Level-Set Variational Implicit-Solvent Modeling of Molecular Solvation

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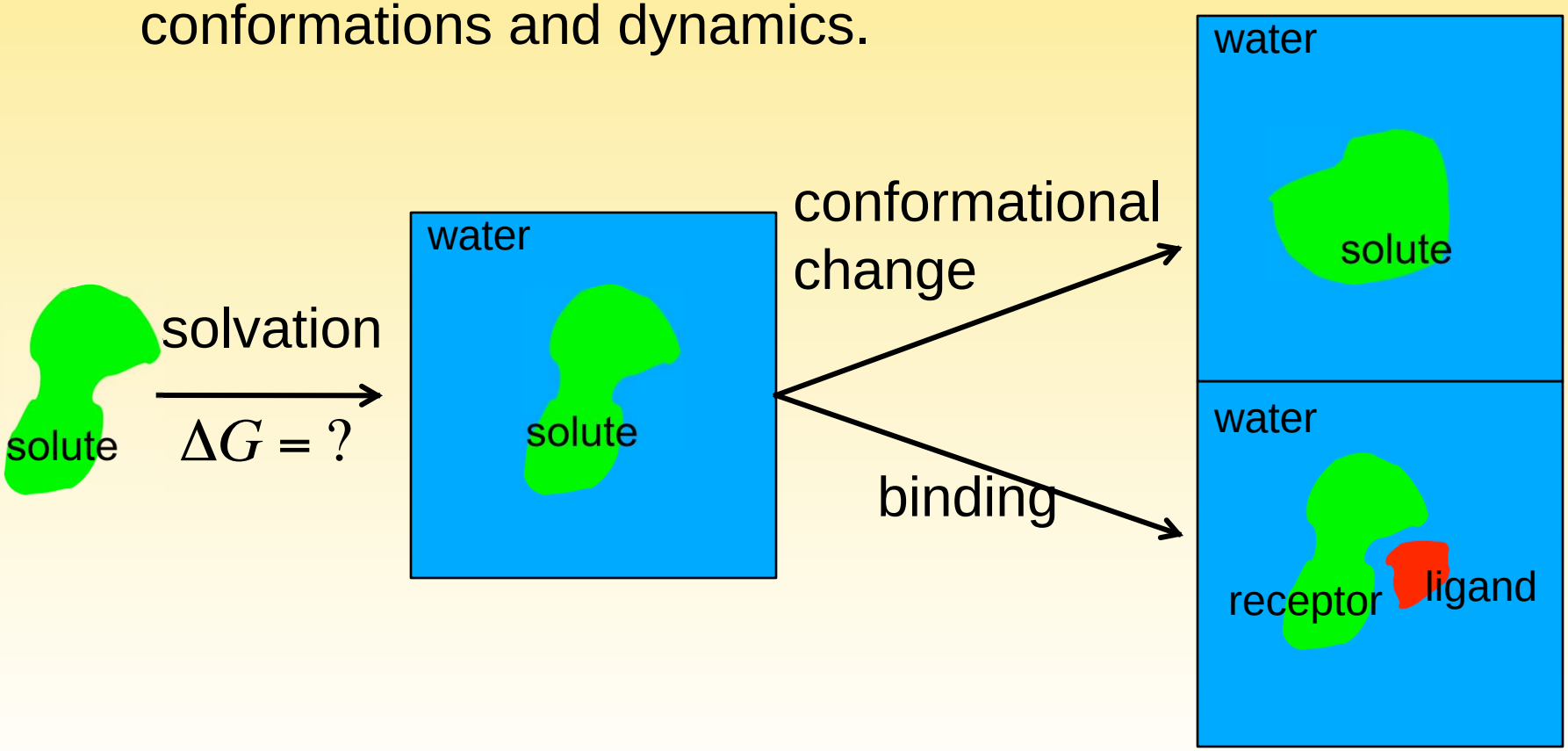
OUTLINE

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

1. Introduction

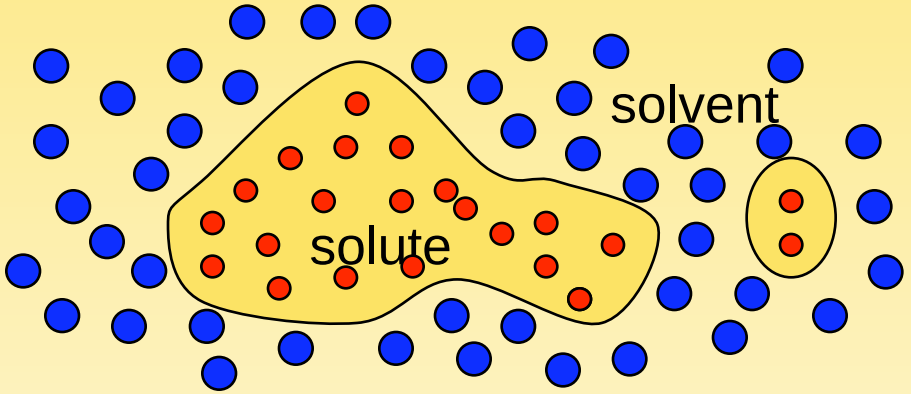
Basic facts

- Biological processes such as molecular recognition and protein folding occur in solution.
- Solute-solvent interactions are crucial in determining solvation free energies, and hence bimolecular conformations and dynamics.

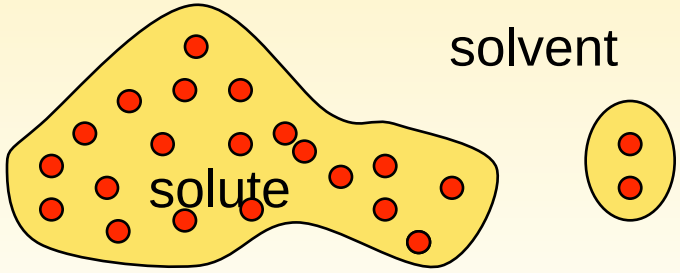


Explicit solvent vs. implicit solvent

- Explicit solvent: solvent atoms treated explicitly (e.g., MD).
  - First principle
  - Accurate
  - Small systems
  - Statistics



- Implicit (or continuum) solvent: solvent atoms treated implicitly; and solvent effects are coarse-grained.
  - Mean-field approximation
  - Efficient
  - Large systems
  - Thermodynamics

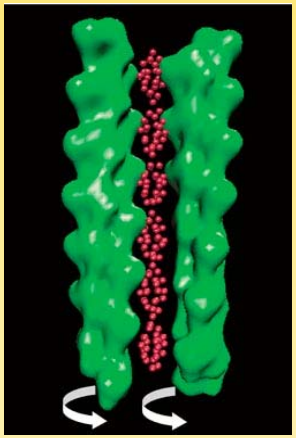


Main interactions in implicit solvation

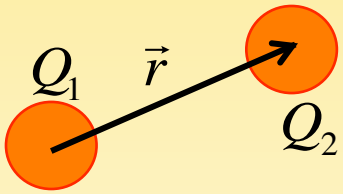
- **Electrostatic interactions**

  Fundamental, many-body, long-range.

  Solvent mediated like-charge attractions.



Angelini *et al.,* PNAS, **100,** 8634 (2003)

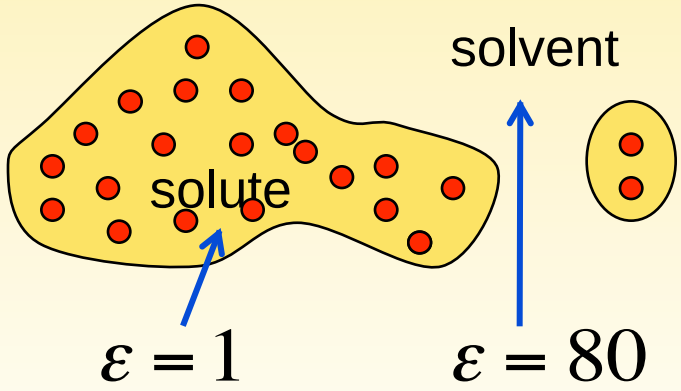


Coulomb's law: $\vec{F} = \frac{1}{4\pi\varepsilon_0}\frac{Q_1 Q_2}{r^3}\vec{r}$

Poisson's equation:

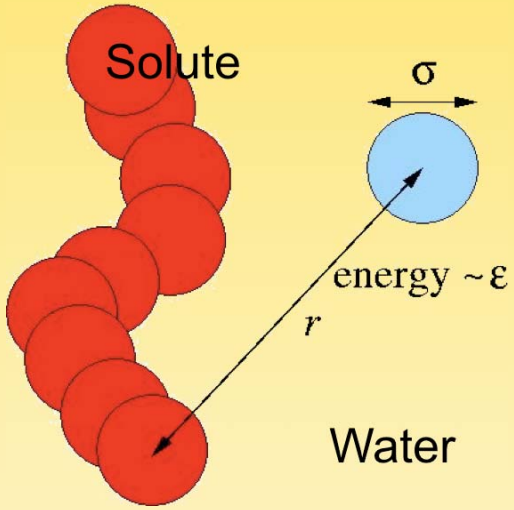
$$-\nabla \cdot \varepsilon\varepsilon_0 \nabla\psi = \rho$$

local dielectric screening by water



With counterions and salt:
The Poisson-Boltzmann (PB) equation.

Excluded volume and van der Waals dispersion



The van der Waals (vdW) equation

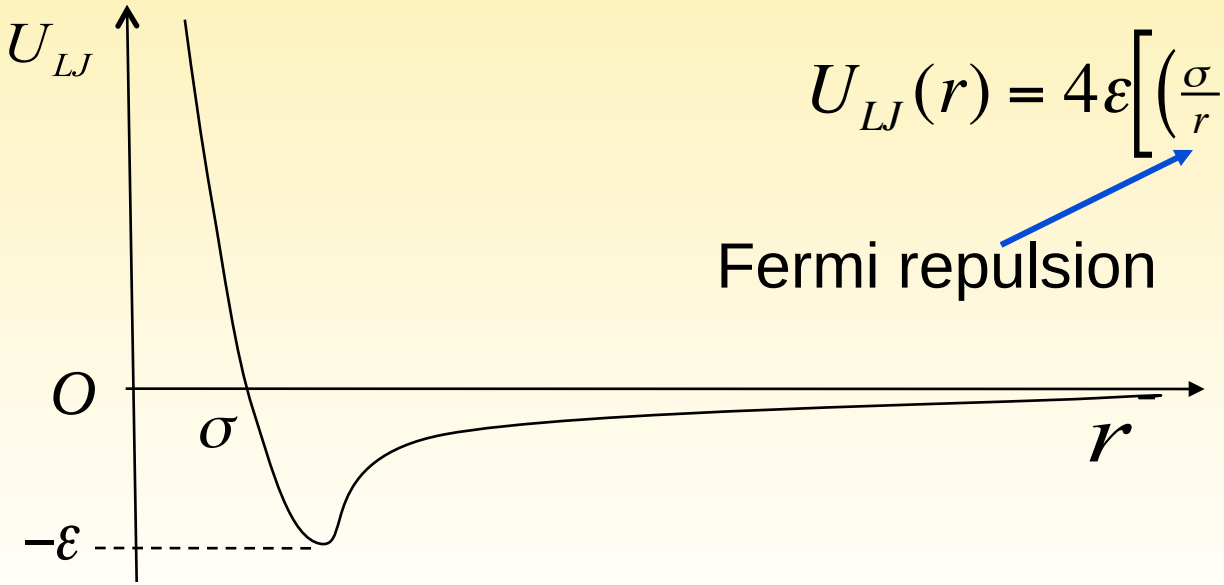
$$\left[P + a\left(\frac{n}{V}\right)^2\right]\left(\frac{V}{n} - b\right) = RT$$

attraction excluded volume

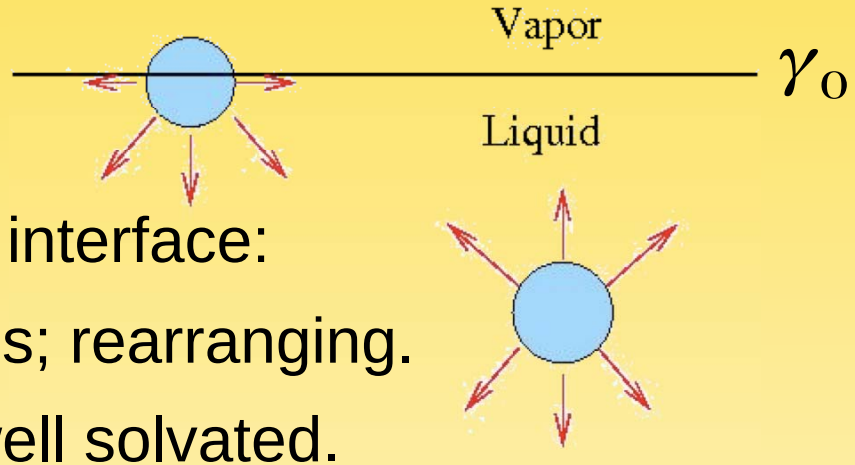
The Lennard-Jones (LJ) potential

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

Fermi repulsion vdW attraction



Hydrophobic interactions

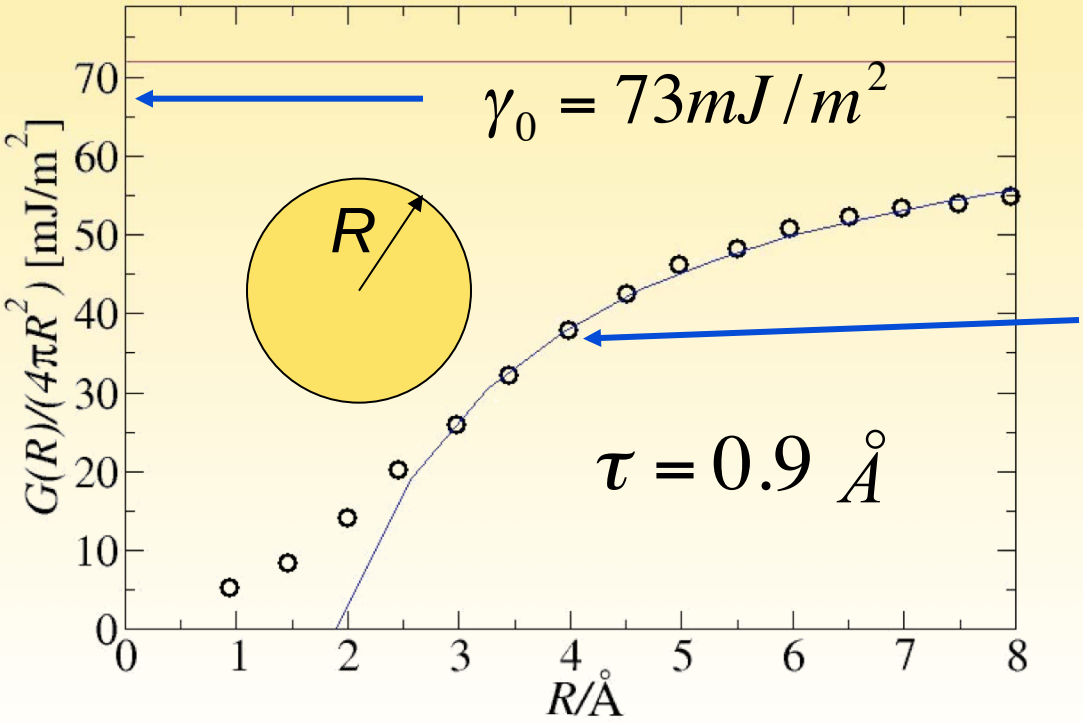


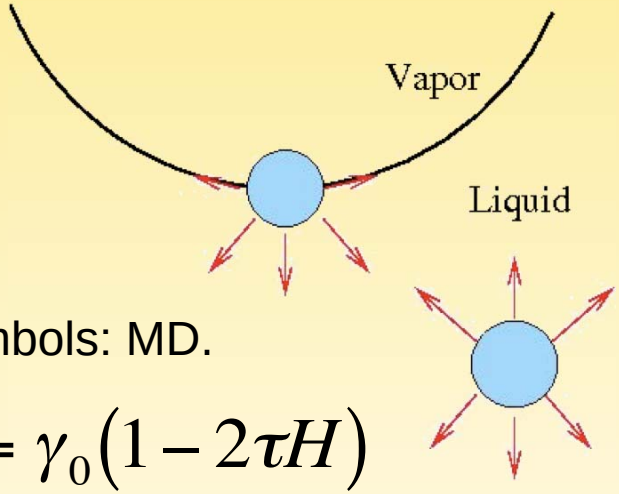
Water does not like to be at an interface:

missing attractive interactions; rearranging.

A hydrophobic particle is not well solvated.

Curvature effects at small cales





Symbols: MD.

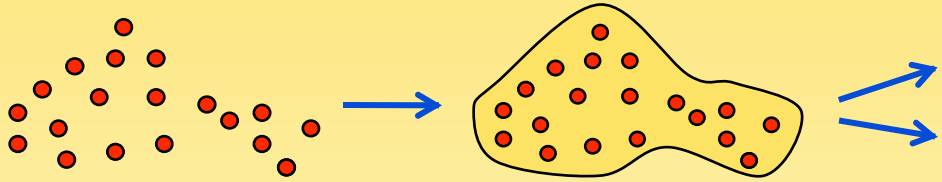
$$\gamma = \gamma_0(1 - 2\tau H)$$

τ : the Tolman length

H : mean curvature

Huang *et al.*, J. Chem. Phys. B **105**, 6704 (2001).

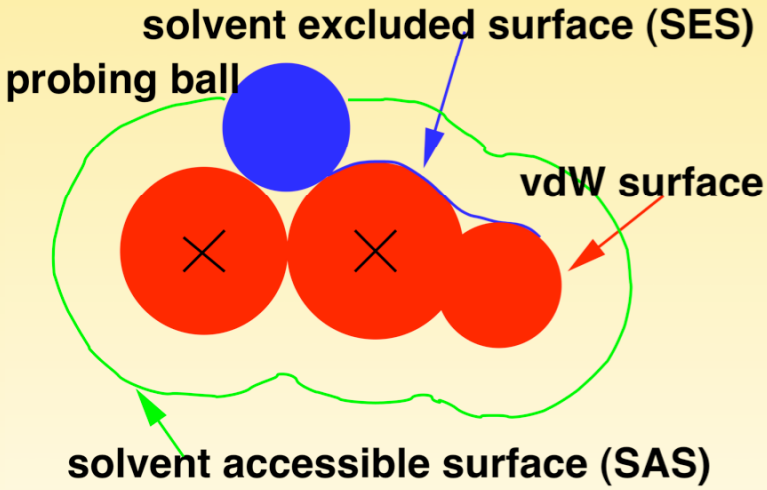
Commonly used implicit-solvent models



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.

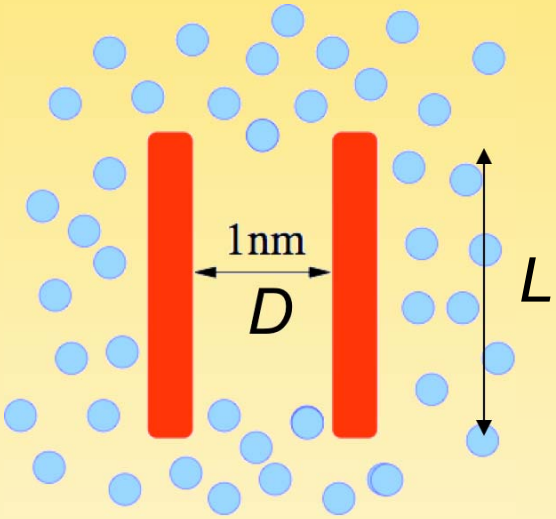


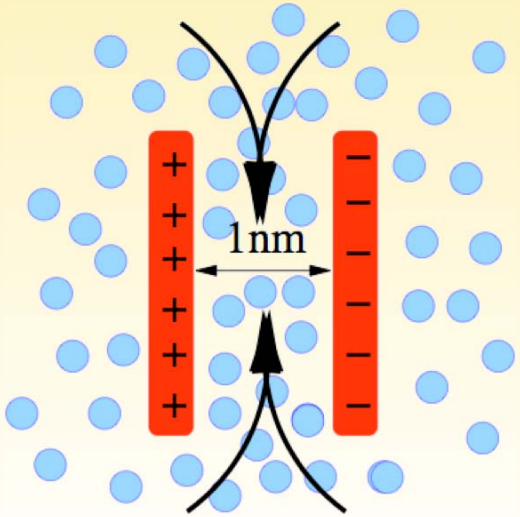
$$G = G_{np} + G_p$$

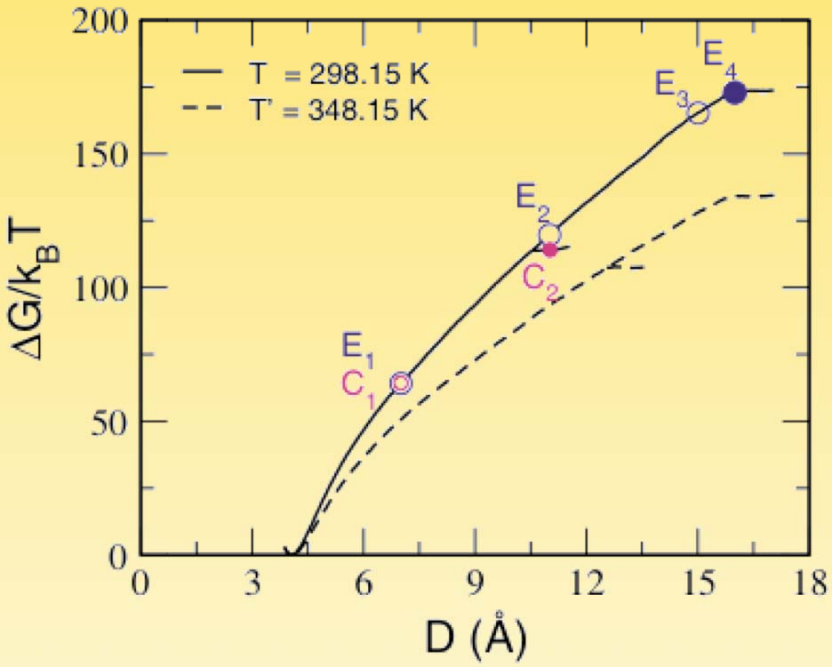
$$G_{np} = \sum_{i}^{\text{solute atoms}} a_i S_i + b_i + PV + G_{\text{vdw}}$$

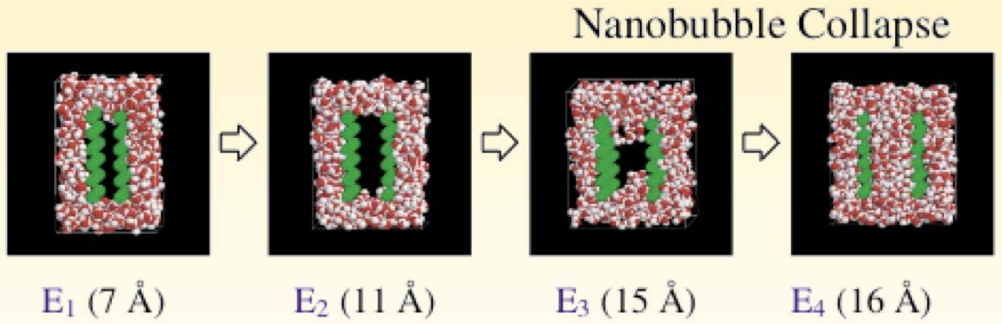
(S_i: Surface area)

Example 1. Capillary evaporation in hydrophobic confinement.





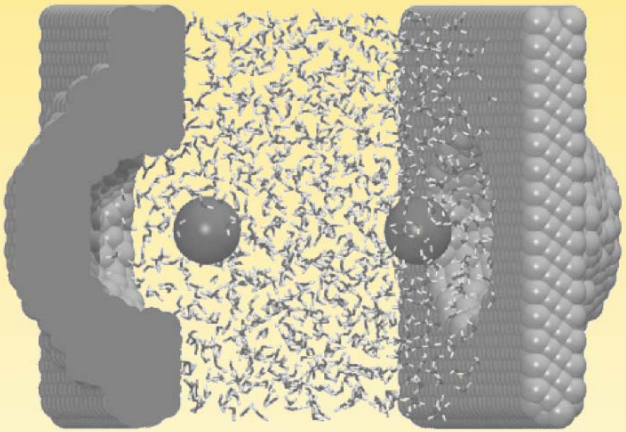




Koishi *et al.*, Phys. Rev. Lett. **93,** 185791 (2004).

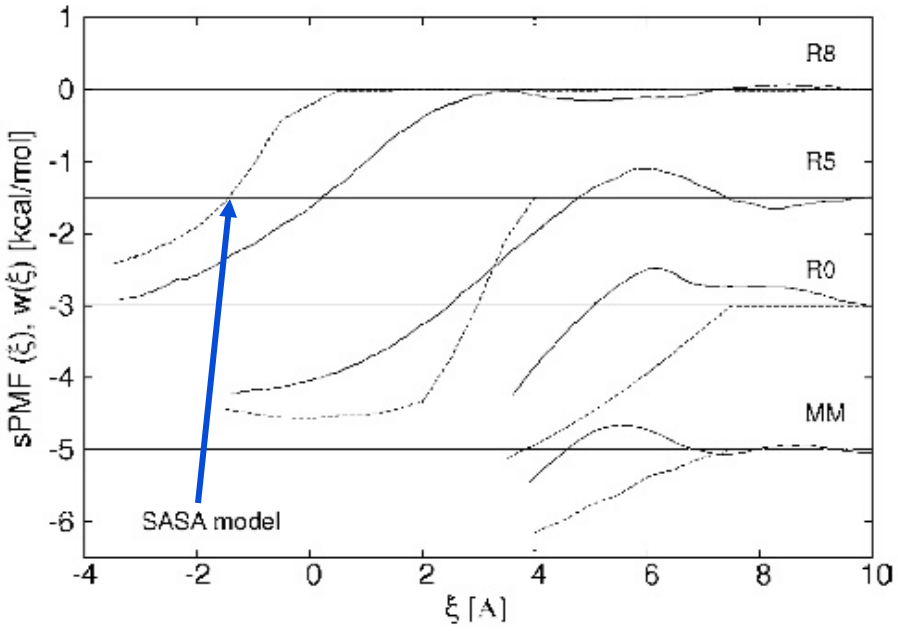
Example 2. A receptor-ligand (pocket wall-methane atom) system.

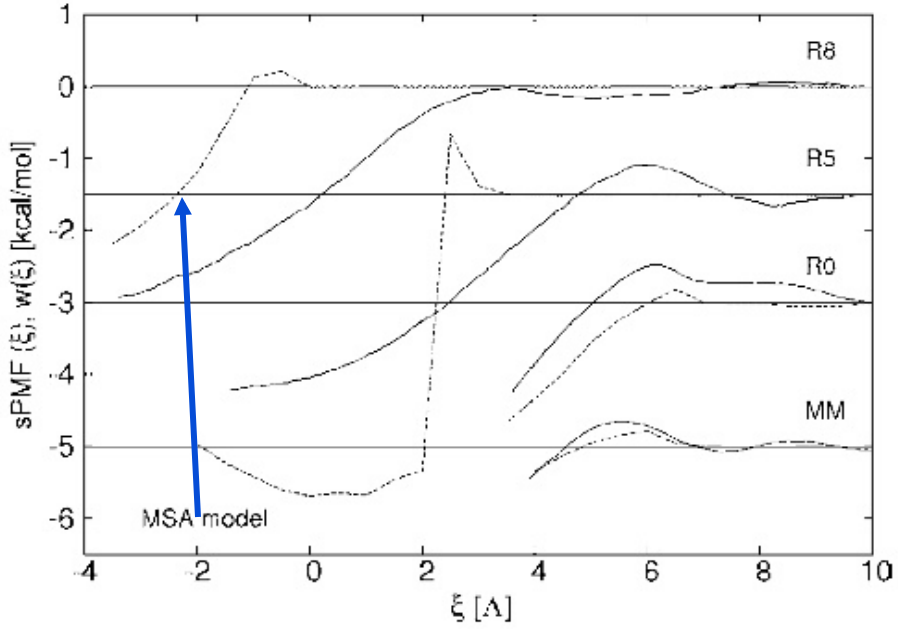
Setny, J. Chem. Phys. **127**, 054505 (2007).



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

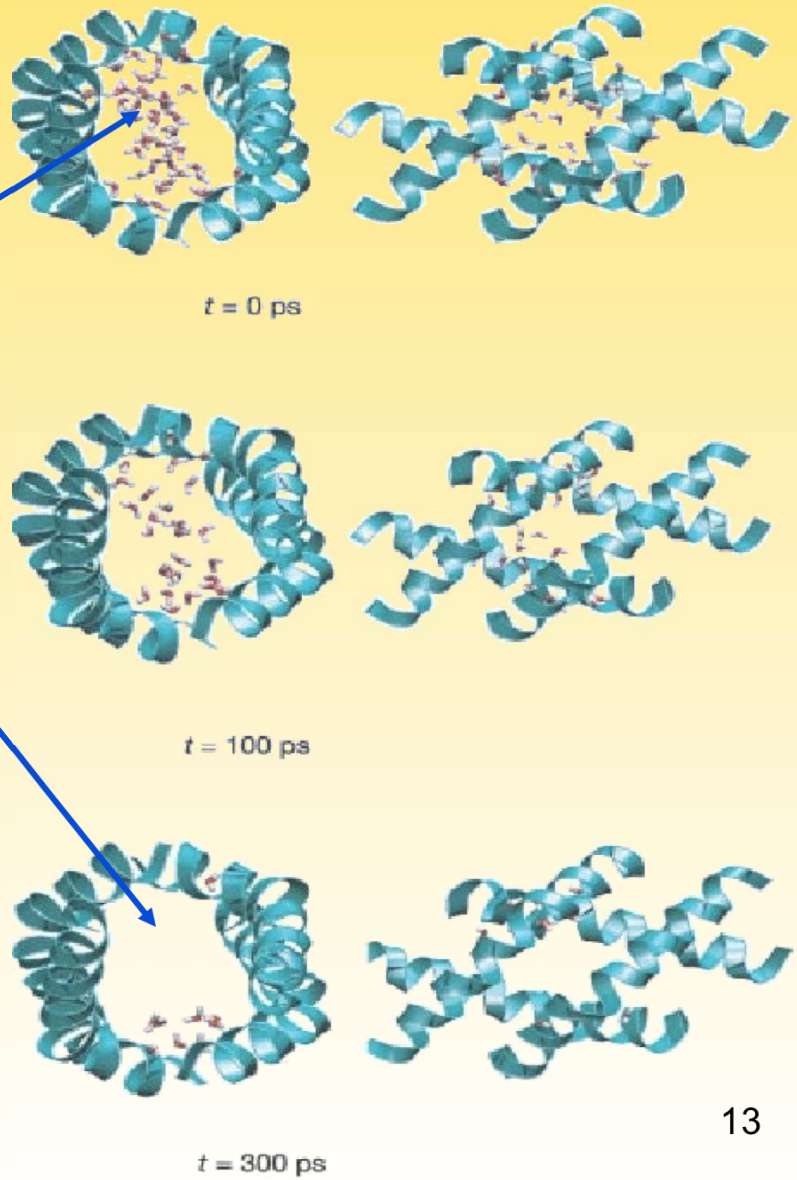
- Water in hydrophobic core
- Stable nanobubble

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

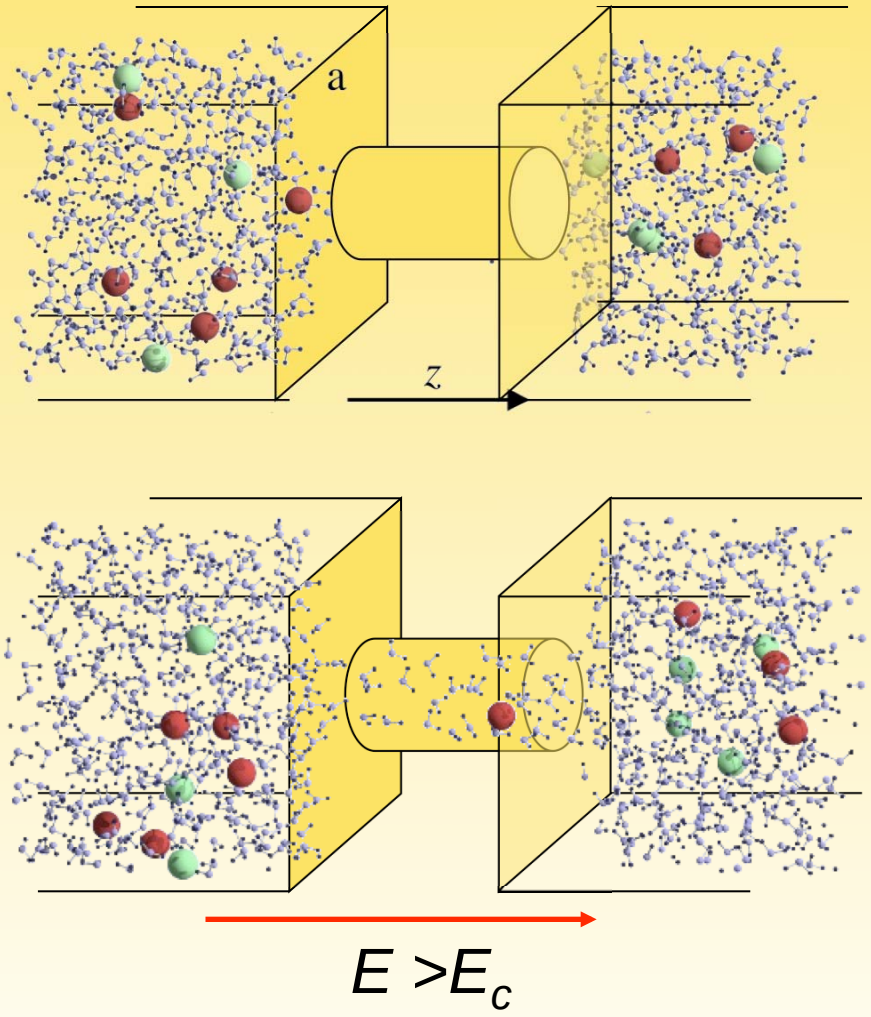
More MD simulations

- Electrostatics
- Curvature

Giovambattista *et al.,* PNAS, **105**, 2274 (2008).
Wang, Friesner, & Berne, J. Phys. Chem. B, **114**, 7294 (2010).



Example 4. Evaporation in hydrophobic channels



Pore length ~ 1nm
Pore radius ~ 0.5nm

MD: a narrow hydrophobic pore can be empty of water:

Nanobubble blocks ion permeation!

But: pore fills when a critical electric field ($E>E_c$) is applied across the pore:

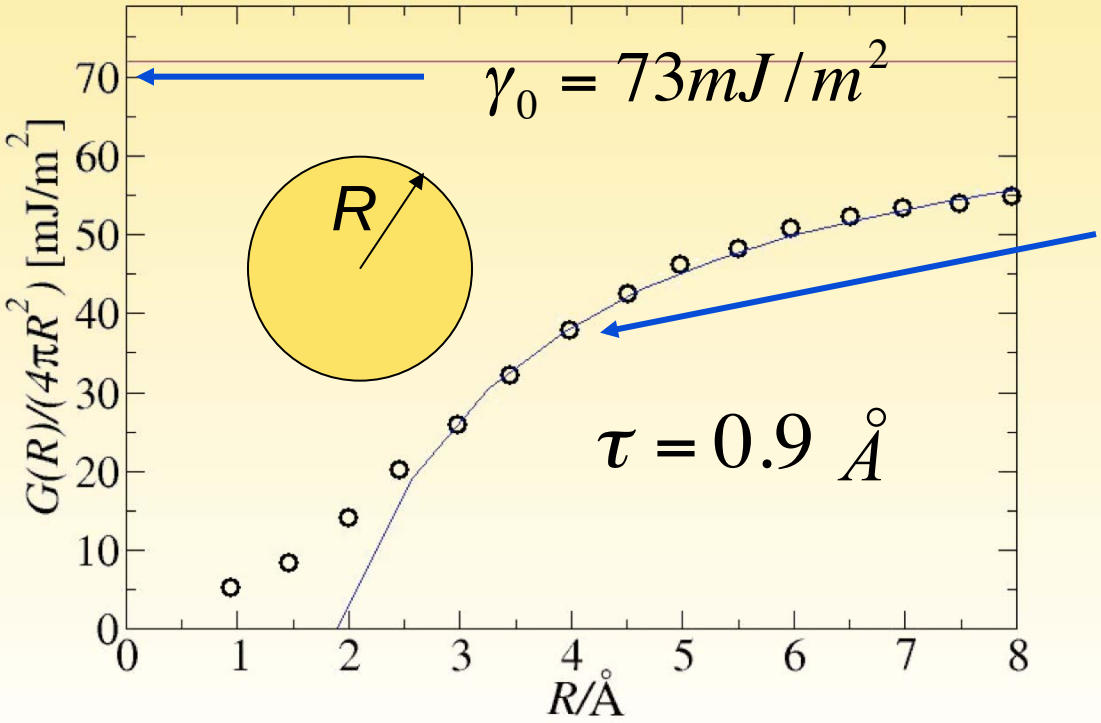
Ions can permeate!

Dzubiella, Allen, & Hansen, J. Chem. Phys. **120**, 5001 (2004).

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

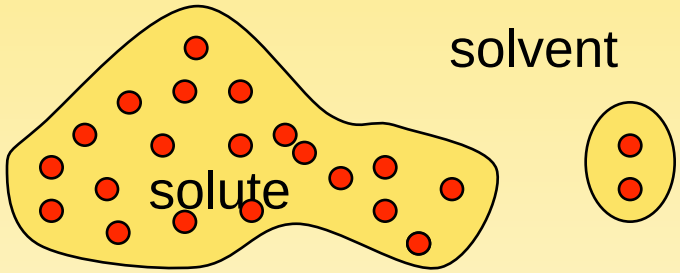
H : mean curvature

Huang *et al.,* 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)

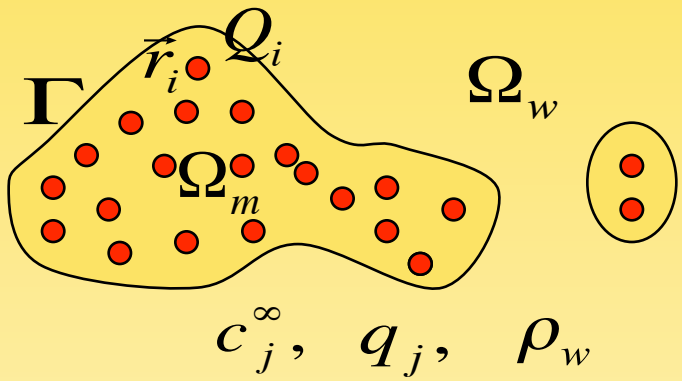


Guiding principles

- 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

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



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

$Pvol(\Omega_m)$: 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

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

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

- rotational and translational 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

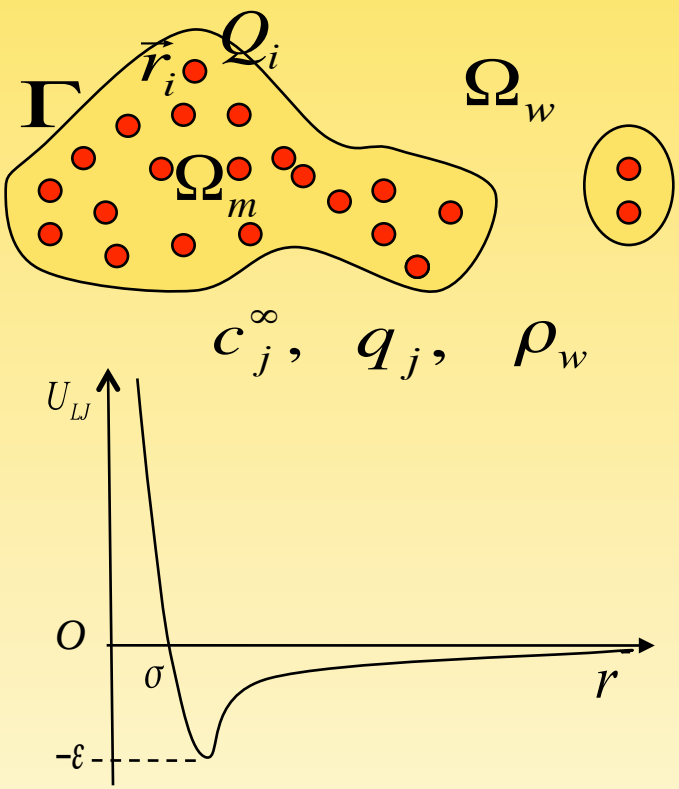
Roth, Harano, & Kinoshita, Phys. Rev. Lett. **97**, 078101 (2006).
Harano, Roth, & Kinoshita, Chem. Phys. Lett. **432**, 275 (2006)

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

van der Waals solute-solvent dispersive 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 Coulomb-field or Yukawa-field approximation

The Poisson-Boltzmann (PB) theory

Electrostatic free energy

$$G_{elec}[\Gamma] = \int \left[-\frac{\varepsilon\varepsilon_0}{2} |\nabla\psi|^2 + \rho_f\psi - \beta^{-1}\chi_w \sum_j c_j^{\infty}(e^{-\beta q_j\psi} - 1) \right] dV$$

ψ = electrostatic potential

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

ρ_f = fixed charges of molecular atoms

χ_w = characteristic function of Ω_w

PBE: $-\nabla\cdot\varepsilon\varepsilon_0\nabla\psi + \chi_w\beta^{-1}\sum_j c_j^{\infty} q_j e^{-\beta q_j\psi} = \rho_f$

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

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

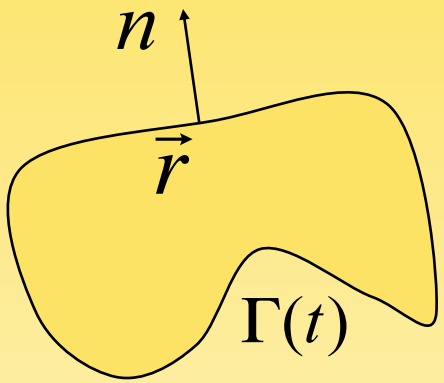
$$\min H[\Gamma;\vec{r}_1,\ldots,\vec{r}_N] \Rightarrow \text{Equilibrium conformations}$$

3. The Level-Set Method

The level-set method

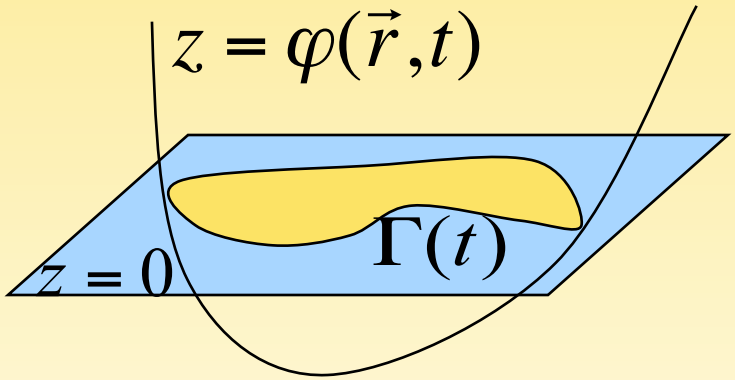
- Interface motion

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



- 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

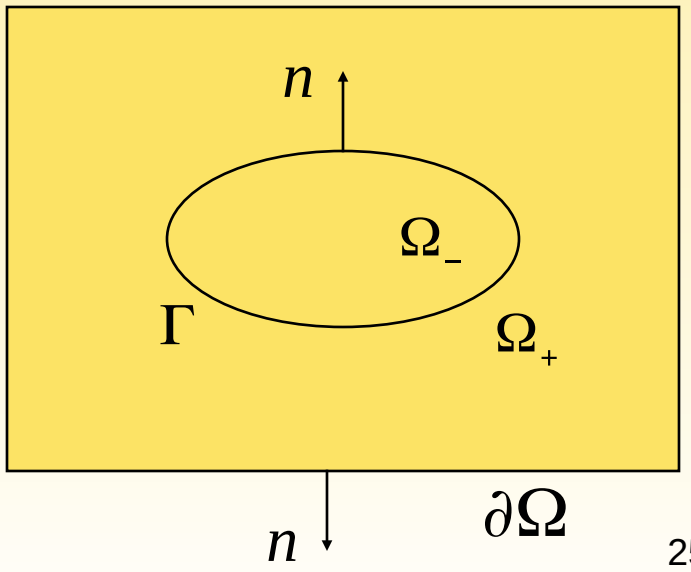
    $$V_n = -H$$

  - Motion by the surface Laplacian of mean curvature

    $$V_n = \Delta_s H$$

- External field

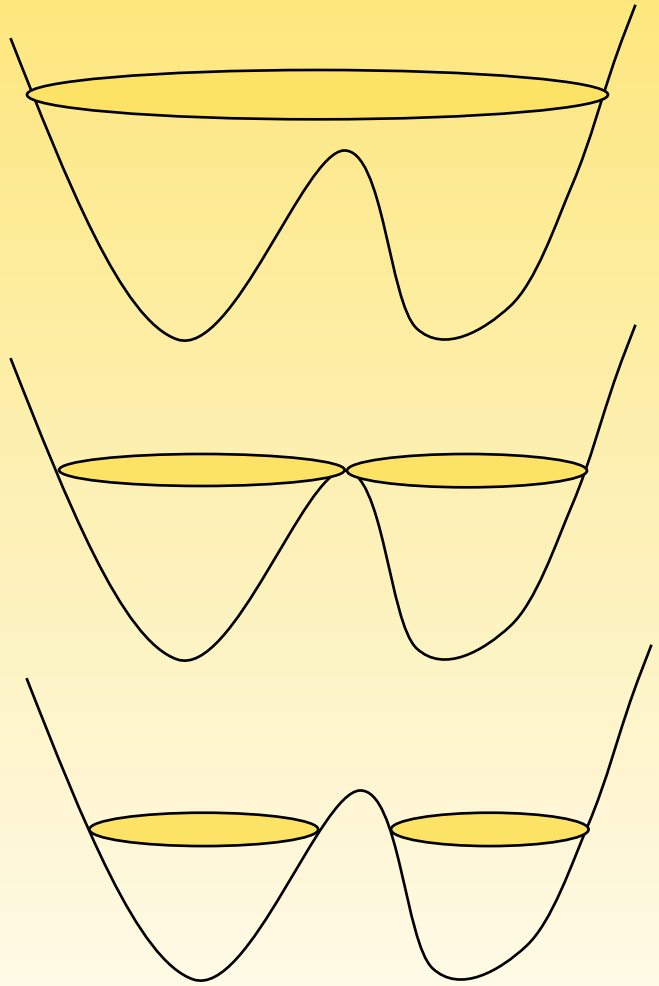
$$\begin{cases} u_t - \Delta u = 0 & \text{in } \Omega_- \cup \Omega_+ \\ u = -H & \text{on } \Gamma \\ \frac{\partial u}{\partial n} = 0 & \text{on } \partial\Omega \\ V_n = \left[\frac{\partial u}{\partial n}\right] & \text{on } \Gamma \end{cases}$$



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

Relaxation

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

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

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

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

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

Effective electrostatic surface force

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

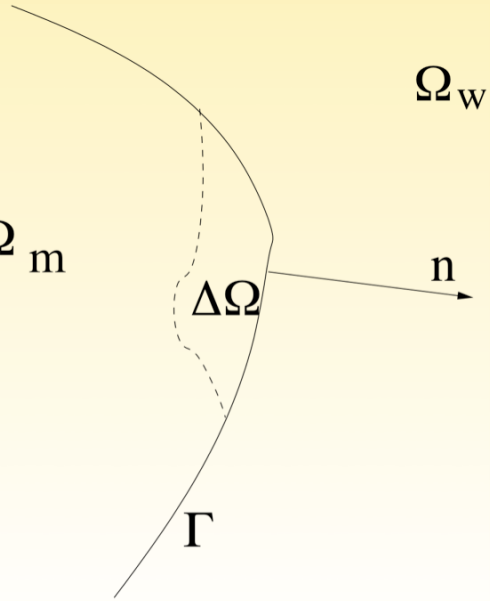
Charge neutrality, convexity, and Jensen's inequality

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

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

Lemma

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



Discretization of the level-set equation

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

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

Forward Euler for time

$$\varphi^{k+1}(x) - \varphi^k(x) = -\Delta t V_n^k(x)\,|\nabla\varphi^k(x)|$$

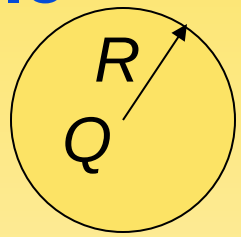
Decomposition $\varphi_t = A + B$

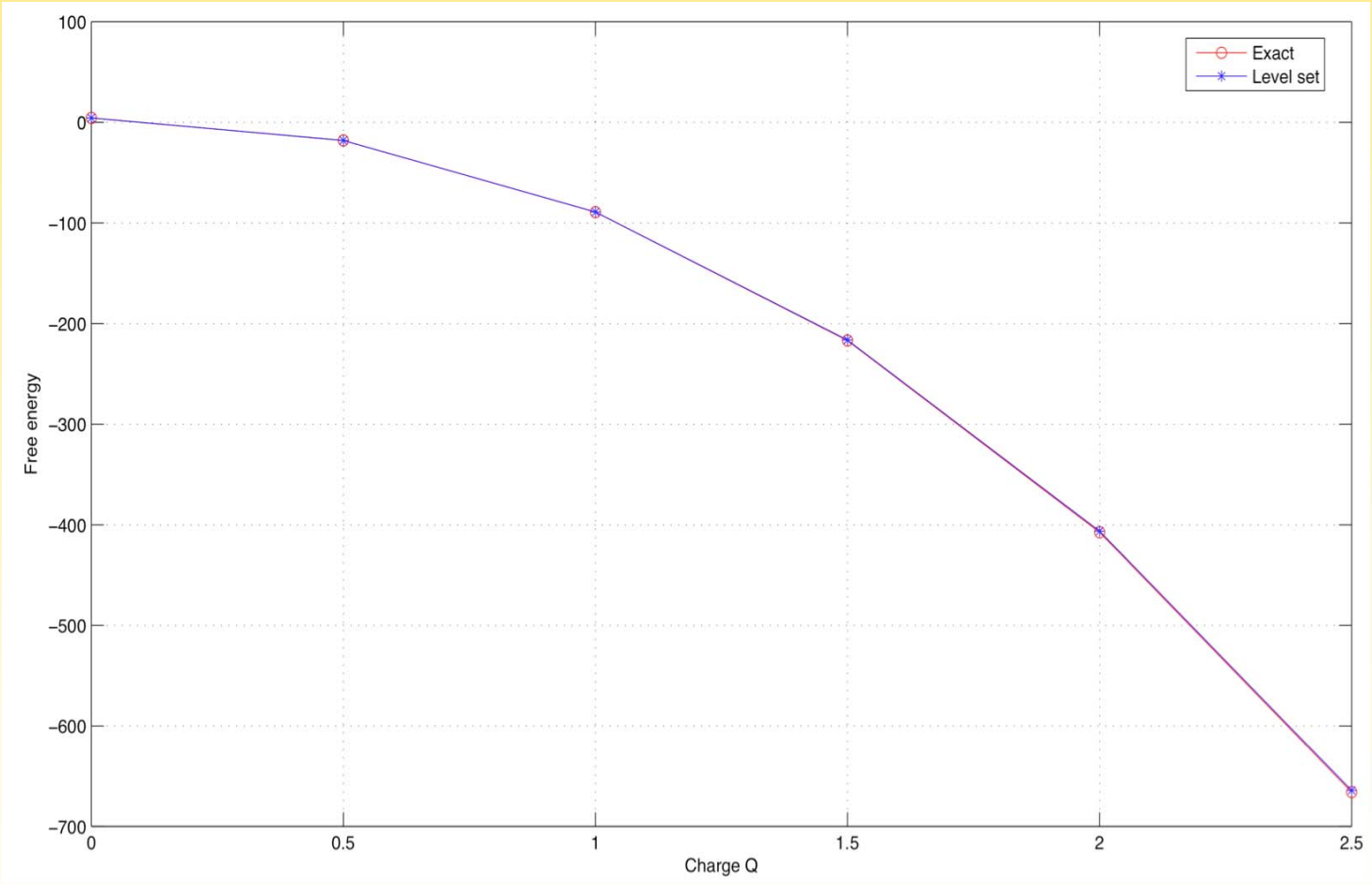
Central differencing for $A = 2\gamma_0[H(\vec{r}) - \tau K(\vec{r})]\,|\nabla\phi|$

Upwinding for $B = [P - \rho_w U(\vec{r})]\,|\nabla\varphi|$

Convergence test on a single charged particle

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





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 and high resolution ⇨
- Dynamics: a different situation

4. Numerical Results

Parameters

- Pressure difference

  P (bar)
- Planar surface tension

  γ_0 $(k_B T)$
- The Tolman length

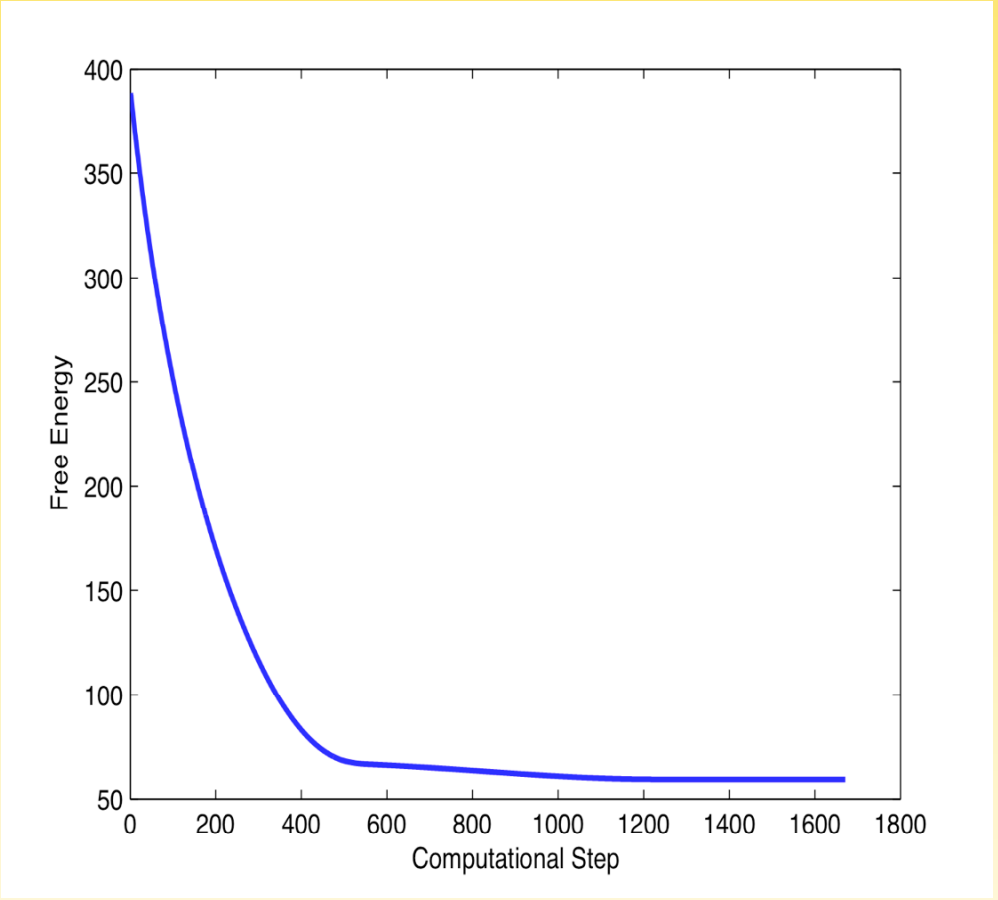
  τ $(\mathring{A})$
- Water density

  ρ_w $(\mathring{A}^{-3})$
- LJ parameters

  σ $(\mathring{A})$

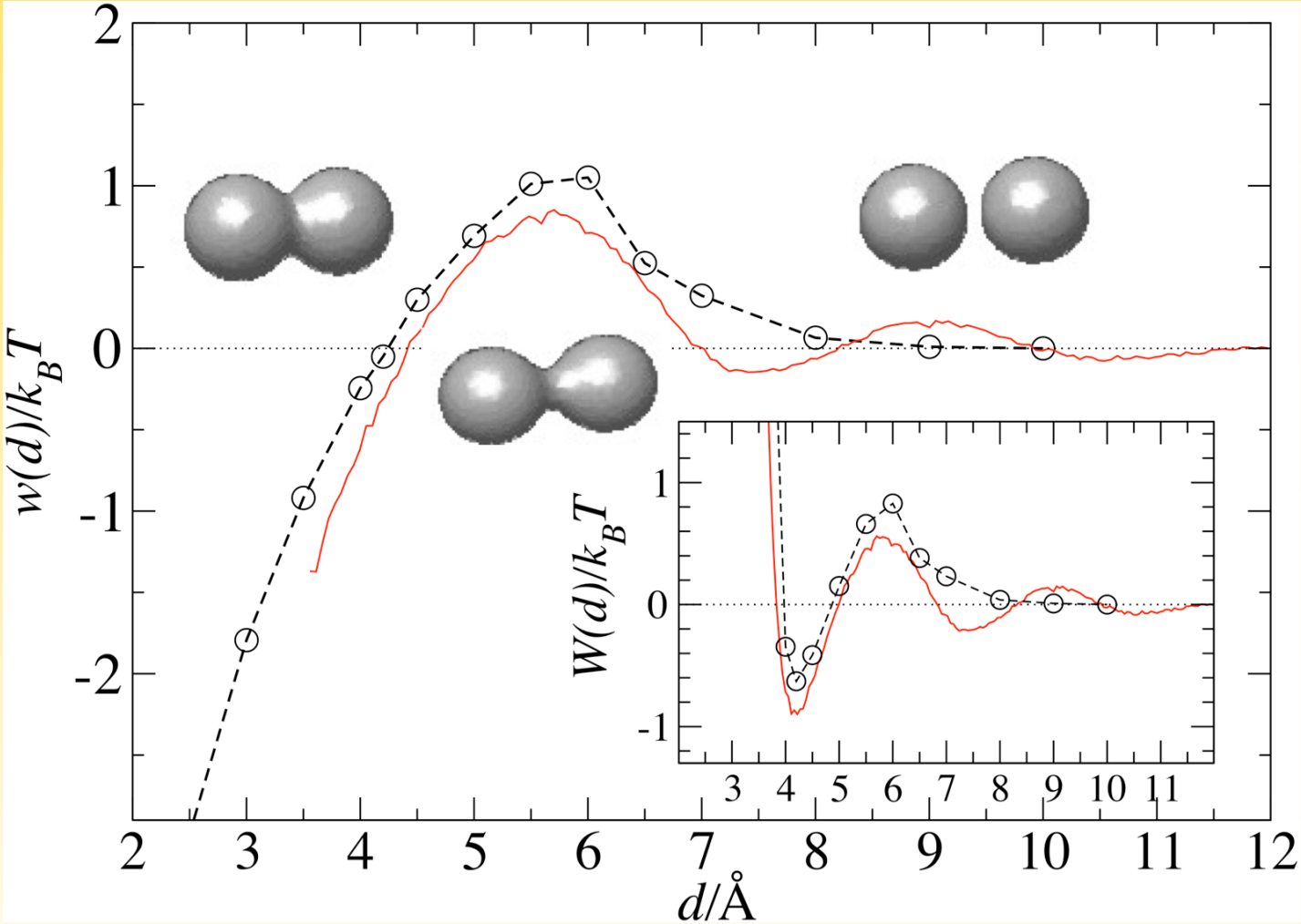
  ε $(k_B T)$
- Point charges

  Q_i (e)



A typical plot of free energy vs. optimization steps.

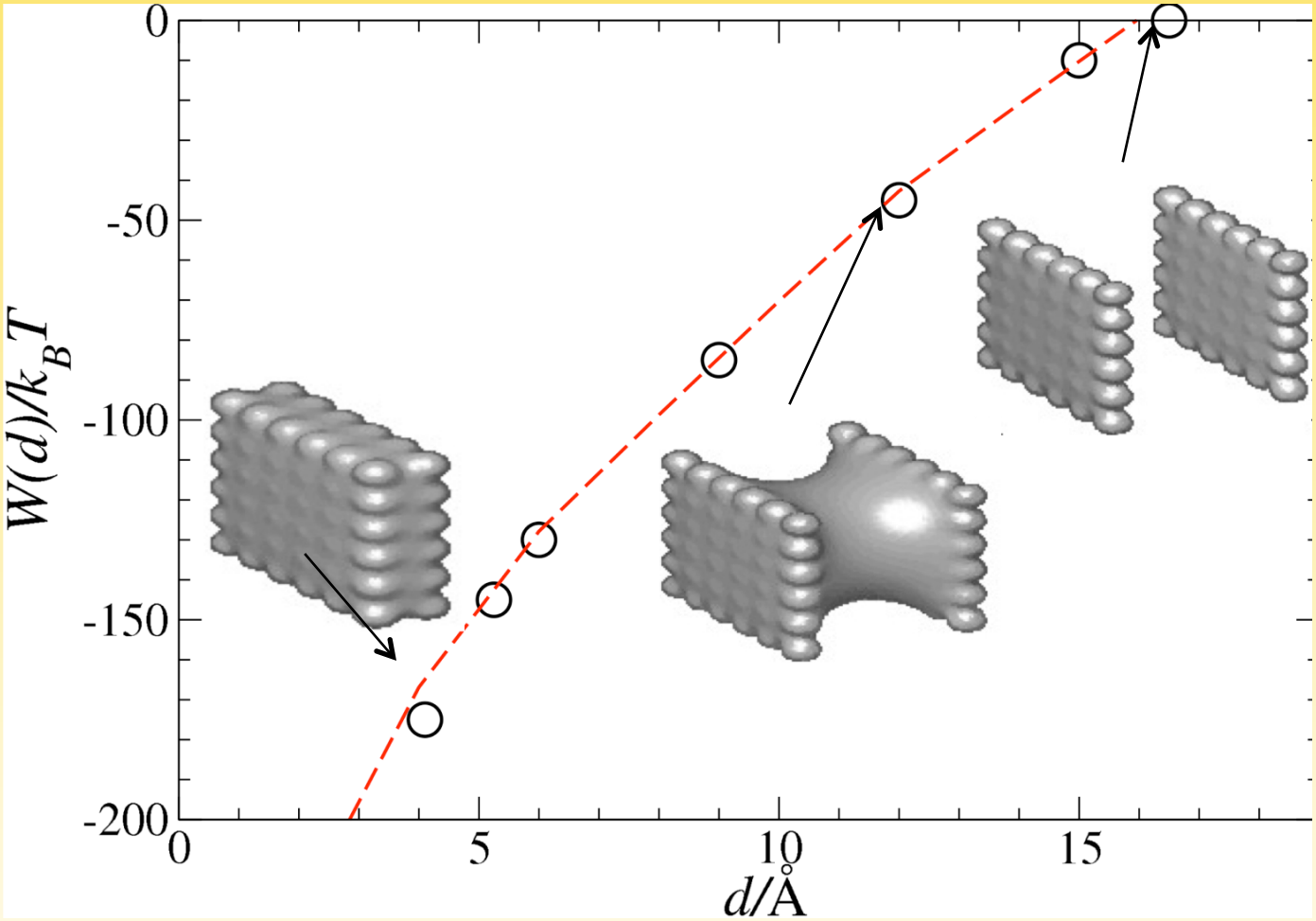
Example 1. Two xenon atoms



PMF: the level-set method (circles) and MD simulations (solid line).

Paschek, J. Chem. Phys. **120**, 6674 (2004).

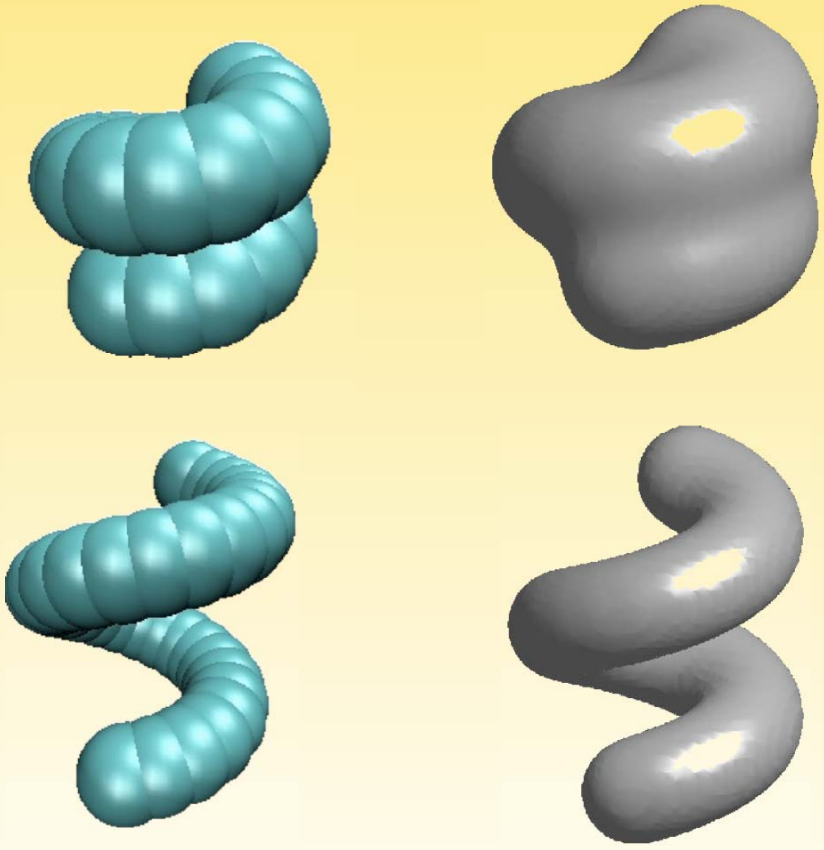
Example 2. Two paraffin plates



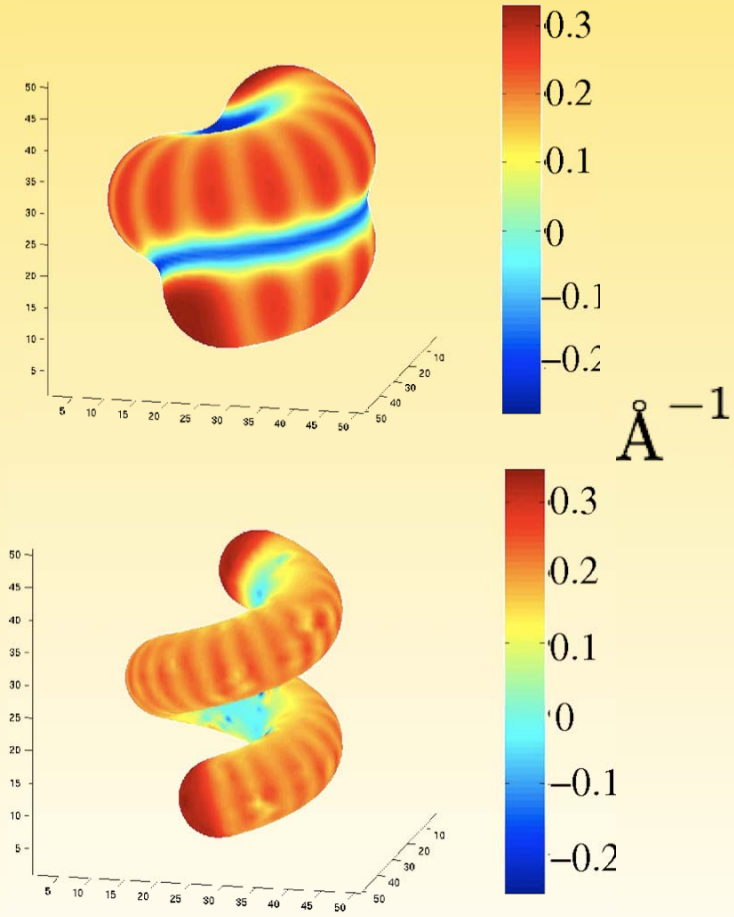
Level-set (circles) vs. MD (line) calculations.

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

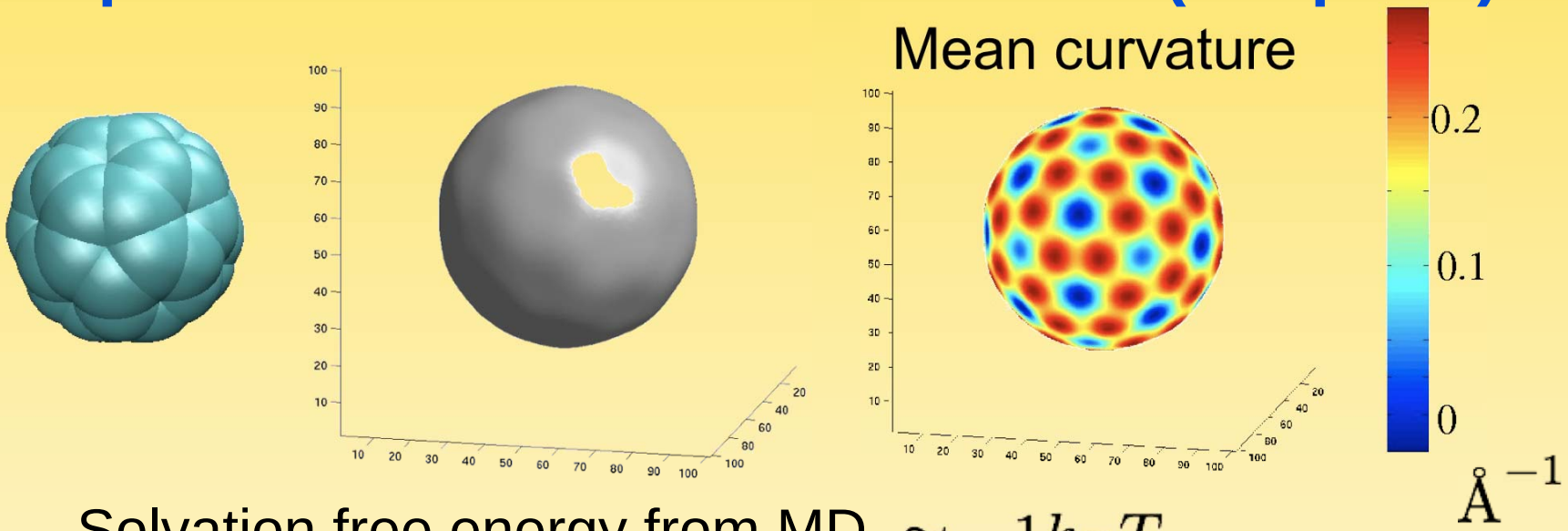
Example 3. Two helical alkanes (~30 atoms)



Mean curvature



Example 4. 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>

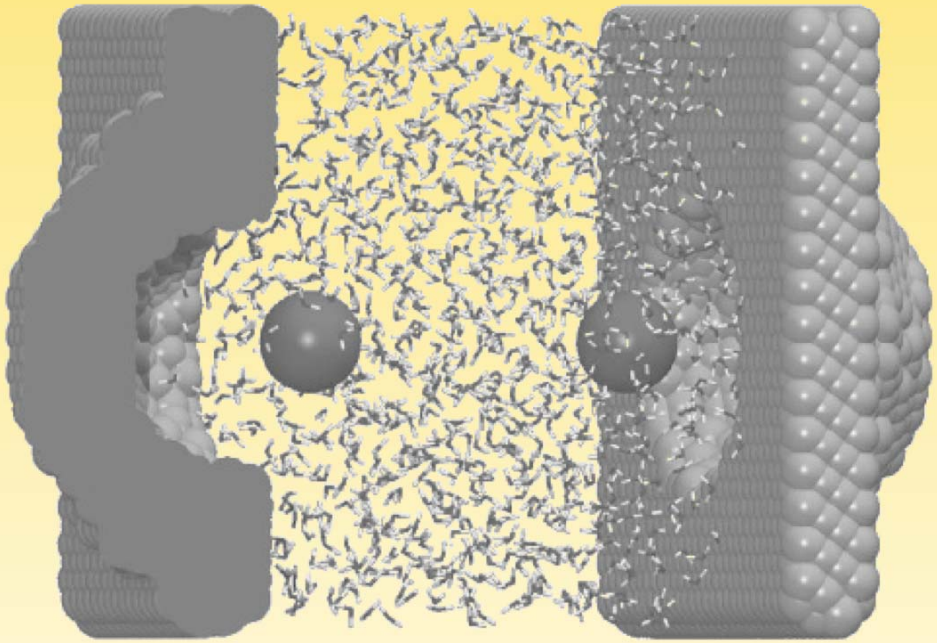
Solvation free energy is a difference of big numbers:

Solvation entropy $\simeq 49 k_B T$

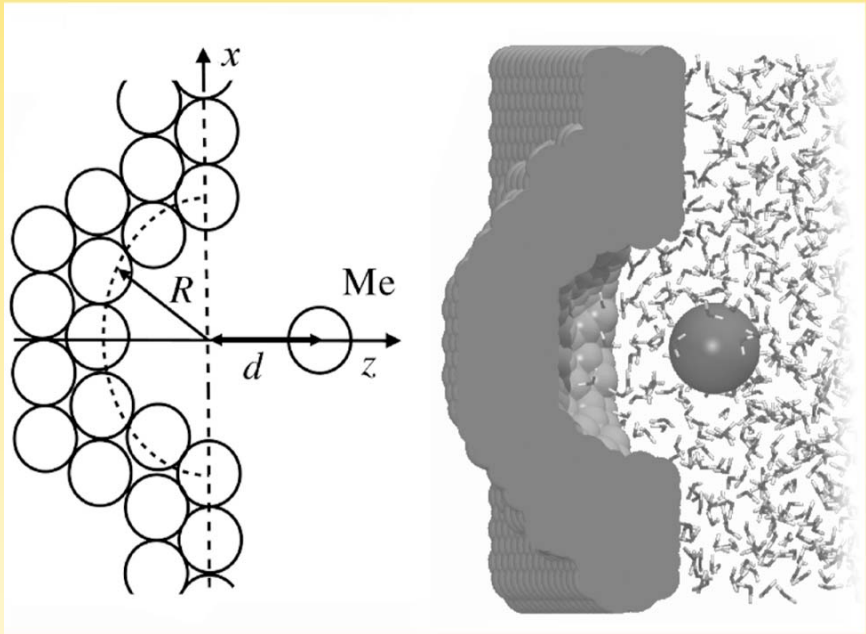
Solvation enthalpy $\simeq -50 k_B T$

A big problem for solvation free-energy calculations!

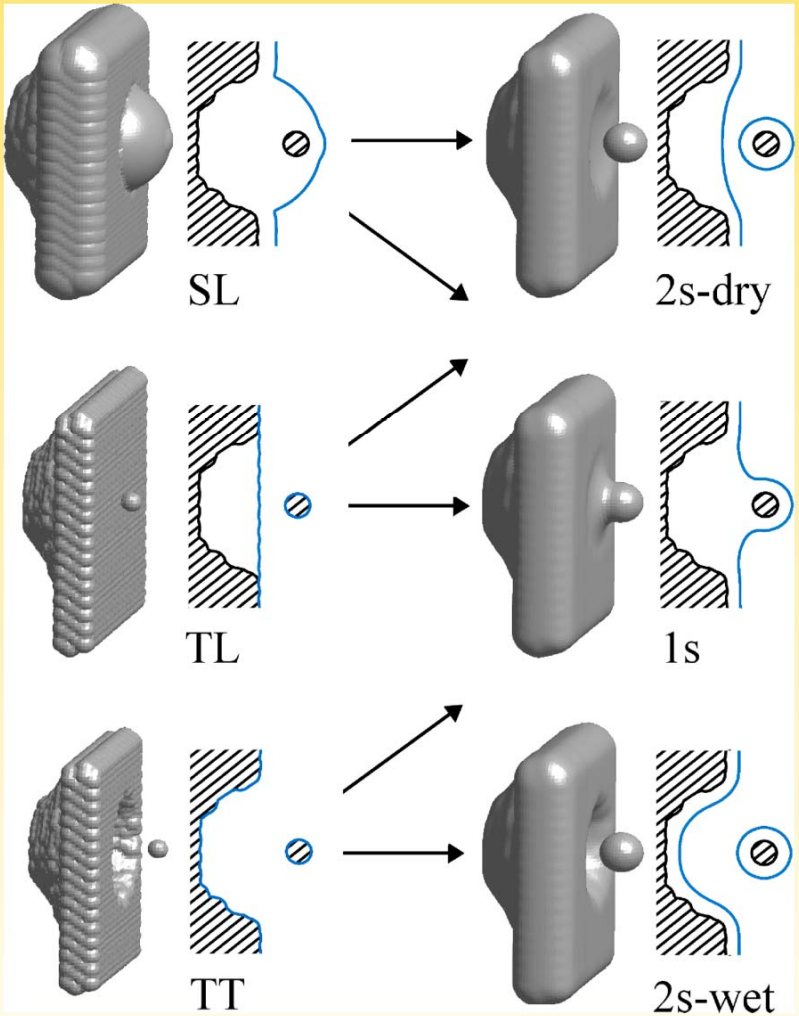
Example 5. A Hydrophobic receptor-ligand system

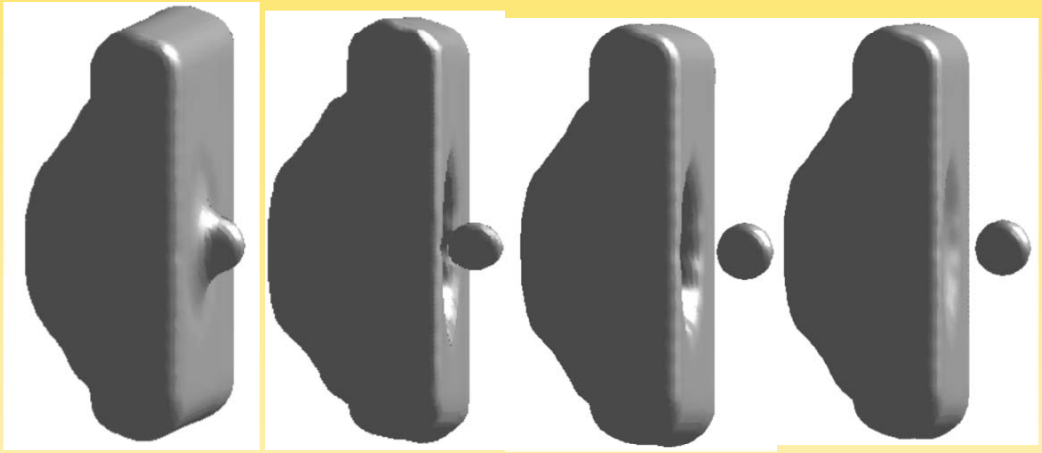


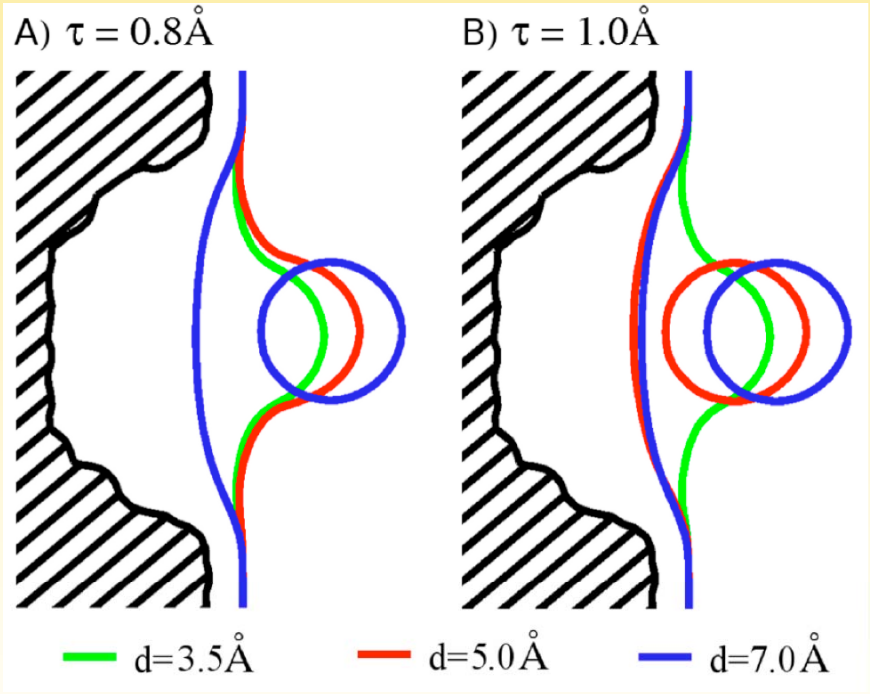
Each wall consists of 4,242 atoms.

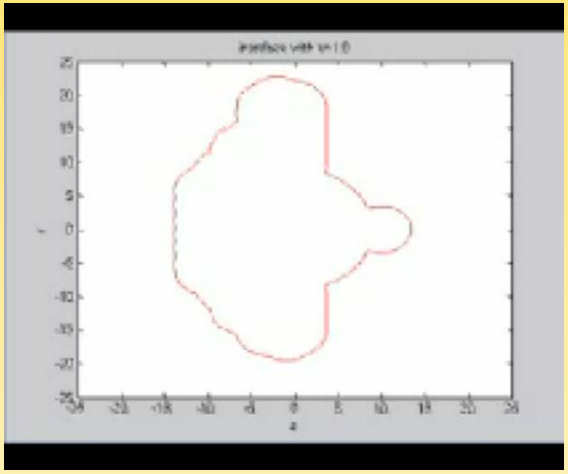


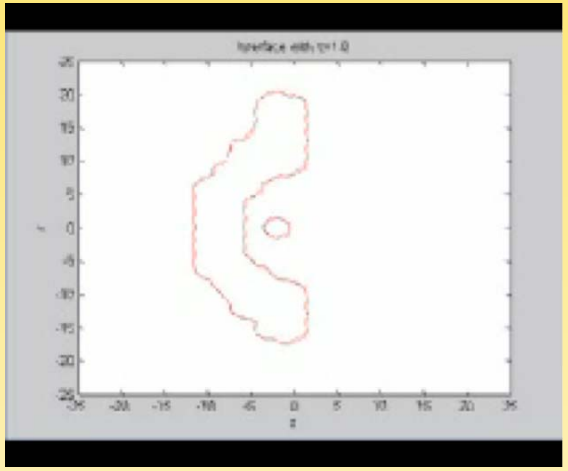
System setup for the level-set VISM calculation.

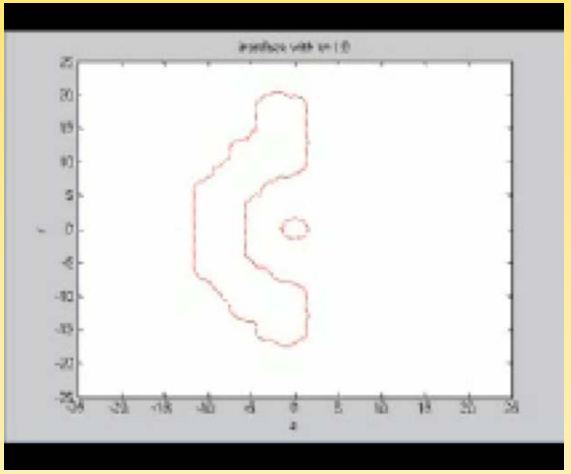

SL
2s-dry
TL
1s
TT
2s-wet

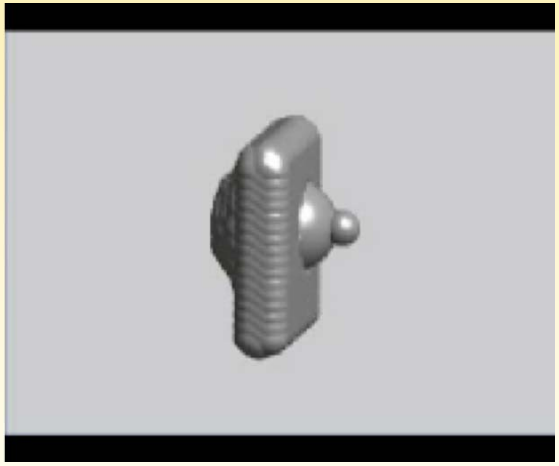


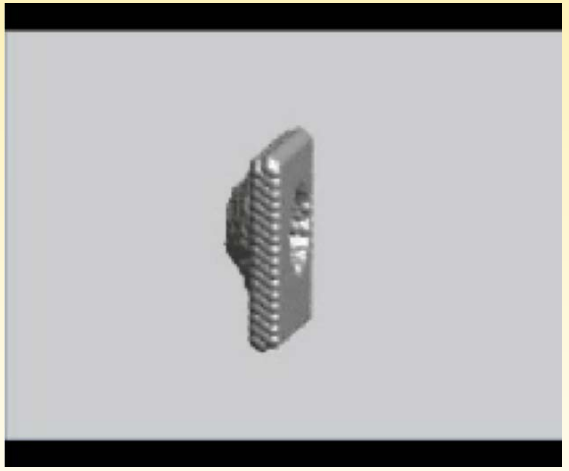

A) τ = 0.8Å
B) τ = 1.0Å
d=3.5Å
d=5.0Å
d=7.0Å

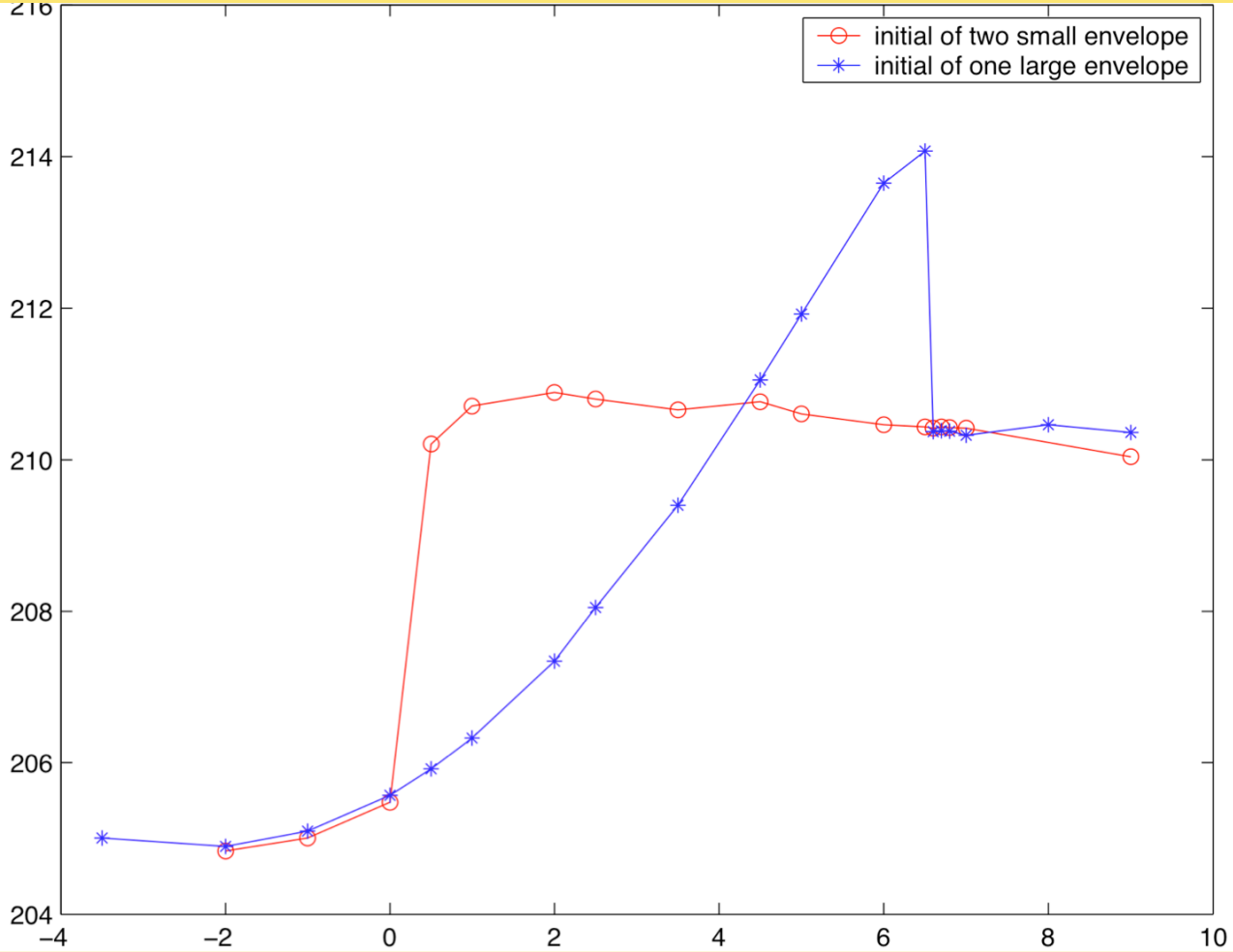






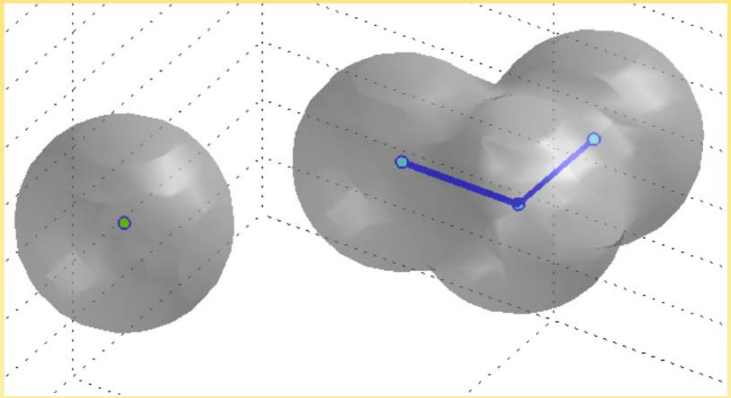


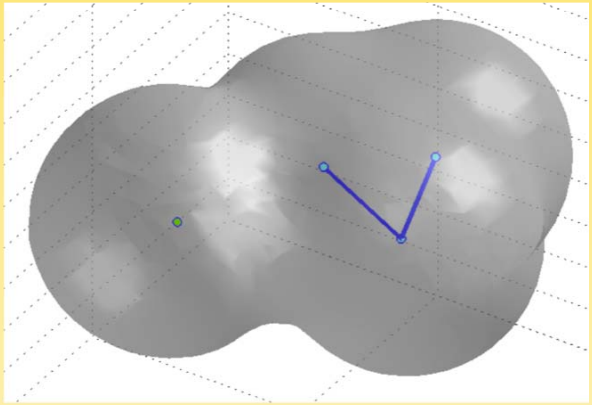




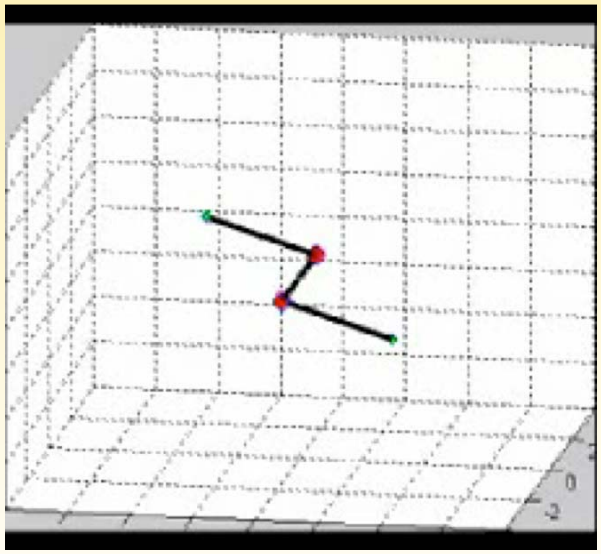
Free energy vs. the distance between ligand and wall: a bimodal behavior.

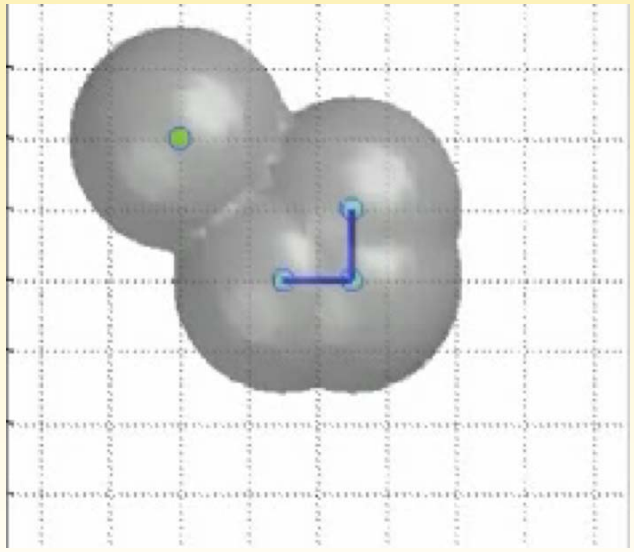
Example 6. A model system of 4 atoms

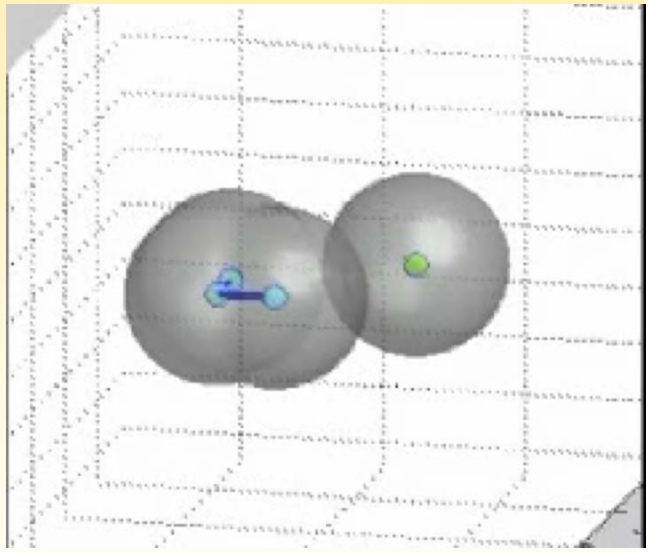




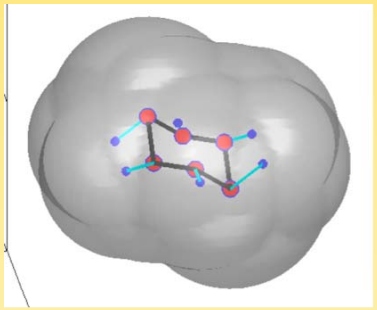
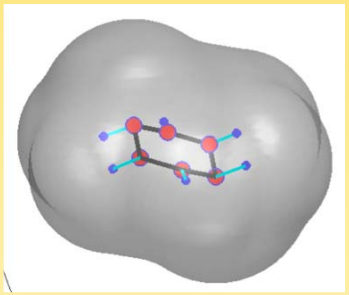
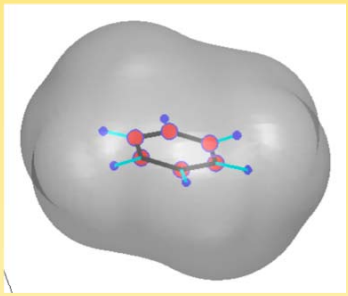
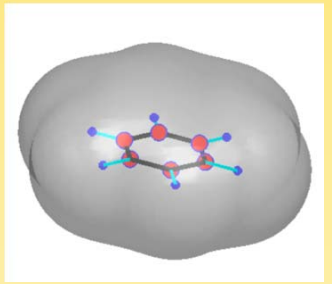
Left: initial positions. Right: final positions.

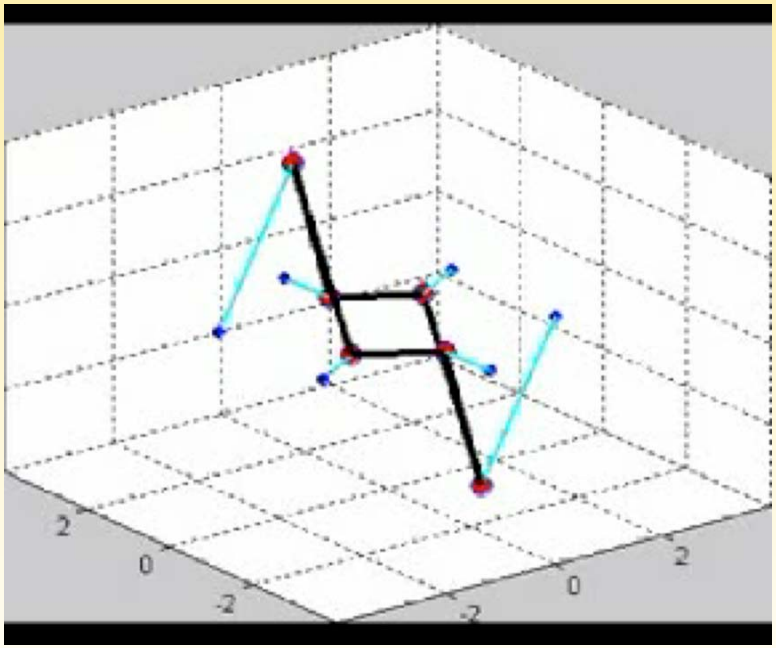


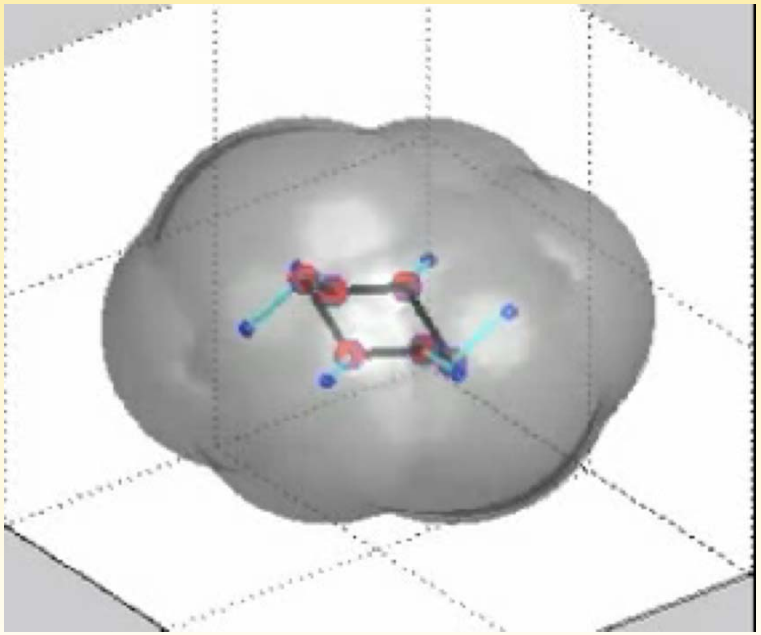




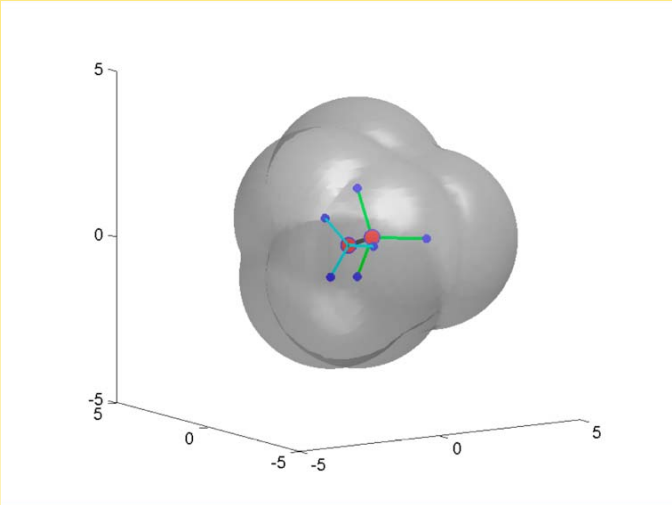
Example 7. A benzene molecule

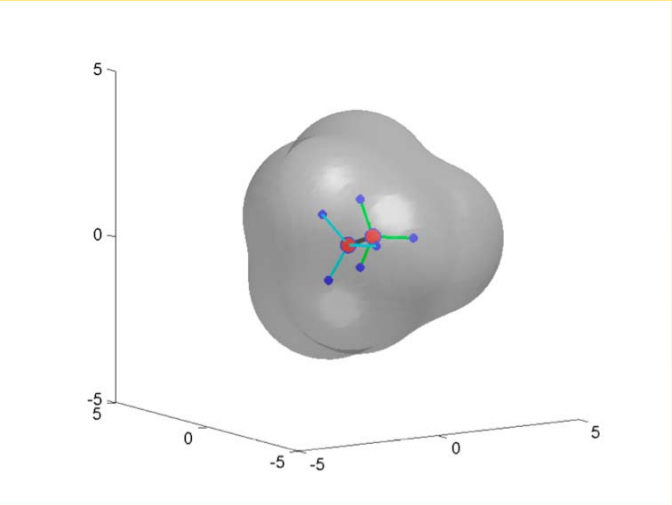





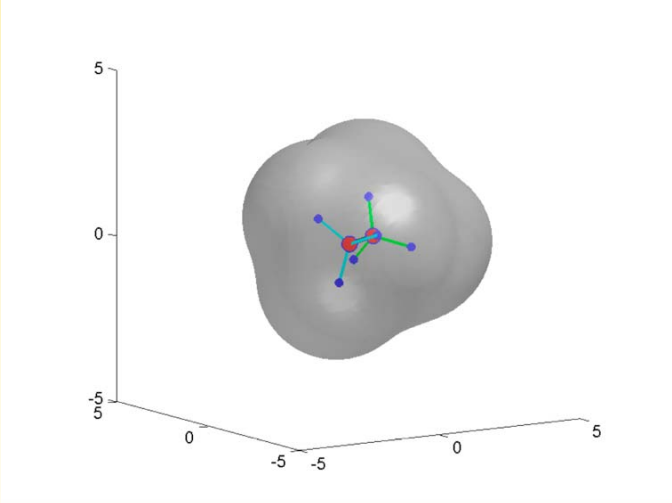


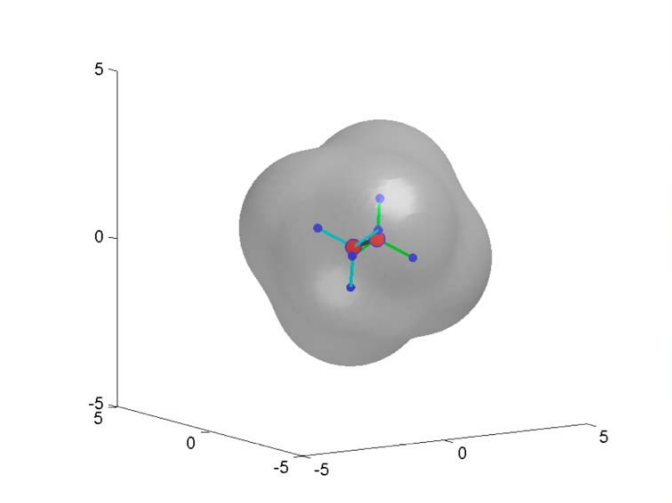


Example 8. An ethane molecule

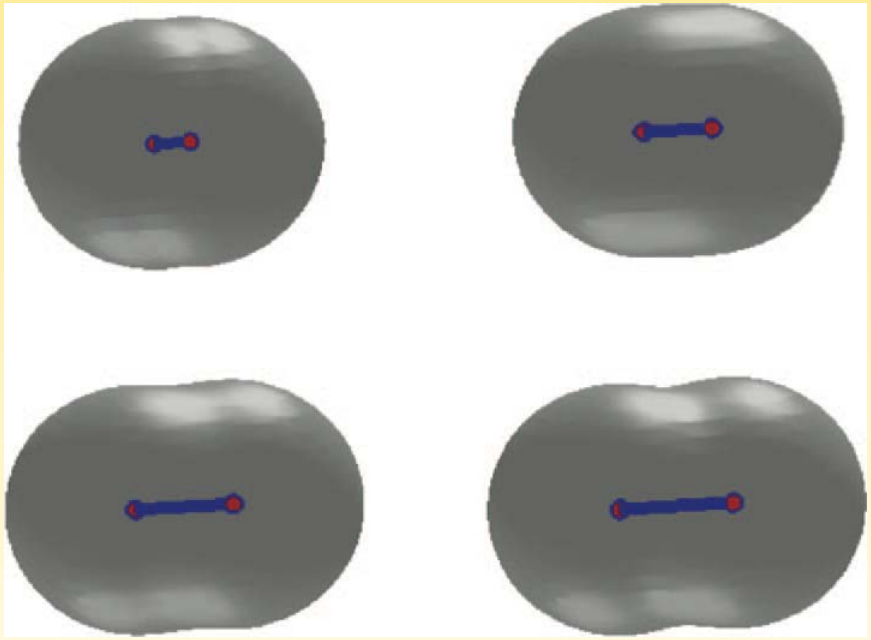


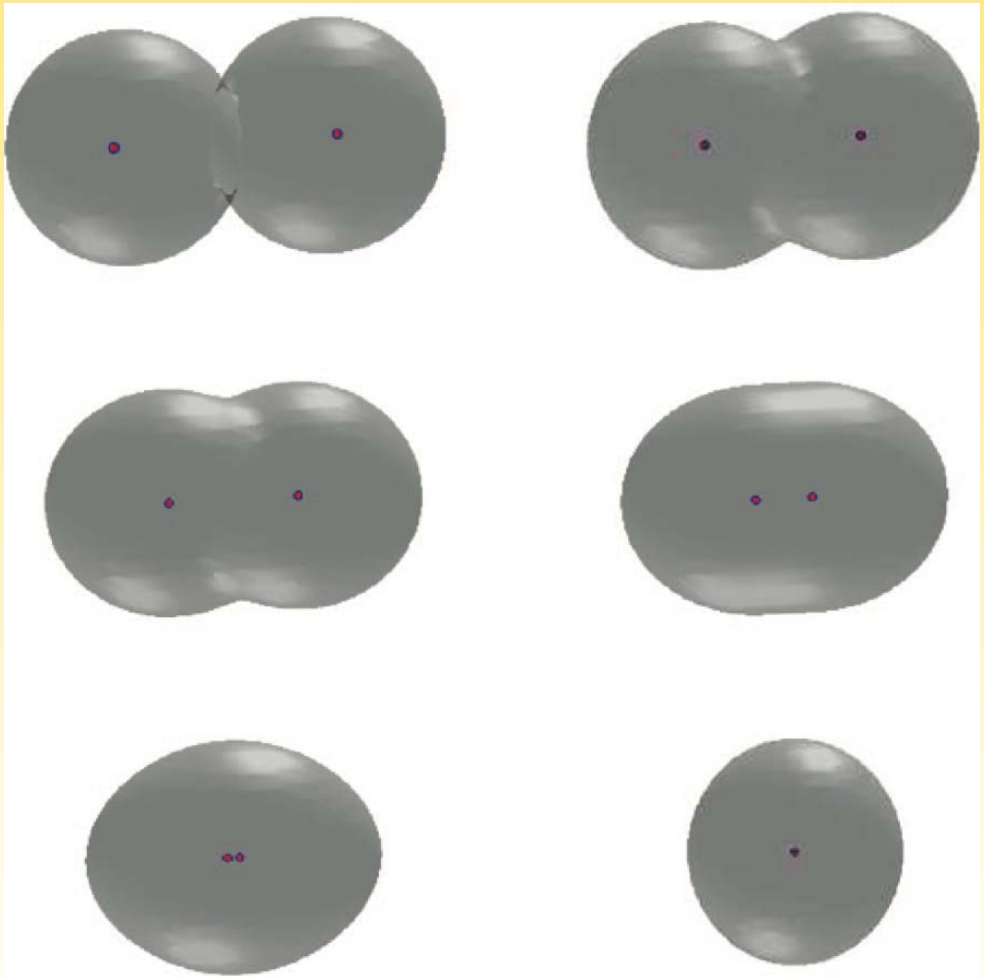






Example 9. A two-particle system: the surface motion influences the particle motion





5. Conclusions

Accomplishments

- Modeling improvement
  - Coupling with molecular mechanics
  - Coulomb-field and Yukawa-field approximations
  - Electrosttic surface forces
- A level-set method for variational solvation
  - Capturing hydrophobic cavities
  - New level-set techniques

Current and future work

- Coupling the PB and level-set calculations
- Monte Carlo level-set VISM
- Solvent dynamics: Rayleigh-Plesset equation
- Multiscale modeling and simulation
- Application to molecular recognition and drug design

- Derivation of the free-energy functional
- Constrained motion by mean curvature

Thank You !