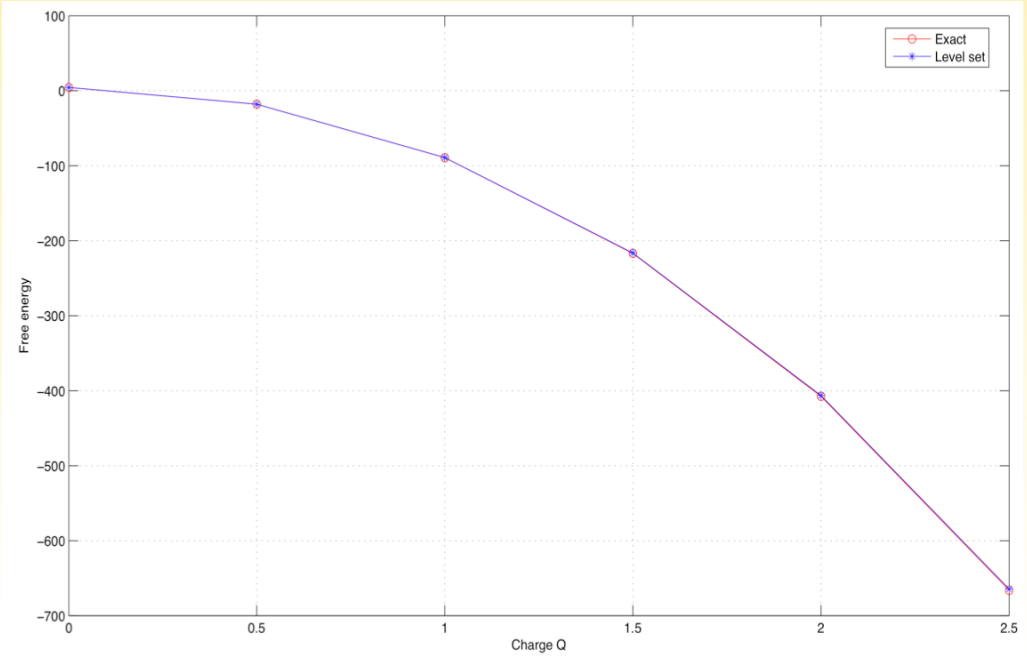
$$G_{elec}[\Gamma] = \frac{1}{32\pi^2\varepsilon_0}\left(\frac{1}{\varepsilon_w} - \frac{1}{\varepsilon_m}\right)\int_{\Omega_w}\left|\sum_{i=1}^{N}\frac{Q_i(\vec{r}-\vec{r}_i)}{|\vec{r}-\vec{r}_i|^3}\right|^2 dV$$

$$\delta_\Gamma G_{elec}[\Gamma](\vec{r}) = -\frac{1}{32\pi^2\varepsilon_0}\left(\frac{1}{\varepsilon_w} - \frac{1}{\varepsilon_m}\right)\left|\sum_{i=1}^{N}\frac{Q_i(\vec{r}-\vec{r}_i)}{|\vec{r}-\vec{r}_i|^3}\right|^2$$



A Single charged particle

$$G(R) = 4\pi(R^2 - 2\tau R) + 16\pi\rho_w\left(\frac{\sigma^{12}}{9R^9} - \frac{\sigma^6}{3R^3}\right) - \frac{Q^2}{8\pi\varepsilon_0}\left(\frac{1}{\varepsilon_m} - \frac{1}{\varepsilon_w}\right)$$



Level-set VISM *vs.* exact solution

The Poisson-Boltzmann (PB) theory

Electrostatic free energy

$$G_{elec}[\Gamma] = \int \left[-\frac{\varepsilon(\vec{r})}{8\pi} |\nabla\psi(\vec{r})|^2 + \rho_f(\vec{r})\psi(\vec{r}) - \beta^{-1}\chi_w \sum_j c_j^{\infty}(e^{\beta q_j \psi(\vec{r})} - 1) \right] dV$$

ψ = electrostatic potential

$$\varepsilon(\vec{r}) = \begin{cases} \varepsilon_m & \text{in solute region } \Omega_m \\ \varepsilon_w & \text{in solvent region } \Omega_w \end{cases}$$

ρ_f = fixed charges of molecular atoms

χ_w = characteristic function of Ω_w

PBE: $$\nabla \cdot \varepsilon(\vec{r})\nabla\psi(\vec{r}) + 4\pi\beta^{-1}\chi_w \sum_j c_j^{\infty} q_j e^{-\beta q_j \psi(\vec{r})} = -4\pi\rho_f(\vec{r})$$

Effective electrostatic surface force

$$\delta_\Gamma G_{elec}[\Gamma](\vec{r}) = \frac{1}{8\pi}\left(\frac{1}{\varepsilon_m} - \frac{1}{\varepsilon_s}\right) | \varepsilon(\vec{r})\nabla\psi(\vec{r}) |^2 - \beta^{-1}\sum_j c_j^\infty (e^{\beta q_j \psi(\vec{r})} - 1)$$

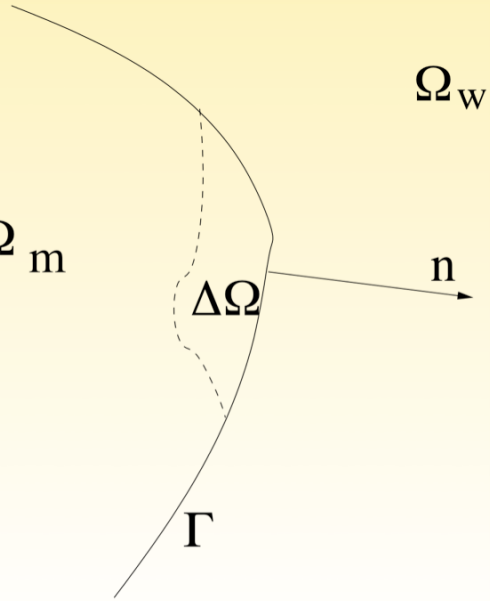
Charge neutrality, convexity, and Jensen's inequality

$\Rightarrow$ $\delta_\Gamma G_{elec}[\Gamma] > 0$ Force attractive to solutes!

See: B. Chu, Molecular Forces, Wiley, 1967.

Lemma

$$\int (\delta_{\Gamma,z} u_\Gamma) v dV = (u_m - u_w) v(z)$$



Electrostatic free-energy functional of ionic concentratios

$$G[c] = \int_\Omega \left\{ \frac{1}{2}\rho\psi + \beta^{-1} \sum_{j=1}^{M} c_j \left[\ln(\Lambda^3 c_j) - 1 \right] - \sum_{j=1}^{M} \mu_j c_j \right\} dV$$

$$\rho(x) = \rho_f(x) + \sum_{j=1}^{M} q_j c_j(x)$$

$$\nabla \cdot \varepsilon_0 \varepsilon \nabla \psi = -4\pi \left(\rho_f + \sum_{j=1}^{M} q_j c_j \right)$$

$+$ Boundary Conditions (e.g., $\psi = 0$ on $\partial\Omega$)

- Λ : the thermal de Broglie wavelength
- μ_j: chemical potential for the jth ionic species

Equilibrium conditions

$$(\delta G[c])_j = q_j\psi + \beta^{-1} \ln(\Lambda^3 c_j) - \mu_j = 0 \iff \text{Boltzmann distributions}$$

Minimum electrostatic free-energy

$$G_{min} = \int_\Omega \left[-\frac{\varepsilon_0 \varepsilon}{8\pi} |\nabla\psi|^2 + \rho_f \psi - \beta^{-1} \sum_{j=1}^{M} c_j^\infty \left(e^{-\beta q_j \psi} - 1 \right) \right] dV$$

Theorem (B.L. 2009).

- The functional G has a unique minimizer $c = (c_1, \ldots, c_M)$ which is also the unique equilibrium.
- There exist constants $\theta_1 > 0$ and $\theta_2 > 0$ such that
$$\theta_1 \leq c_j(x) \leq \theta_2 \qquad \forall x \in \Omega \; \forall j = 1, \ldots, M.$$
- The equilibrium concentrations and corresponding potential are related by the Boltzmann distributions.
- The corresponding potential is the unique solution to the PBE.

Remark. Bounds are not physical! A drawback of the PB theory.

Proof. By the direct method in the calculus of variations, using:

- Convexity.
$$G[\lambda u + (1-\lambda)v] \leq \lambda G[u] + (1-\lambda)G[v] \quad (0 < \lambda < 1);$$
- Lower bound. Let $\alpha \in \mathbb{R}$. Then the function $s \mapsto s(\ln s + \alpha)$ is bounded below on $(0, \infty)$;
- A lemma (cf. next slide). **Q.E.D.**

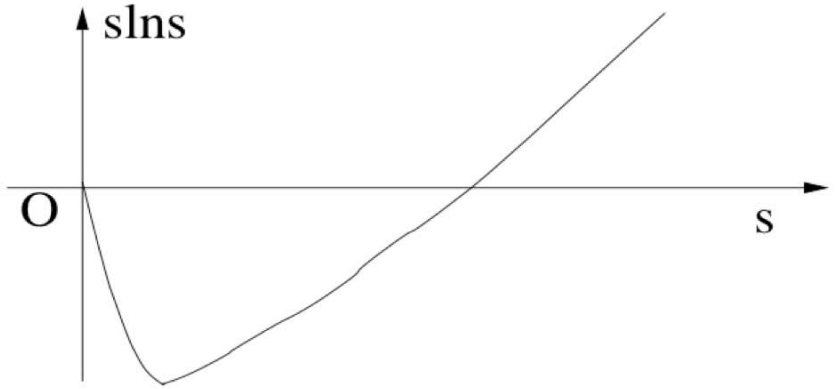
$$G[c] = \int_\Omega \left\{ \frac{1}{2}\rho\psi + \beta^{-1} \sum_{j=1}^{M} c_j \left[\ln(\Lambda^3 c_j) - 1 \right] - \sum_{j=1}^{M} \mu_j c_j \right\} dV$$

Lemma (B.L. 2009). Given $c = (c_1, \ldots, c_M)$. There exists $\hat{c} = (\hat{c}_1, \ldots, \hat{c}_M)$ that satisfies the following:

- $\hat{c}$ is close to c;
- $G[\hat{c}] \leq G[c]$;
- there exist constants $\theta_1 > 0$ and $\theta_2 > 0$ such that

$$\theta_1 \leq \hat{c}_j(x) \leq \theta_2 \qquad \forall x \in \Omega \; \forall j = 1, \ldots, M.$$

Proof. By construction using the fact that the entropic change is very large for $c_j \approx 0$ and $c_j \gg 1$. **Q.E.D.**



Electrostatic free-energy functional

$$G[c] = \int_\Omega \left\{ \frac{1}{2}\rho\psi + \beta^{-1} \sum_{j=0}^{M} c_j \left[\ln(a_j^3 c_j) - 1 \right] - \sum_{j=1}^{M} \mu_j c_j \right\} dV$$

$$\rho(x) = \rho_f(x) + \textstyle\sum_{j=1}^{M} q_j c_j(x)$$

$$\nabla \cdot \varepsilon_0 \varepsilon \nabla \psi = -4\pi \left(\rho_f + \textstyle\sum_{j=1}^{M} q_j c_j \right)$$

$+$ Boundary Conditions (e.g., $\psi = 0$ on $\partial\Omega$)

$$c_0(x) = a_0^{-3} \left[1 - \textstyle\sum_{i=1}^{M} a_i^3 c_i(x) \right]$$

- a_j $(1 \le j \le M)$: linear size of ions of jth species
- a_0: linear size of a solvent molecule
- c_0: local concentration of solvent

Remark. $G[c]$ is convex in $c = (c_1, \ldots, c_M)$.

Theorem (B.L. 2009). The functional G has a unique minimizer $(c_1, \ldots, c_M)$ which is also the unique local minimizer. It is characterized by the following two conditions:

- *Bounds.* There exist $\theta_1, \theta_2 \in (0,1)$ such that

$$\theta_1 \leq a_j^3 c_j(x) \leq \theta_2 \qquad \forall x \in \Omega \; \forall j = 0, 1, \ldots, M;$$

- *Equilibrium conditions* (i.e.,$(\delta G[c])_j = 0$ for $j = 1, \ldots, M$)

$$\left(\frac{a_j}{a_0}\right)^3 \log\left(a_0^3 c_0\right) - \log\left(a_j^3 c_j\right) = \beta\left(q_j \psi - \mu_j\right) \quad \forall j = 1, \ldots, M.$$

Proof. Similar to the case without size modification. **Q.E.D.**

Remark. The bounds are non-physical microscopically!

Lemma (B.L. 2009). Given $c = (c_1, \ldots, c_M)$. There exists $\hat{c} = (\hat{c}_1, \ldots, \hat{c}_M)$ that satisfies the following:

- $\hat{c}$ is close to c;
- $G[\hat{c}] \leq G[c]$;
- there exist θ_1 and θ_2 with $0 < \theta_1 < \theta_2 < 1$ such that

$$\theta_1 \leq a_j^3 \hat{c}_j(x) \leq \theta_2 \qquad \forall x \in \Omega \; \forall j = 0, 1, \ldots, M.$$

Proof. By construction in two steps. First, take care of c_0. Then, take care of c_j $(j = 1, \ldots, M)$. **Q.E.D.**

6. Conclusions

- Variational implicit-solvent model
  - Coupling polar and nonpolar interactions
  - Capturing hydrophobic cavities
  - Curvature correction
- Extension
  - Coupling with molecular mechanics
  - Electrosttic surface forces
- A level-set method for variational solvation
  - Capturing hydrophobic cavities
  - New level-set techniques

- Poisson-Boltzmann theory
  - Mathematical analysis: bounds
  - Extension to include the excluded volume effect
- Further development
  - Coupling the PB and level-set calculations
  - Stochastic level-set VISM
  - Solvent dynamics: Rayleigh-Plesset equation
  - Multiscale modeling and simulation
- Mathematical problems
  - Derivation of the free-energy functional
  - Constrained motion by mean curvature

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Thank You !