Level-Set Minimization of Potential Controlled Hadwiger Valuations for Molecular Solvation

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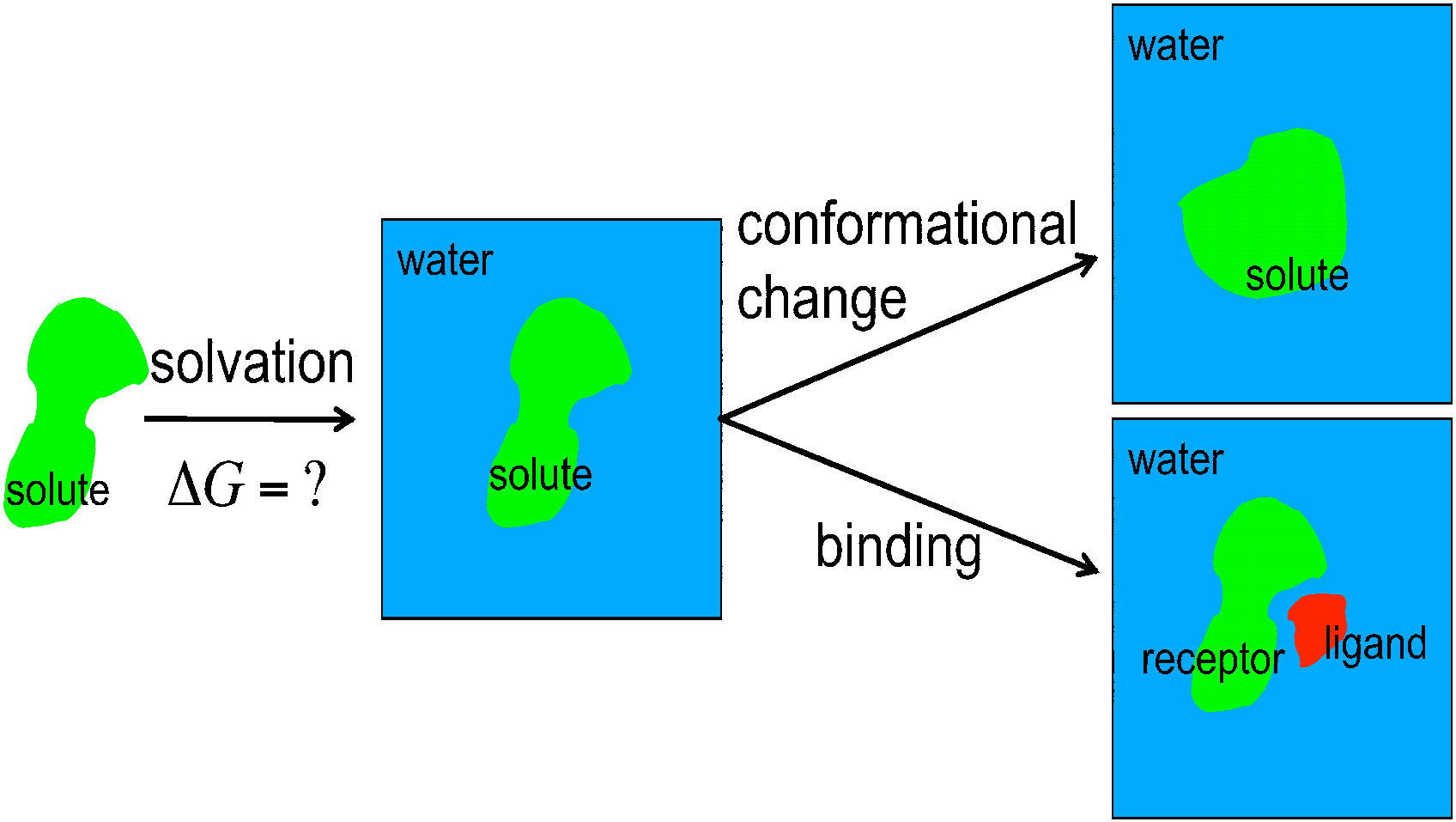
Outline

1. Free-Energy Functional and Level-Set Equation
2. Discretization and Algorithm
3. A Technique of Numerical Integration
4. Convergence Test
5. Application to Molecular Solvation
6. Conclusions

1. Free-Energy Functional and Level-Set Equation


solute
solvation
$\Delta G = ?$
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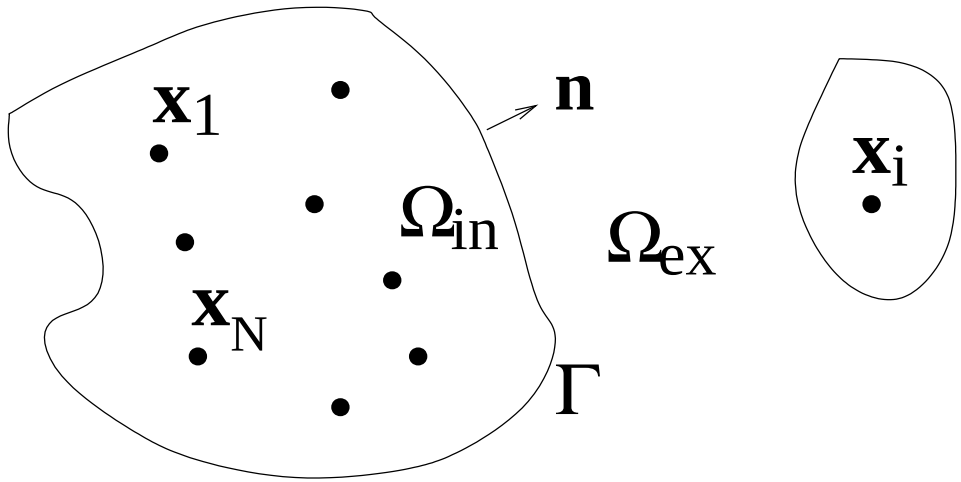
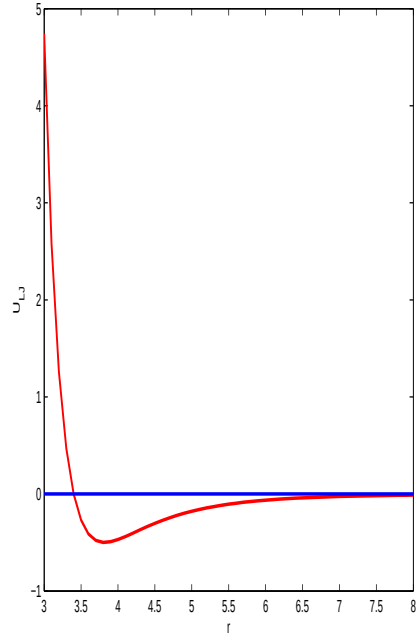
A variational implicit-solvent model
(Dzubiella–Swanson–McCammon 1996)





$$G[\Gamma] = P_0 \mathrm{Vol}\,(\Omega_{in}) + \gamma_0 \mathrm{Area}\,(\Gamma) - 2\gamma_0\tau \int_\Gamma H\, dS + \rho_0 \int_{\Omega_{ex}} U dV$$

$$U(x) = \sum_{i=1}^{N} U_{LJ}^{(i)}(|x - x_i|) = \sum_{i=1}^{N} 4\epsilon_i \left[\left(\frac{\sigma_i}{r}\right)^{12} - \left(\frac{\sigma_i}{r}\right)^{6} \right].$$

Hadwiger's Theorem

Let

$$C = \{\text{ all convex compact subsets of } \mathbb{R}^3 \},$$

$$M = \{\text{ finite unions of members of } C \},$$

$$F : M \to \mathbb{R} : \text{ translationally and rotationally invariant.}$$

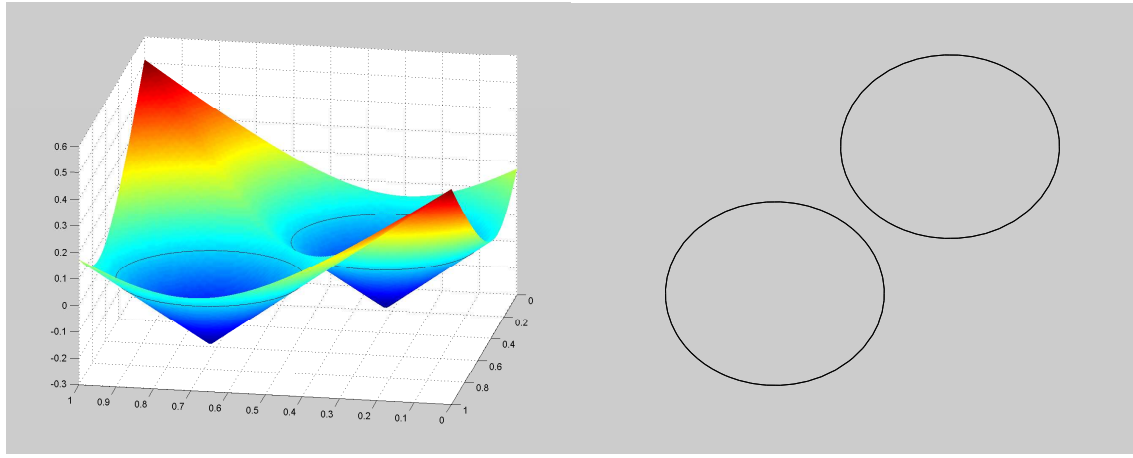
Assume

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

$$F(U_k) \to F(U) \quad \text{if } U, U_k \in C \ (k \geq 1) \text{ and } U_k \to U.$$

Then there exist $a_1, \ldots, a_4 \in \mathbb{R}$ such that for all $U \in M$

$$F(U) = a_1 \text{Vol}\,(U) + a_2 \text{Area}\,(\partial U) + a_3 \int_{\partial U} H \, dS + a_4 \int_{\partial U} K \, dS.$$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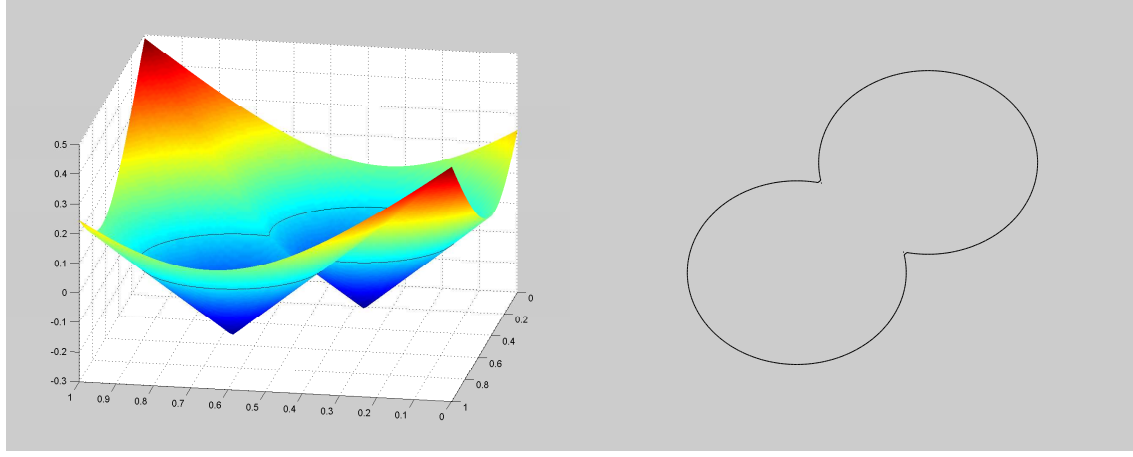
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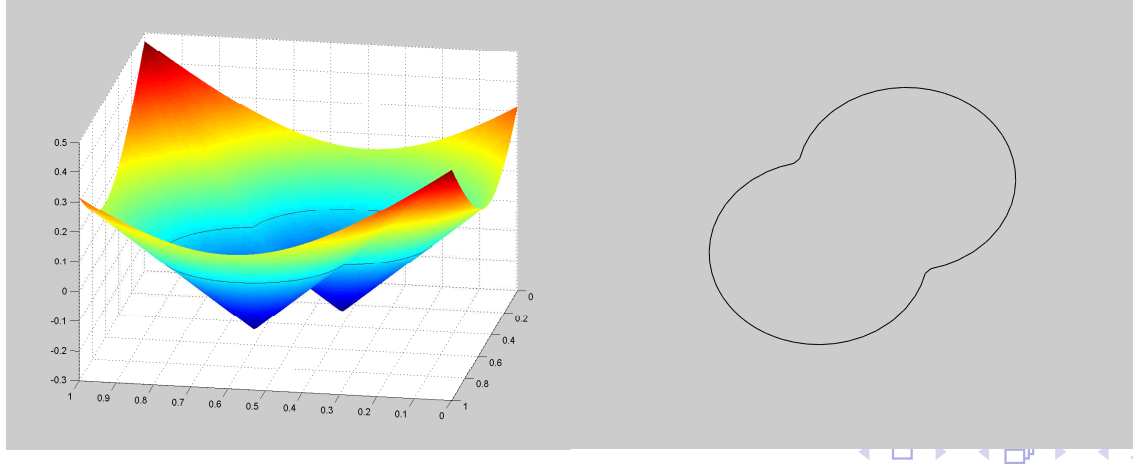
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0 0.2 0.4 0.6 0.8 1

Level-set representation of a moving surface

$$\Gamma(t) = \{x : \phi(x, t) = 0\}.$$

Level-set equation

$$\partial_t \phi + v_n |\nabla \phi| = 0.$$

Unit normal and normal velocity

$$n = \frac{\nabla \phi}{|\nabla \phi|} \quad \text{and} \quad v_n = \frac{dx}{dt} \cdot n.$$

Mean curvature and Gaussian curvature

$$H = \frac{1}{2}(\kappa_1 + \kappa_2) = \frac{1}{2}\nabla \cdot n \quad \text{and} \quad K = \kappa_1 \kappa_2 = n \cdot \text{adj}\left(\nabla^2 \phi\right) n.$$

Level-set optimization method

$$\partial_t \phi + v_n |\nabla \phi| = 0,$$
$$v_n = -\delta_\Gamma G[\Gamma] = -P_0 - 2\gamma_0 (H - \tau K) + \rho_0 U.$$

Recall

$$G[\Gamma] = P_0 \mathrm{Vol}\,(\Omega_{in}) + \gamma_0 \mathrm{Area}\,(\Gamma) - 2\gamma_0 \tau \int_\Gamma H\, dS + \rho_0 \int_{\Omega_{ex}} U dV.$$

A steepest descent method

$$\frac{d}{dt} G[\Gamma(t)] = \int_{\Gamma(t)} \delta_\Gamma G[\Gamma(t)] \left[\frac{dx(t)}{dt} \cdot n \right] dS = -\int_{\Gamma(t)} [v_n(x)]^2\, dS \leq 0.$$

2. Discretization and Algorithm

Time discretization by forward Euler's method

$$\frac{\phi^{(k+1)}(x) - \phi^{(k)}(x)}{\Delta t_k} = -v_n^{(k)}(x)\,|\nabla \phi^{(k)}(x)|.$$

Spatial discretization: Decomposition of normal velocity

$$\begin{aligned} \partial_t \phi = -v_n |\nabla \phi| &= A + B, \\ \text{“parabolic part”} \qquad A &= 2\gamma_0 (H - \tau K)|\nabla \phi|, \\ \text{“hyperbolic part”} \qquad B &= (P_0 - \rho_0 U)|\nabla \phi|. \end{aligned}$$

- Central differencing with parameter correction for $A = A(\phi)$.
- Upwinding schemes for $B = B(\phi)$.

Time step

$$\Delta t = \frac{0.5h}{\max_x \left[\text{Trace}\,(C(x))/h + P_0 + 2\rho_0 |U(x)|\right]}.$$

Introduce

$$P = I - \frac{\nabla\phi \otimes \nabla\phi}{|\nabla\phi|^2}: \quad \lambda = 0,\ 1,\ 1, \quad u_1 = \nabla\phi,\ u_2, u_3 \perp \nabla\phi,$$

$$\Pi = \frac{1}{|\nabla\phi|} P\left(\nabla^2\phi\right) P: \quad \lambda = 0,\ \kappa_1,\ \kappa_2, \quad u_1 = \nabla\phi,\ u_2, u_3 \perp \nabla\phi.$$

Then

$$H = \frac{1}{2}\text{Trace}\,\Pi \quad \text{and} \quad K = \frac{1}{2}\left[(\text{Trace}\,\Pi)^2 - \text{Trace}\,\left(\Pi^2\right)\right].$$

$$A(\phi) = 2\gamma_0\left[H(\phi) - \tau K(\phi)\right]|\nabla\phi| = \gamma_0 C(\phi) : \nabla^2\phi,$$

where

$$C(\phi) = \left[1 - 2\tau H(\phi)\right] P(\phi) + \tau\Pi(\phi) = Q^{-1}\begin{bmatrix} a_1 & 0 & 0 \\ 0 & a_2 & 0 \\ 0 & 0 & 0 \end{bmatrix} Q.$$

has eigenvalues $a_1 = 1 - \tau\kappa_1$ and $a_2 = 1 - \tau\kappa_2$.

Linearization of the "parabolic" part $A = A(\phi)$

$$\delta A(\phi)(\psi) = \frac{d}{d\varepsilon}\Big|_{\varepsilon=0} A(\phi + \varepsilon\psi) = \gamma_0 D(\phi) : \nabla^2\psi + E(\nabla\phi, \nabla^2\phi, \nabla\psi),$$

$$D(\phi) = [1 - 4\tau H(\phi)]\, P(\phi) + 2\tau\Pi(\phi) : \quad \lambda = 0,\ 1 - 2\tau\kappa_1,\ 1 - 2\tau\kappa_2.$$

$$\boxed{\text{linearized parabolicity} \Longleftrightarrow 1 - 2\tau\kappa_1 > 0,\ 1 - 2\tau\kappa_2 > 0}$$

Recall

$$A(\phi) = \gamma_0 C(\phi) : \nabla^2\phi = Q^{-1} \begin{bmatrix} a_1 & 0 & 0 \\ 0 & a_2 & 0 \\ 0 & 0 & 0 \end{bmatrix} Q : \nabla^2\phi.$$

Eigenvalues of $C(\phi)$: $a_1 = 1 - \tau\kappa_1$ and $a_2 = 1 - \tau\kappa_2$.

Parameter correction to enforce the parabolicity

$$\boxed{\text{For } i = 1, 2: \qquad \text{if} \quad a_i < 0.5 \quad \text{then re-set} \quad a_i = 0.5.}$$

Algorithm

(1) Initialization:

- Input all parameters;
- Fix a computational box and discretize it with a uniform grid;
- Compute P_0 and $\rho_0 U(x)$ at all grid points except $x_1, \ldots, x_N$;
- Generate an initial surface $\Gamma = \{x : \phi(x) = 0\}$: a loose wrap (e.g., a large ball) or a tight-wrap, e.g.,

$$\phi(x) = \min_{1 \le i \le N} (|x - x_i| - \sigma_i).$$

(2) Local level-set method:

- Choose a narrow band around the surface with width $12 \sim 16$ grid points.
- At each grid point in the band, compute $\nabla\phi$, $\nabla^2\phi$, H, and K using centered difference schemes.
- At grid points near the band boundary, use a lower-order scheme.

Algorithm (continued)

(3) Compute the free energy using

$$\int_{\Omega_{in}} f \, dV = \int_{\mathbb{R}^3} (1 - \text{Heav}(\phi)) \, dV,$$

$$\int_{\Gamma} g \, dS = \int_{\mathbb{R}^3} g|\nabla\phi|\delta(\phi) dV.$$

(4) Calculate and extend $-v_n|\nabla\phi| = A + B$.

- Parameter correction to enforce the parabolicity.
- Fast sweep to extend P_0 and $\rho_0 U$.
- A WENO scheme to discretize the extended P_0 and $\rho_0 U$.

(5) Calculate the time step Δt.

(6) Reinitialize the level-set function ϕ by solving

$$\phi_t + \text{sign}\,(\phi_0)(|\nabla\phi| - 1) = 0$$

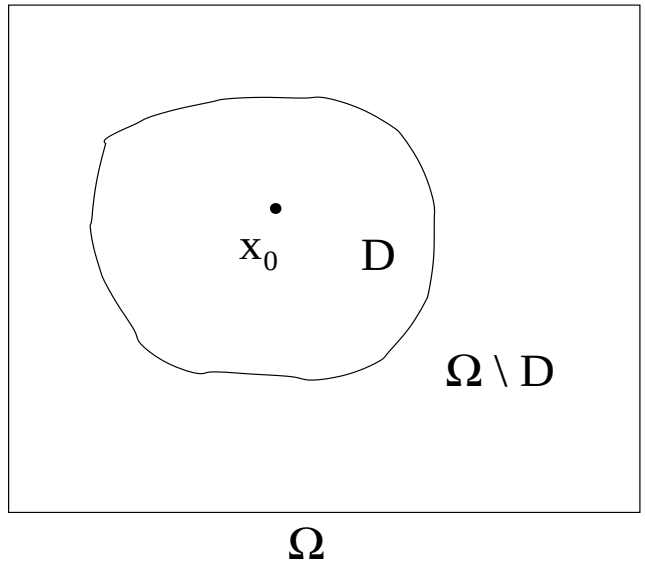
with

$$\text{sign}\,(\phi_0) = \frac{\phi_0}{\sqrt{\phi_0^2 + h}}.$$

- About 12 iterations in time.
- fourth-order Runge-Kutta scheme for time.
- fifth-order WENO for space.

(7) Check the convergence. If not, locate the interface Γ and go to Step (2).

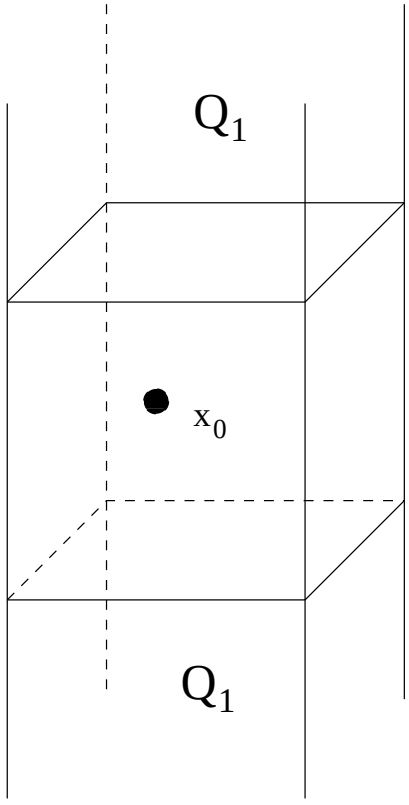
3. A Technique of Numerical Integration

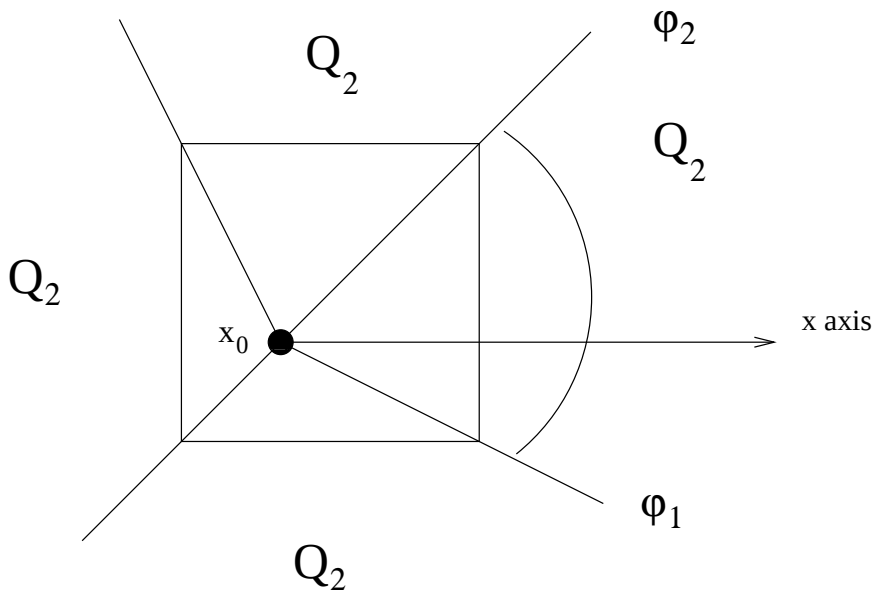


$$\int_{\mathbb{R}^3\setminus D} \frac{1}{|x-x_0|^k}\,dV = \int_{\Omega\setminus D} \frac{1}{|x-x_0|^k}\,dV + \int_{\mathbb{R}^3\setminus\Omega} \frac{1}{|x-x_0|^k}\,dV = I_1 + I_2$$

$$I_1 = \int_{\Omega\setminus D} \frac{1}{|x-x_0|^k}\,dV = \int_{\Omega} \frac{\chi_{\Omega\setminus D}(x)}{|x-x_0|^k}\,dV$$

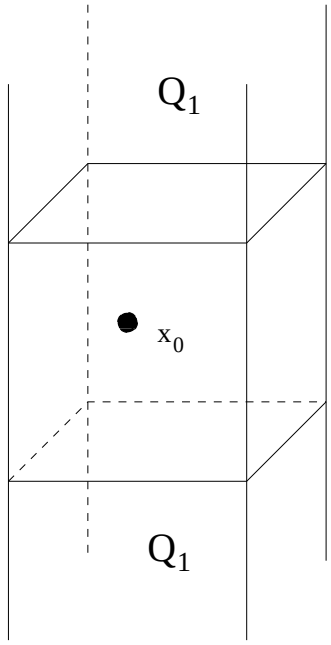
- Approximate $\chi_{\Omega\setminus D}$ by a smooth function.
- The composite trapezoidal rule for one-dimensional integrals.
- A second-order accurate scheme.

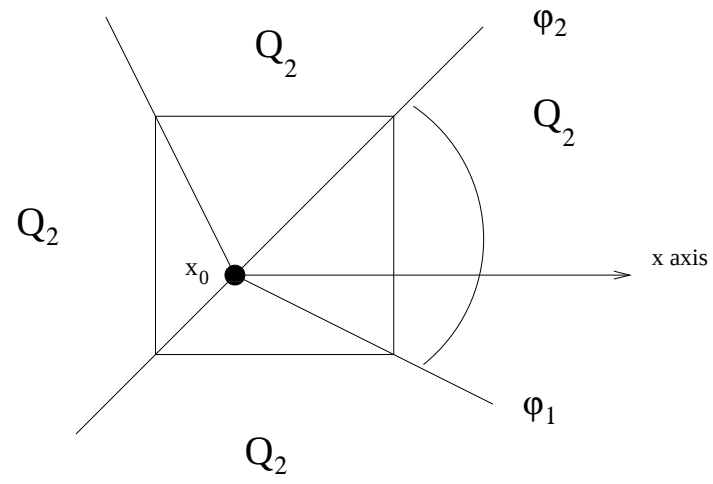




$$I_2 = \int_{\mathbb{R}^3 \setminus \Omega} \frac{1}{|x - x_0|^k} \, dV$$

- The integral I_2 does not depend on D.
- Decompose $\mathbb{R}^3 \setminus \Omega$ into six regions of two types.

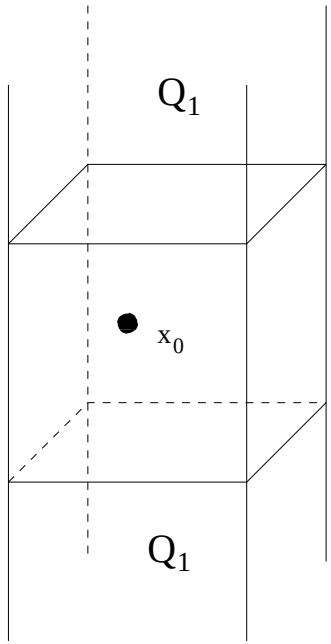


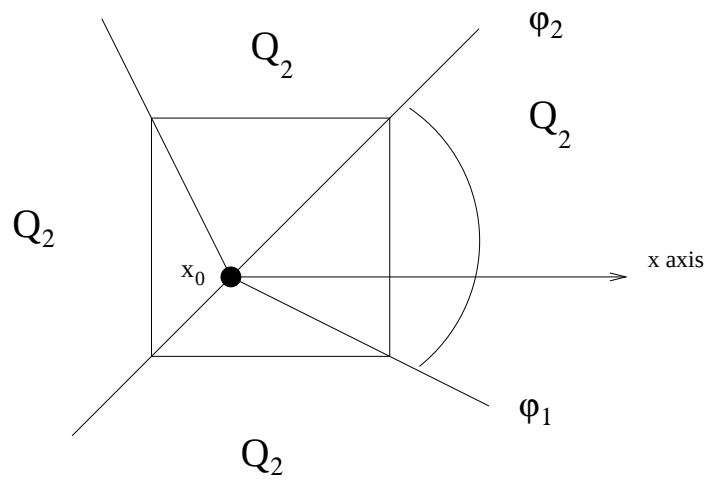


$$\hat{Q}_1 = \left\{ (r, \theta, z) : 0 < r < \frac{\beta}{\cos\theta}, \theta_1 < \theta < \theta_2, L < z < \infty \right\}$$

$$I_{2,1} = \int_{\hat{Q}_1} \frac{1}{|x - x_0|^k} \, dV = \int_L^{\infty} \int_{\theta_1}^{\theta_2} \int_0^{\frac{\beta}{\cos\theta}} \frac{r}{(r^2 + z^2)^{k/2}} \, dr \; d\theta \; dz$$

- Integrated analytically in r and z.
- The composite Simpson's rule for the integral in θ.



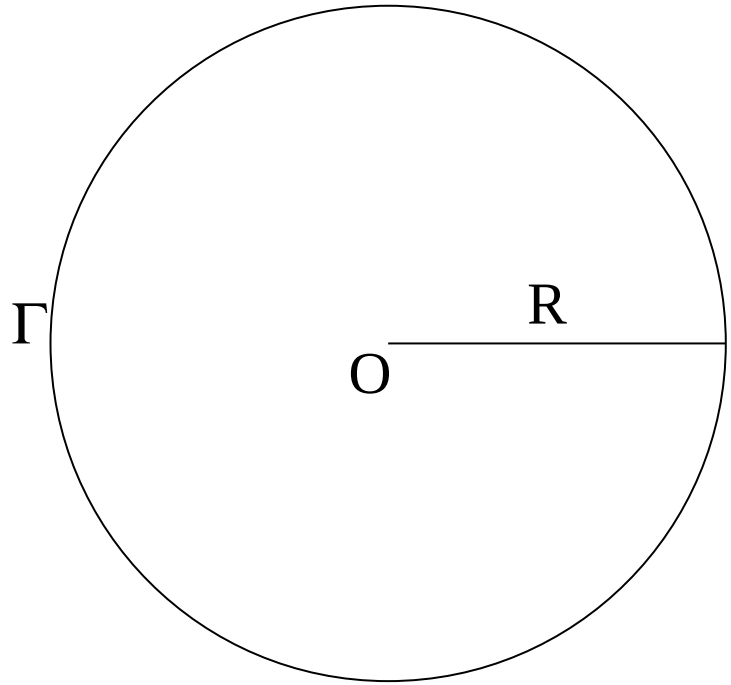


$$Q_2 = \left\{ (\rho, \varphi, \psi) : \frac{\alpha}{\cos\varphi \sin\psi} < \rho < \infty,\ \varphi_1 < \varphi < \varphi_2,\ 0 < \psi < \pi \right\}$$

$$I_{2,2} = \int_{Q_2} \frac{1}{|x - x_0|^k}\, dV = \int_0^{\pi} \int_{\varphi_1}^{\varphi_2} \int_{\frac{\alpha}{\cos\varphi \sin\psi}}^{\infty} \frac{\sin\psi}{\rho^{k-2}}\, d\rho\ d\varphi\ d\psi$$

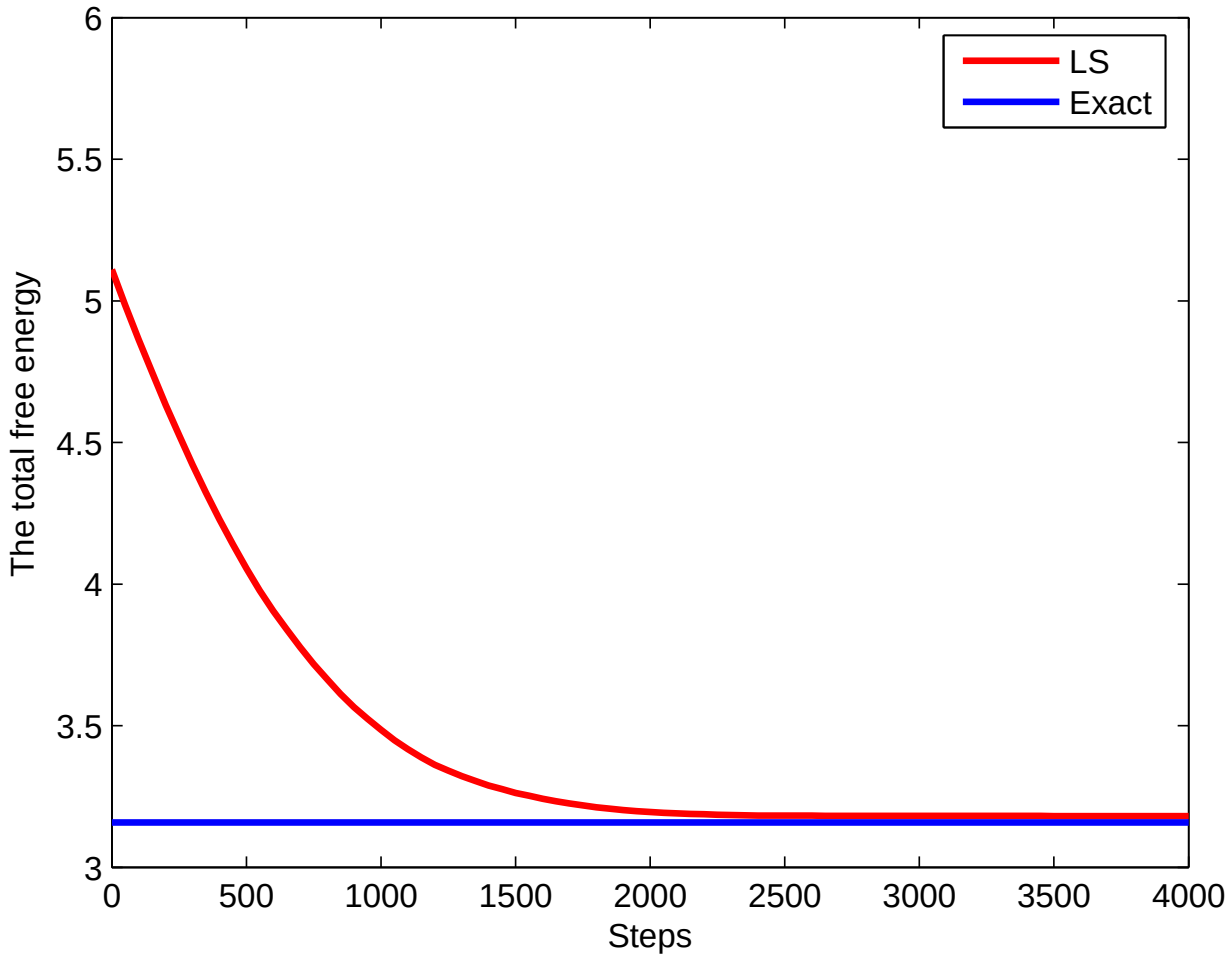
- Calculated analytically.

4. Convergence Test

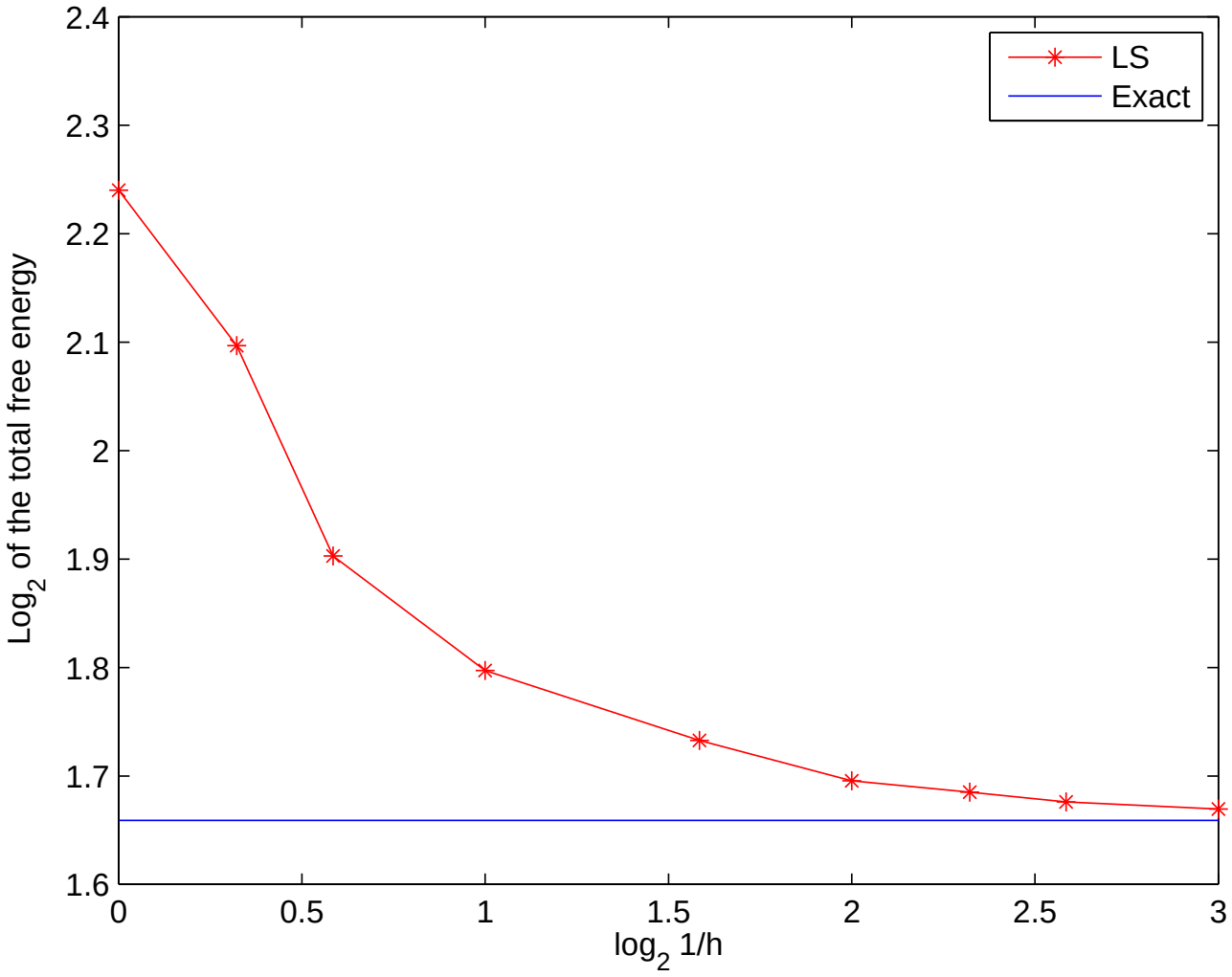


A one-particle system

$$G(R) = \frac{4}{3} P_0 \pi R^3 + 4\gamma_0 \pi R^2 - 4\gamma_0 \tau \pi R + 16\pi \rho_0 \epsilon \left(\frac{\sigma^{12}}{9R^9} - \frac{\sigma^6}{3R^3} \right).$$

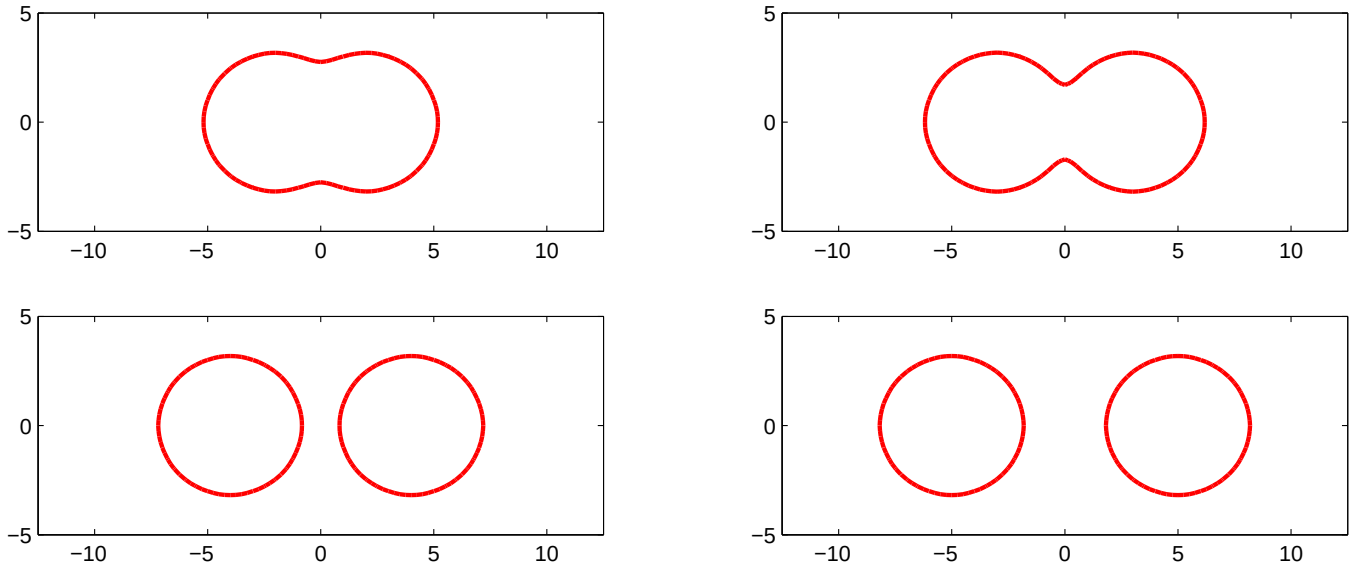


The decay of the free energy with respect to level-set iteration steps.

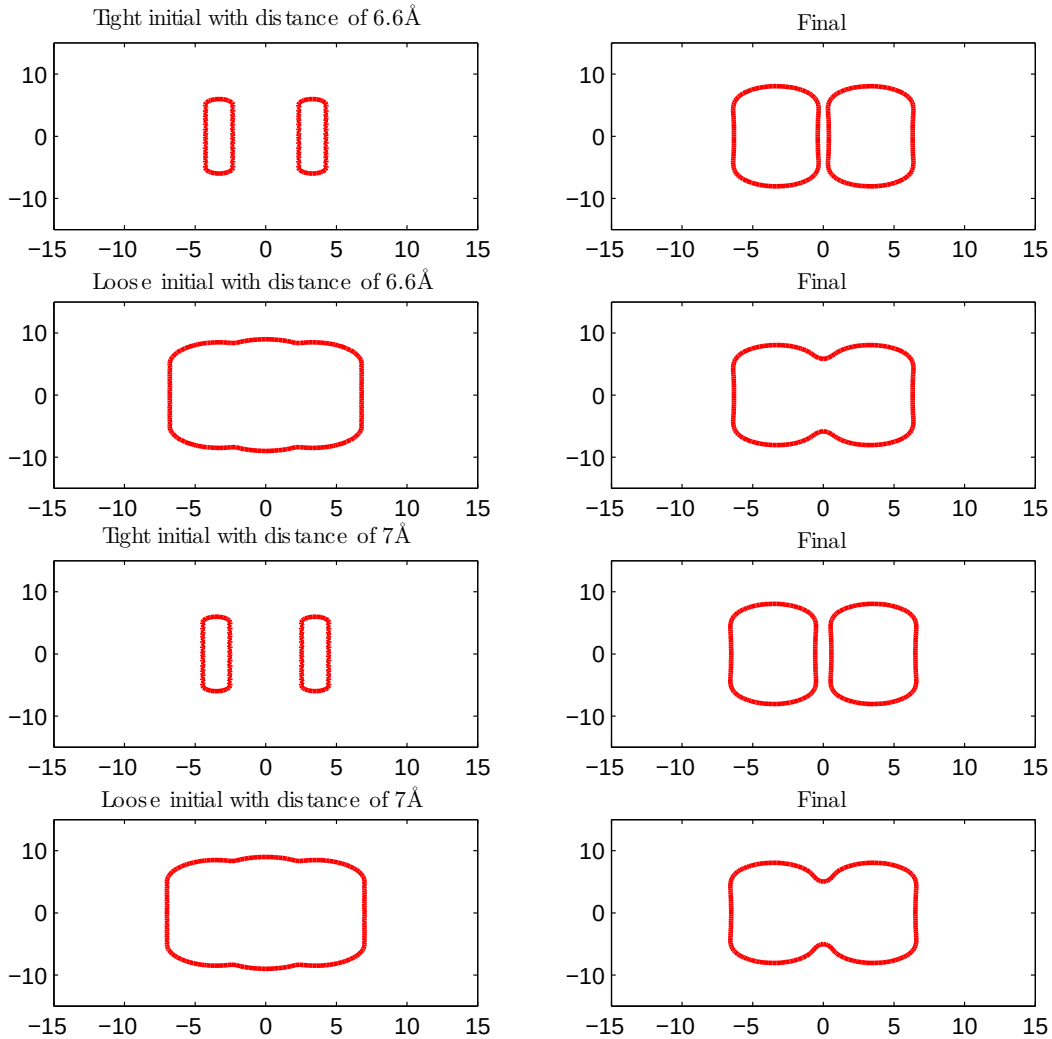


The free energy vs. step size in logarithmic scale.

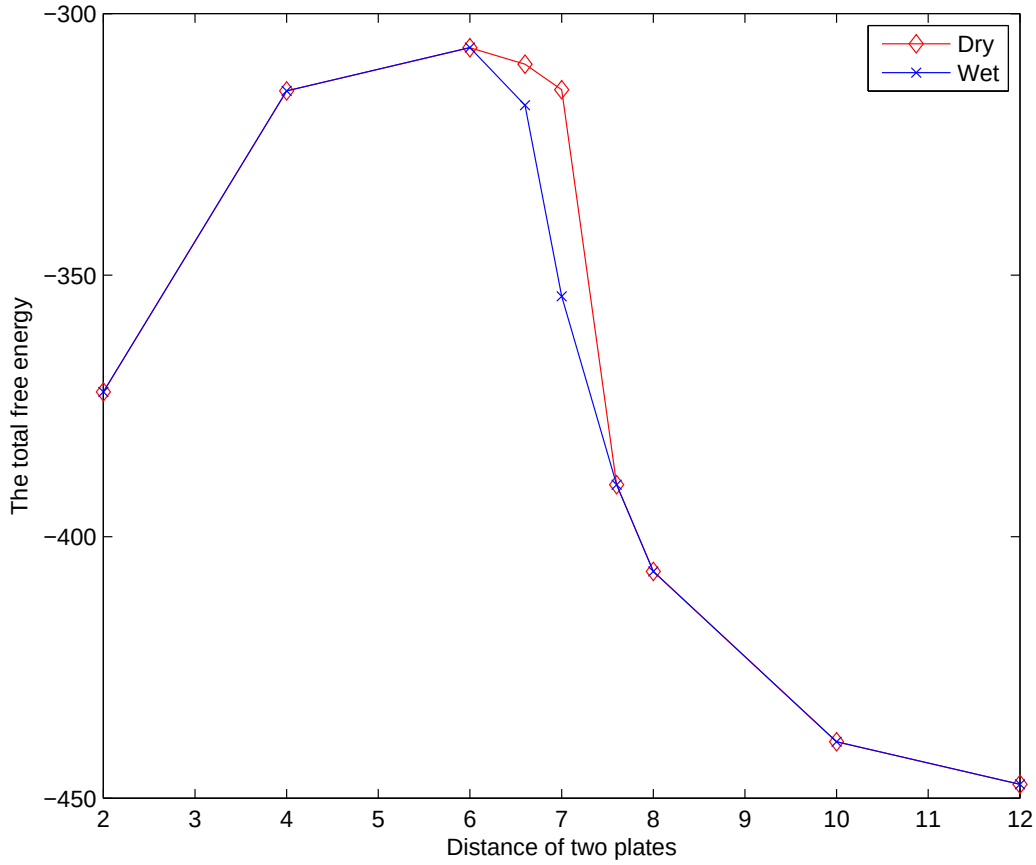
5. Application to Molecular Solvation



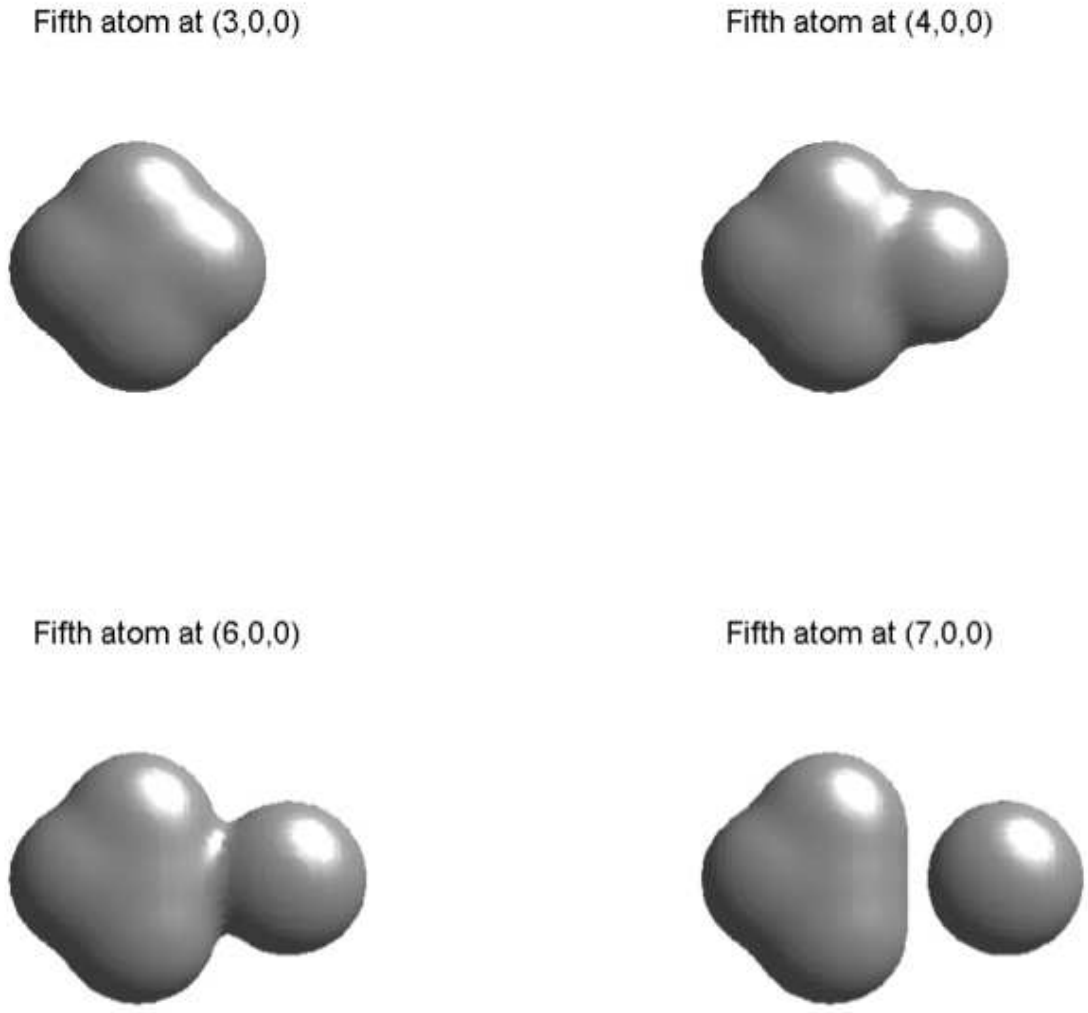
A two-atom system. Cross sections of the free-energy minimizing surfaces at distance $d = 4$Å (upper left), $d = 6$Å (upper right), $d = 8$Å (lower left), and $d = 10$Å (lower right).



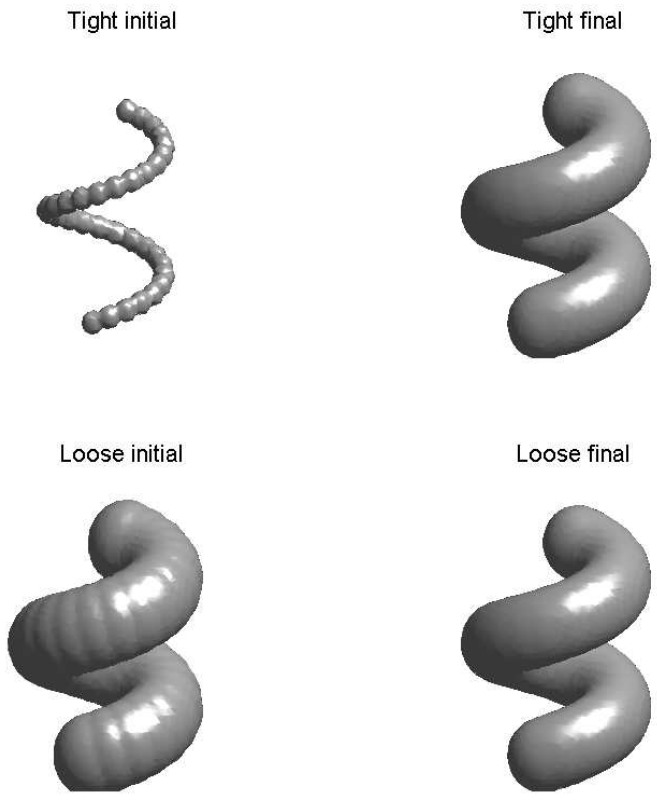
A two-plate system. Cross sections of initial and final surfaces at two different separations $d = 6.6$Å (left) and $d = 7$Å (right).



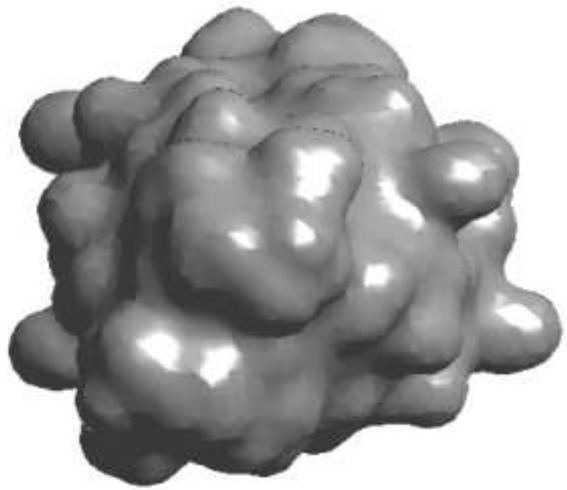
A two-plate system (continued). The free energy vs. the plate separation distance, showing a hysteresis loop.



Topological changes in a system of 5 atoms.



A helical polymer. Two different initial surfaces and their corresponding final surfaces.



The free-energy minimizing surface of an artificial molecule.

6. Conclusions

Developed and tested a level-set optimization method

- Discretization: centered differencing for curvatures, upwinding for lower-order hyperbolic terms
- Parameter correction: mathematical regularization and physical modeling
- Tested second-order convergence rate
- Application to solvation of simple, nonpolar molecules
  - Initial surfaces determine final, free-energy minimizing surfaces
  - Efficiency vs. accuracy.

Current work

- Improve the accuracy lost in the difference of large geometrical and LJ parts of the free energy
- Speed up the computation
- Convergence analysis
- Add the surface integral of the Gaussian curvature
- Include electrostatics
- Monte Carlo level-set method for searching local minima
- Application to large biomolecular systems

Reference

L.-T. Cheng, B. Li, and Z. Wang, Level-set minimization of potential controlled Hadwiger valuations for molecular solvation, J. Comp. Phys., 2010 (accepted).

Thank you!