Modeling Lipid Membrane at Celluar to Subcelluar Scales: Numerical Simulations
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Accurate Gradient and Force Computation for Elliptic Interface Problems

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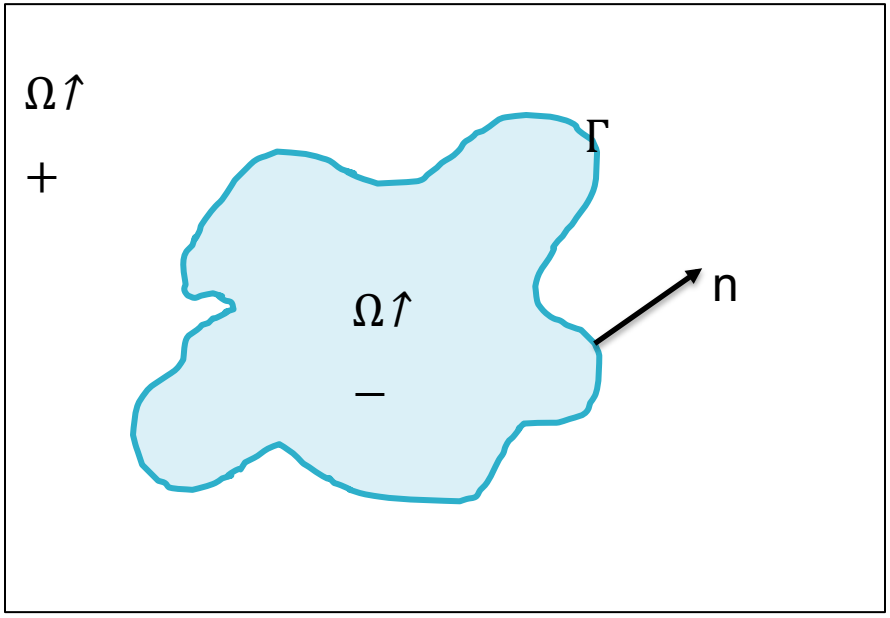
Elliptic Interface Problems

$$\nabla \cdot (\beta(\mathbf{x})\nabla u(\mathbf{x})) - \kappa(\mathbf{x})u(\mathbf{x}) = q(\mathbf{x}), \quad \mathbf{x} \in \Omega\backslash\Gamma, \quad \Omega = \Omega^+ \cup \Omega^-$$

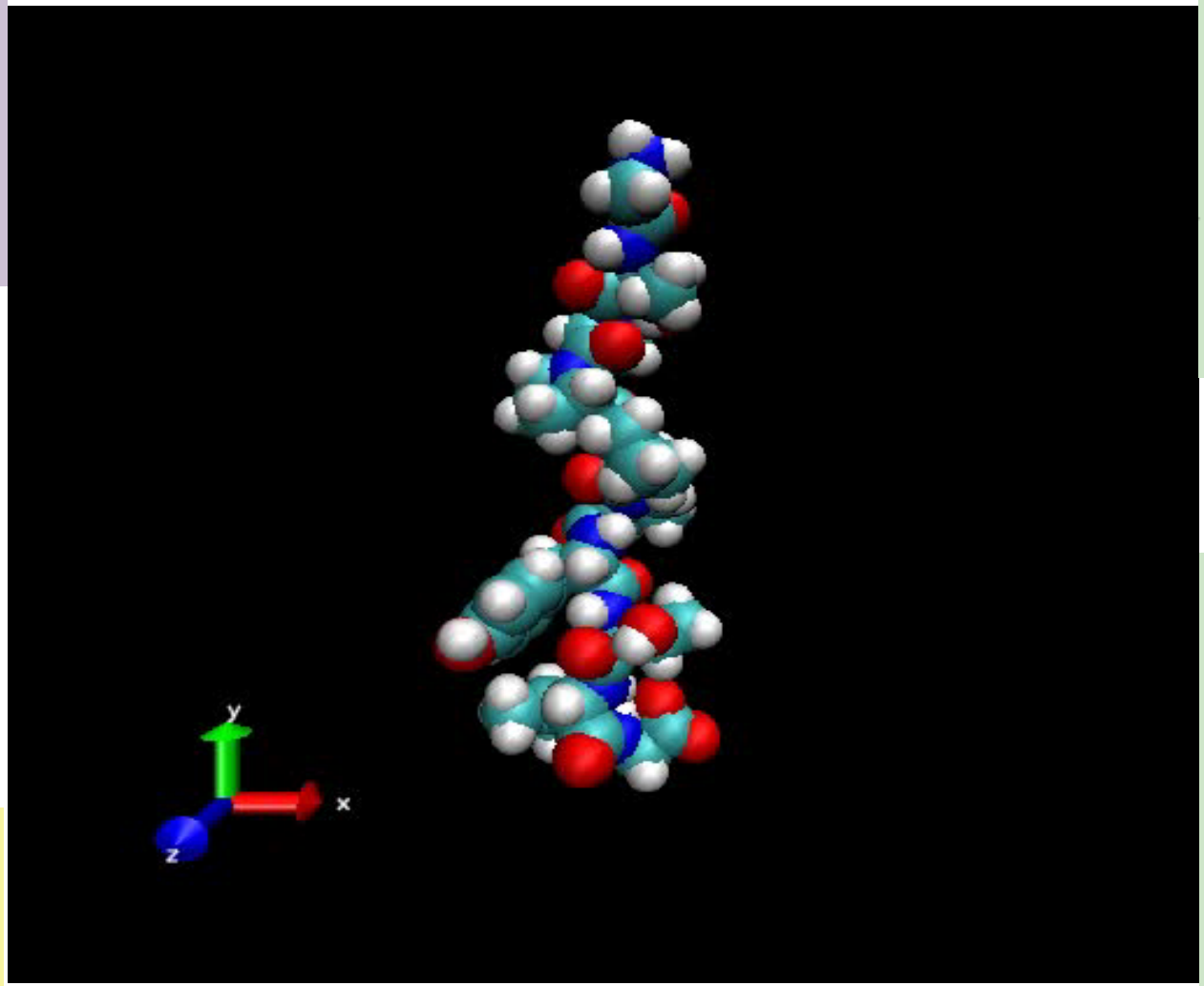
$$[u](\mathbf{X}) = w(\mathbf{X}), \quad [\beta(\mathbf{X})u_n(\mathbf{X})] = v(\mathbf{X}), \quad \mathbf{X} \in \Gamma,$$



Outline

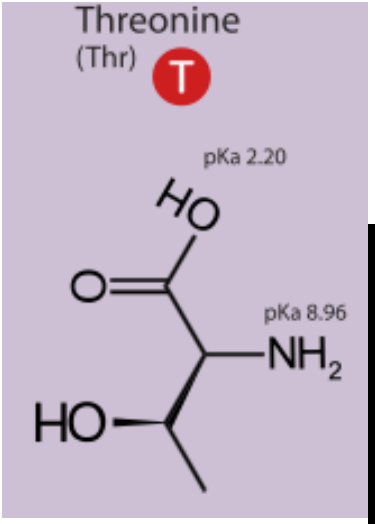
- Molecular Simulation and Solvent Models
- Matched Interface and Boundary Methods
  - The Capture of Interface Jumps
  - The Regularization of Singular Sources
- Force and Gradient Computation Using MIB
- Summary and Future Work

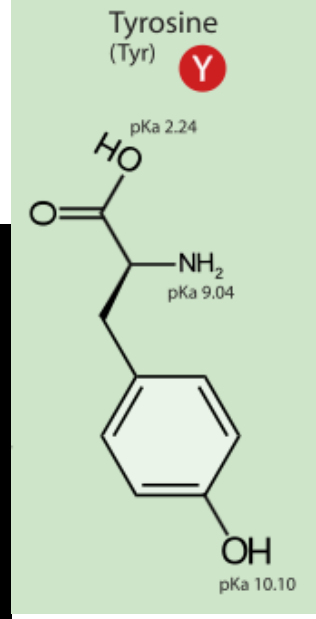
Molecular Simulation

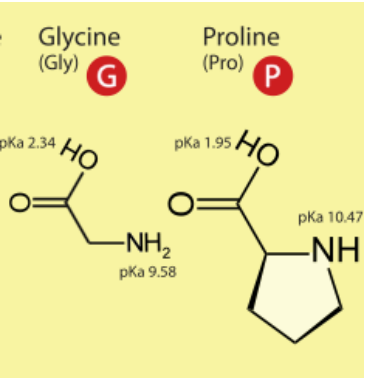


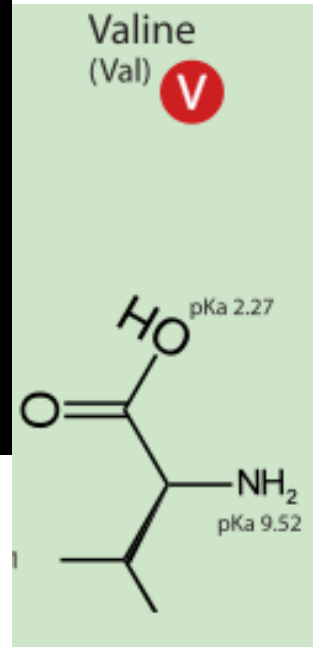
Amino acid sequence: GTPPPPYTVG

[Geng & Wei, J. Comput. Phys. 2011]









Molecular Simulation

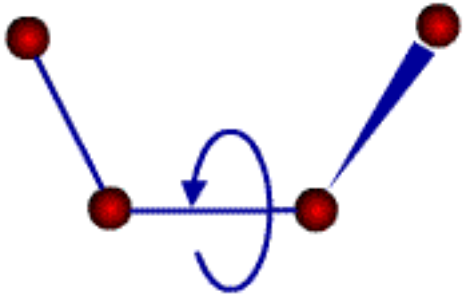
Molecular Mechanics (Newton's Laws of Motion)

$$\mathbf{a} = \frac{\mathbf{F}}{m}$$

Potential Function

Bond stretching

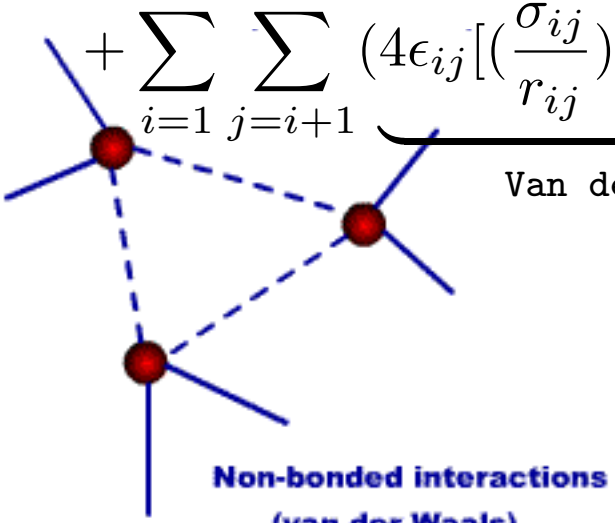
Angle Bending



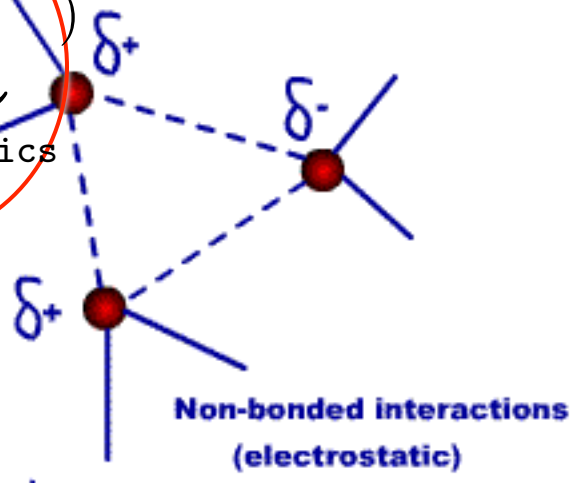
Bond rotation (torsion)

$$E = \sum_{\text{bonds}} \frac{k_i}{2}(l_i - l_{i,0})^2 + \sum_{\text{angles}} \frac{k_i}{2}(\theta_i - \theta_{i,0})^2 + \sum_{\text{torsions}} \frac{V_n}{2}(1 + \cos(n\omega - \gamma))$$

$$+ \sum_{i=1}^{N} \sum_{j=i+1}^{N} \underbrace{(4\epsilon_{ij}[(\frac{\sigma_{ij}}{r_{ij}})^{12} - (\frac{\sigma_{ij}}{r_{ij}})^{6}]}_{\text{Van der Waals}} + \underbrace{\frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}}_{\text{electrostatics}})$$



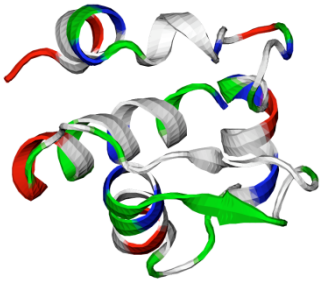
Non-bonded interactions
(van der Waals)

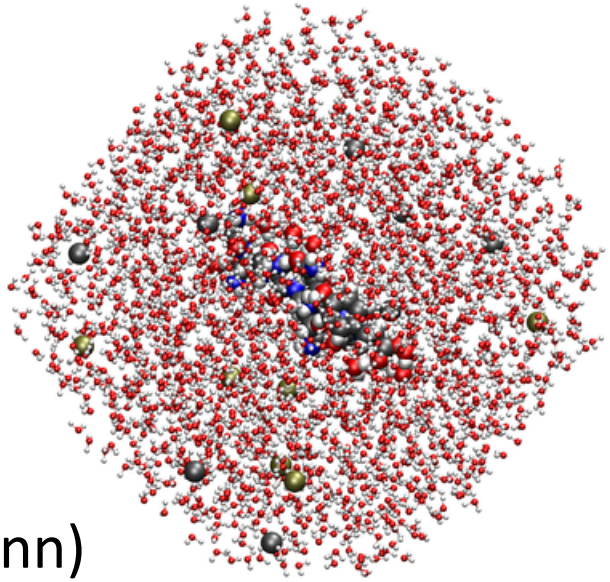


Non-bonded interactions
(electrostatic)

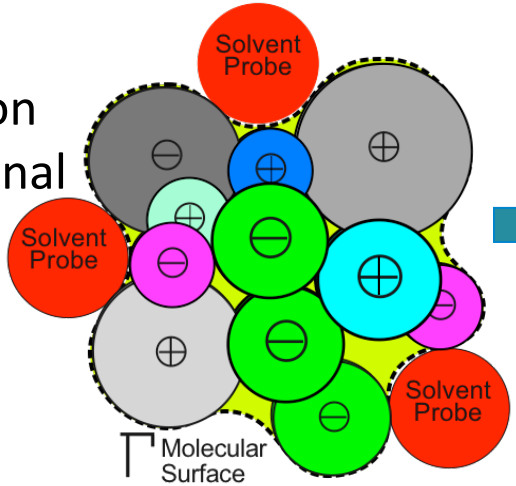
Solvent Models

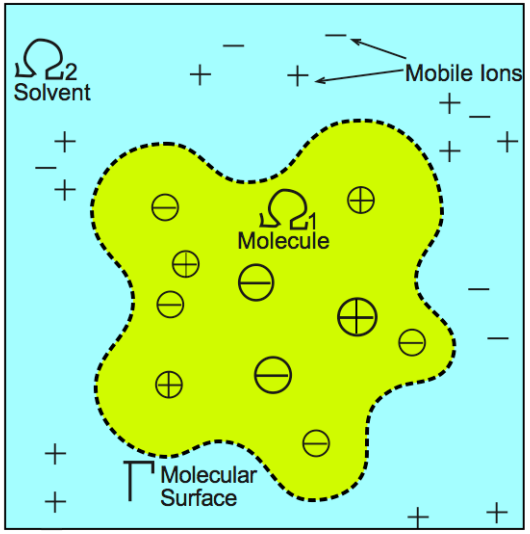
- Explicit solvent model
  - Atomic level description
  - Computationally demanding



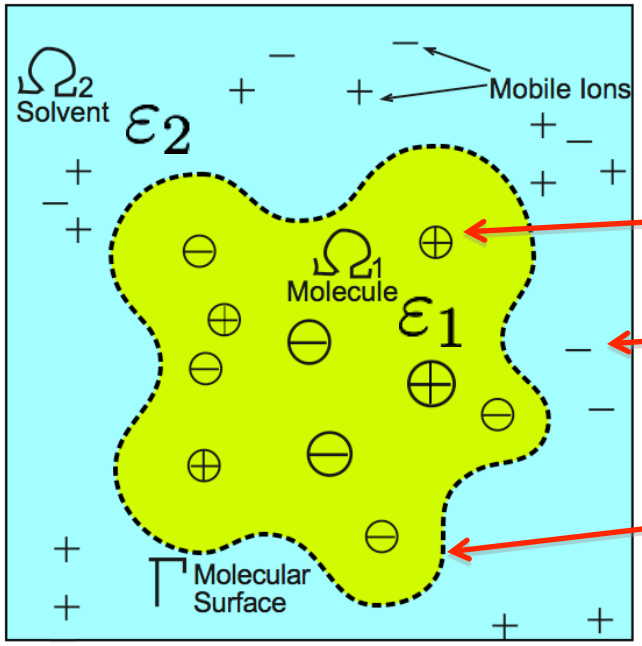


- Implicit solvent model (e.g. Poisson-Boltzmann)
  - Water approximated as a continuum
  - Ions described by a statistical distribution
  - Reduced computational cost





Poisson-Boltzmann (PB) Equation



$$\epsilon_1 \nabla^2 \phi_1(\mathbf{x}) = -\sum_{i=1}^{N_c} q_i \delta(\mathbf{x} - \mathbf{x}_i) \quad \text{in } \Omega_1,$$

$$\epsilon_2 \nabla^2 \phi_2(\mathbf{x}) = \bar{\kappa}^2 \sinh \phi_2(\mathbf{x}) \quad \text{in } \Omega_2,$$

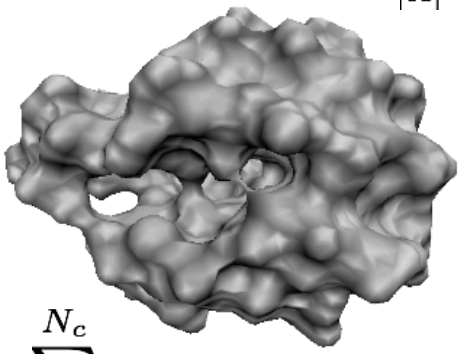
Interface jump conditions on Γ:

$$\phi_1(\mathbf{x}) = \phi_2(\mathbf{x}) \quad \text{and} \quad \varepsilon_1 \frac{\partial \phi_1(\mathbf{x})}{\partial \nu} = \varepsilon_2 \frac{\partial \phi_2(\mathbf{x})}{\partial \nu}$$

Boundary condition at infinity: $\lim_{|\mathbf{x}| \to \infty} \phi_2(\mathbf{x}) = 0$

Numerical Challenges:

1. Interface Jump Conditions



2. Complex molecular surface
3. Singular atomic charge distribution $\sum_{i=1}^{N_c} q_i \delta(\mathbf{x} - \mathbf{x}_i)$
4. Boundary condition at infinity $\lim_{|\mathbf{x}| \to \infty} \phi_2(\mathbf{x}) = 0$

Poisson-Boltzmann Application

- Chemistry: interfaces and colloids
  - Pioneering work: Chapman (1913), Gouy (1910), Debye-Hückel (1923)
  - Analytical and numerical work: Kirkwood (1934), Carnie (1994), Lenhoff (1994)
  - Applications: Moallemi et al. (2011), Duval et al.(2011), Dunér et al. (2012), Mampallil et al. (2013)
- EE: semiconductor devices
  - Darling (1989), Ciucci et al. (2011), Dessai et al. (2011), Csontos et al. (2005), Landheer et al. (2007), Mitchell et al. (2000), Rahmat (1996)
- Biology: solvated biomolecules
  - Protein-Protein Interaction: Dong et al. (2003), Huang et al. (2003)
  - Chromatin packing: Beard et al. (2001)
  - Pka: Nielsen et al. (2001)
  - Membrane: Callenberg et al. (2012)
  - Binding Energy: Garcá-García et al. (2003)
  - Solvation Free Energy: Simonson et al. (2002), Wagoner et al. (2006)
  - Ion Channel Profiling: Unwin (2003)

Nonlinear PB --- $\sinh(\phi)$

Linear PB --- ϕ

Existing Finite Difference Based PB Solvers

- Examples
  - APBS - (Baker-Holst, 2000)
  - DelPhi - (Klapper-Hagstrom-Fine-Sharp-Honig, 1986)
  - PBEQ - (Im-Beglov-Roux, 1998)
  - PBSA - (Luo-David-Gilson, 2002)
  - UHBD - (Davis-Madura-Luty-McCammon, 1991)
- Advantages
  - Convenient to implement
  - Robust
  - User Friendly Interface
- Disadvantages
  - Large memory requirement for 3D grid
  - Infinite domain is truncated
  - Approximate treatment of interface
  - Atomic charges are interpolated onto grid

Matched Interface & Boundary Method

- Literature
  - Maxwell Equation: Zhao & Wei (2004)
  - Interface jumps conditions, Zhou, Feig & Wei (2006)
  - Complex geometry, Yu, Geng, & Wei (2007);
  - Charge singularities, Geng, Yu & Wei (2007), Geng & Zhao (2017)
  - Force calculation and molecular dynamics, Geng & Wei (2011)
  - Poisson-Nernst-Planck equation, Zheng & Wei (2011)
  - Kohn-Sham equation, Chen & Wei (2011)
  - Navier-Stokes equation, Zhou, Liu & Harry (2013)
  - Finite Element MIB, Xia & Wei (2014)
- Key Ideas
  - Repeatedly use interface jump conditions
  - Local high order interpolation for geometric singularities
  - Green's function based charge regularization

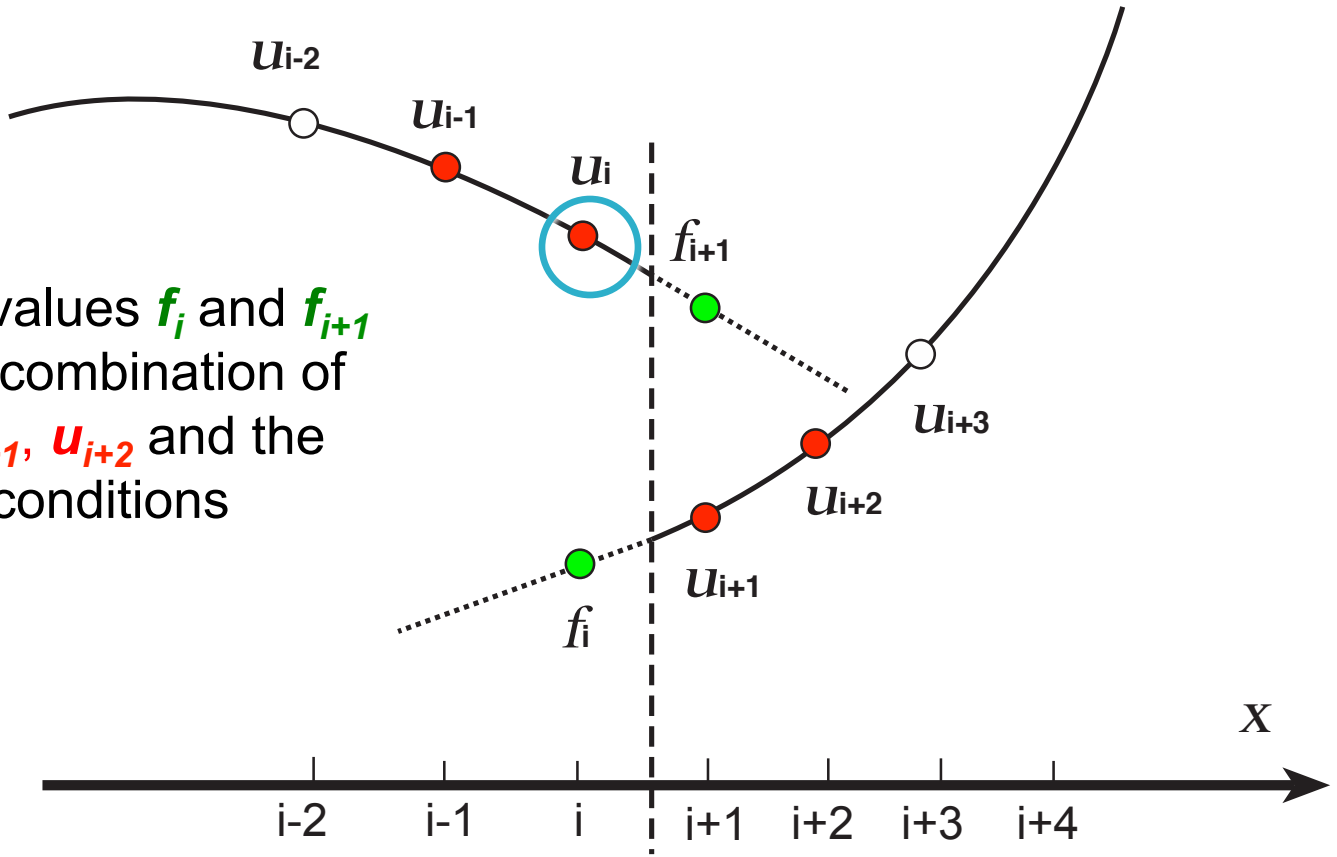
A 1-D illustration of MIB method

To solve $u'' = g(x)$ subject to interface jump conditions:

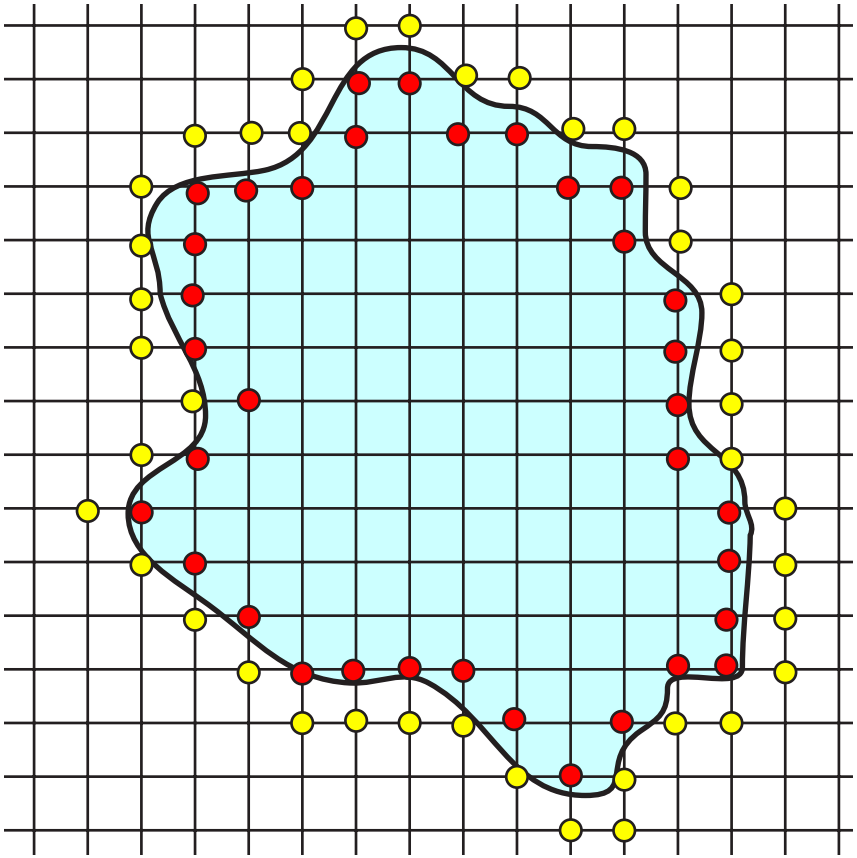
$$[u]_{\Gamma} = u^+ - u^- = \varphi(x) \quad \text{and} \quad [\varepsilon u_\nu]_{\Gamma} = \varepsilon^+ u_x^+ - \varepsilon^- u_x^- = \psi(x)$$

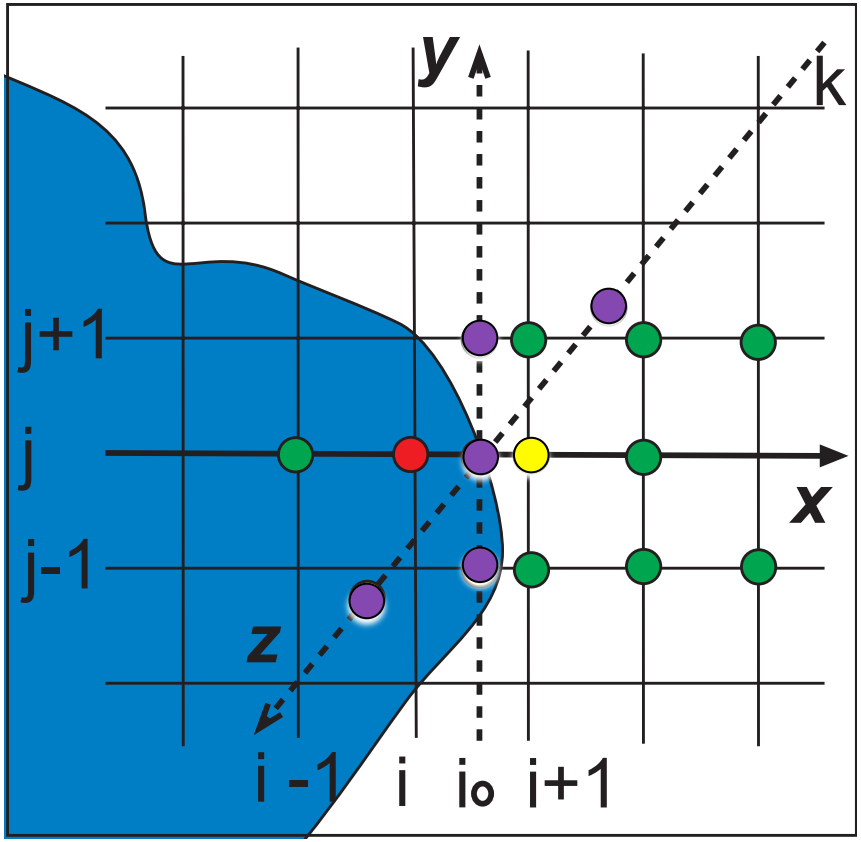
Finite difference: $\dfrac{u_{i+1} + u_{i-1} - 2u_i}{h^2}$ MIB: $\dfrac{f_{i+1} + u_{i-1} - 2u_i}{h^2}$

Fictitious values f_i and f_{i+1} are linear combination of u_{i-1}, u_i, u_{i+1}, u_{i+2} and the two jump conditions



2-D Fictitious Domain and Interpolation

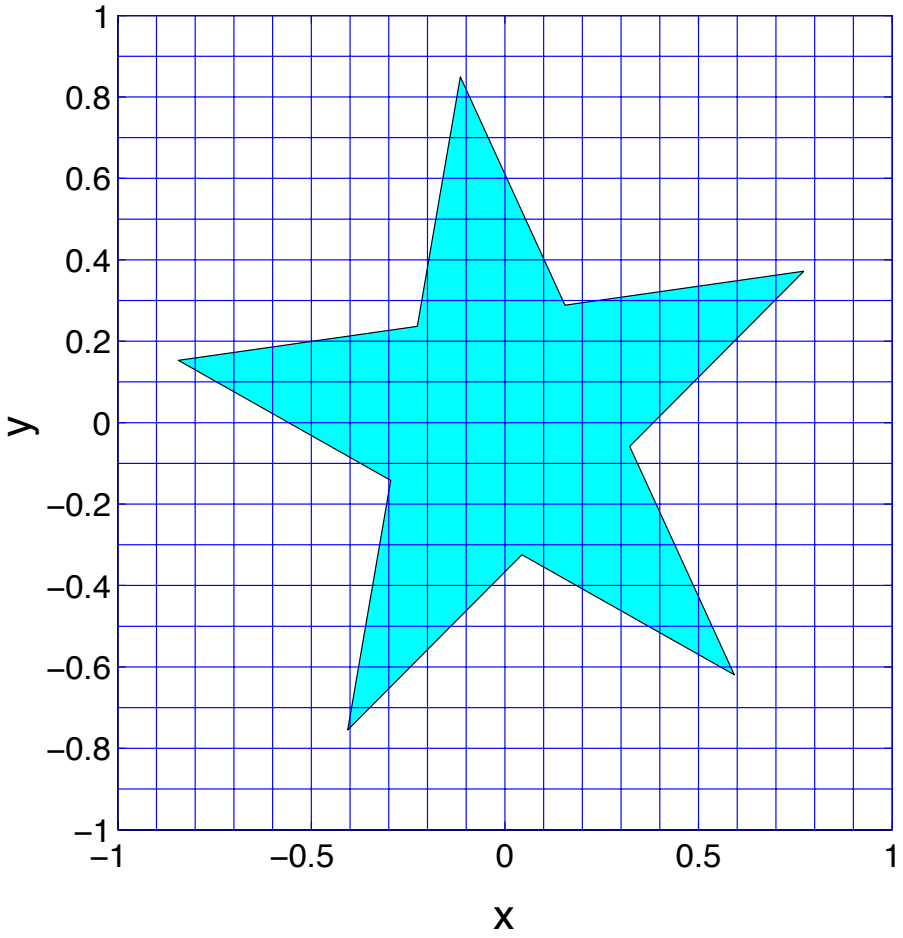


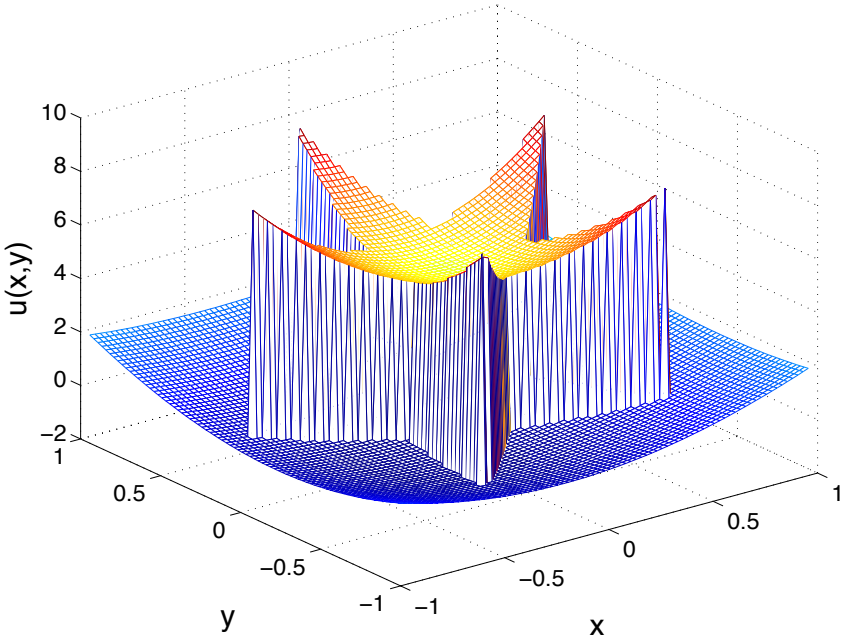


Fictitious values at the red/yellow pair are linear combination of the regular values at the 10 grid points (green/red/yellow) and the interface jump conditions.

[Zhou, Feig & Wei, J Comput. Chem. (2006)]

Complex Geometry





Fictitious values are linear combination of the regular values at even more points and the interface jump conditions.

[Yu, Geng & Wei, J. Phys. Chem. (2007)]

Regulation I: Three Components Decomposition

$$\begin{cases} -\nabla\cdot(\varepsilon(\mathbf{r})\nabla\phi(\mathbf{r}))+\bar{\kappa}^2(\mathbf{r})\phi(\mathbf{r})=\sum_{i=1}^{N_m} q_i\delta(\mathbf{r}-\mathbf{r_i}) \\ \phi_1(\mathbf{r})=\phi_2(\mathbf{r}), \quad \varepsilon_1\dfrac{\partial\phi_1(\mathbf{r})}{\partial\nu}=\varepsilon_2\dfrac{\partial\phi_2(\mathbf{r})}{\partial\nu} \quad \text{on } \Gamma \end{cases}$$

$$\phi=\phi^*+\phi^0+\tilde{\phi}$$

$$\phi^*(\mathbf{r})=\sum_{i=1}^{N_m}\frac{z_i}{4\pi\varepsilon_1(\mathbf{r}-\mathbf{r}_i)} \quad \text{in} \quad \Omega_1$$

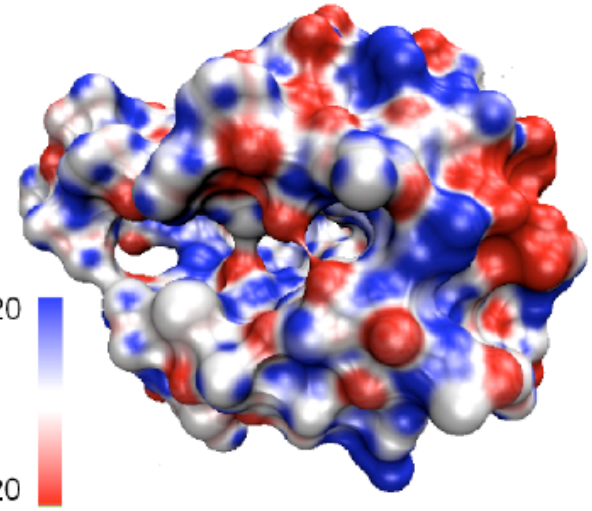
$$\begin{cases} \triangle\phi^0=0 & \text{in} \quad \Omega_1 \\ \phi^0=-\phi^* & \text{on} \quad \Gamma \end{cases}$$

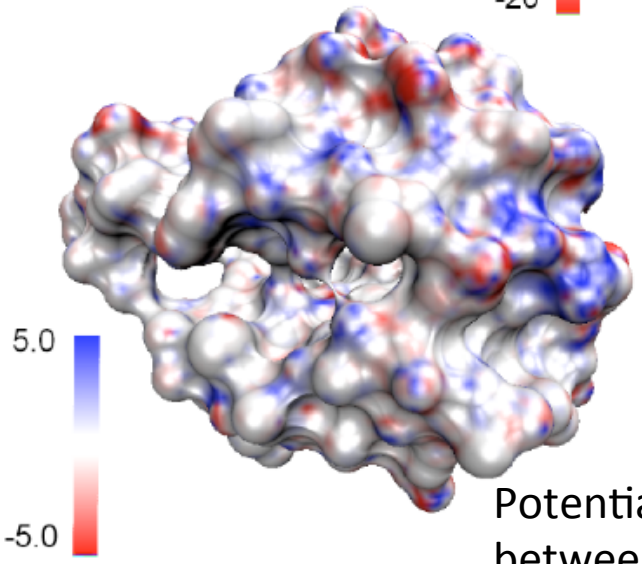
$$\begin{cases} -\nabla\cdot(\varepsilon(\mathbf{r})\nabla\tilde{\phi}(\mathbf{r}))+\bar{\kappa}^2\tilde{\phi}(\mathbf{r})=0 \\ [\tilde{\phi}]_\Gamma=0 \text{ and } [\varepsilon\tilde{\phi}_\nu]_\Gamma=\varepsilon_1\nabla(\phi^*+\phi^0)\cdot\nu|_\Gamma \end{cases}$$

[Geng, Yu & Wei, J. Phys. Chem. (2007)]

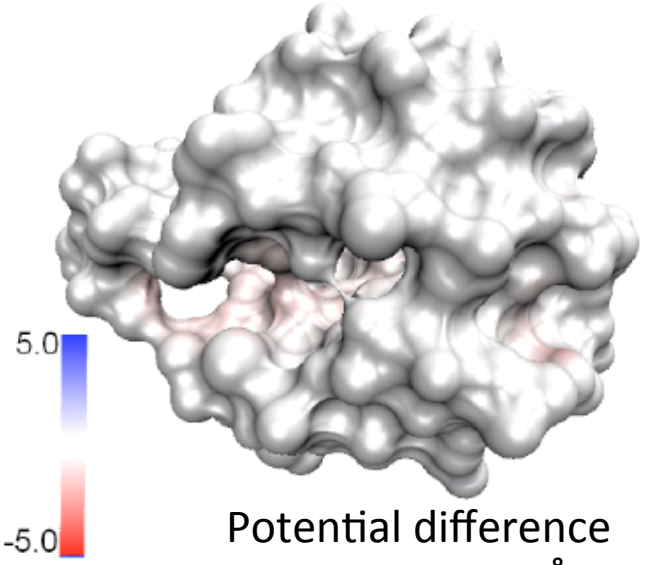
Potential mapping and convergence testing on 451C

Surface Potential





Potential difference between h=0.25Å and h=0.5Å solved by APBS



Potential difference between h=0.25Å and h=0.5Å solved by MIB-PB

[Geng, Yu & Wei, J. Phys. Chem. (2007)]

Regulation II: Two Components Decomposition

$$\phi = \phi_C + \phi_{\mathrm{RF}} \quad \text{where} \quad \phi_C(\mathbf{r}) = G(\mathbf{r}) = \sum_{i=1}^{N_c} \frac{q_i}{\epsilon_1 |\mathbf{r} - \mathbf{r}_i|}$$

solves

$$\begin{cases} -\epsilon_1 \Delta \phi_C(\mathbf{r}) &= \sum_{i=1}^{N_c} 4\pi q_i \delta(\mathbf{r} - \mathbf{r}_i) \quad \text{in } \mathbb{R}^3; \\ \phi_C(\mathbf{r}) &= 0. \qquad\qquad\qquad\qquad\quad \text{as } |\mathbf{r}| \to \infty. \end{cases}$$

Define

$$\tilde{\phi} = \begin{cases} \phi_{\mathrm{RF}}^- & \text{in } \Omega^- \\ \phi^+ & \text{in } \Omega^+. \end{cases}$$

solving

$$\begin{cases} -\nabla \cdot (\epsilon_1 \nabla \tilde{\phi}) &= 0 & \text{in } \Omega^- \\ -\nabla \cdot (\epsilon_2 \nabla \tilde{\phi}) + \bar{\kappa}^2 \tilde{\phi} &= 0 & \text{in } \Omega^+ \\ \left[\tilde{\phi}\right] &= G & \text{on } \Gamma \\ \left[\epsilon \frac{\partial \tilde{\phi}}{\partial n}\right] &= \epsilon_1 \frac{\partial G}{\partial n} & \text{on } \Gamma \\ \tilde{\phi} &= \phi_b & \text{on } \partial\Omega \end{cases}$$

[Geng & Zhao, J. Comput. Phys. (2017)]

Accuracy Tests of rMIB

	Poisson Equation						PB Equation					
	MIB			rMIB			MIB			rMIB		
h	e_ϕ	ord.	E_{sol}	e_ϕ	ord.	E_{sol}	e_ϕ	ord.	E_{sol}	e_ϕ	ord.	E_{sol}
1	3.9e-2		-3175.6	3.1e-2		-3181.4	3.8e-2		-3202.5	3.0e-2		-3209.0
1/2	1.1e-2	1.9	-3136.2	8.2e-3	1.9	-3137.7	1.1e-2	1.8	-3161.8	8.5e-3	1.8	-3163.3
1/4	1.6e-3	2.8	-3121.8	1.1e-3	2.9	-3122.1	1.7e-3	2.7	-3147.5	1.2e-3	2.9	-3147.8
1/8	4.6e-4	1.8	-3123.7	3.3e-4	1.7	-3123.7	4.8e-4	1.8	-3149.5	3.5e-4	1.7	-3149.5
1/16	9.0e-5	2.3	-3124.2	9.4e-5	1.8	-3124.2	9.8e-5	2.3	-3150.0	8.6e-5	2.0	-3150.0

Solving PB equation and Poisson equations on a spherical cavity with six off-centered charges: spherical radius r=2, ϵ↓1 =1, ϵ↓2 =80, κ=1 for PB and κ=0 for Poisson.

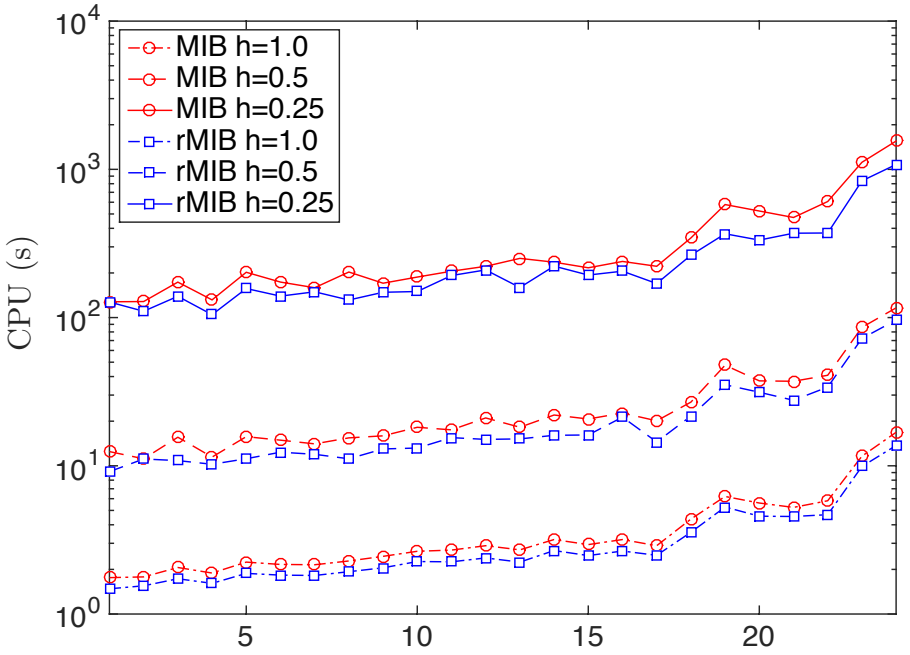
[Geng & Zhao, J. Comput. Phys. (2017)]

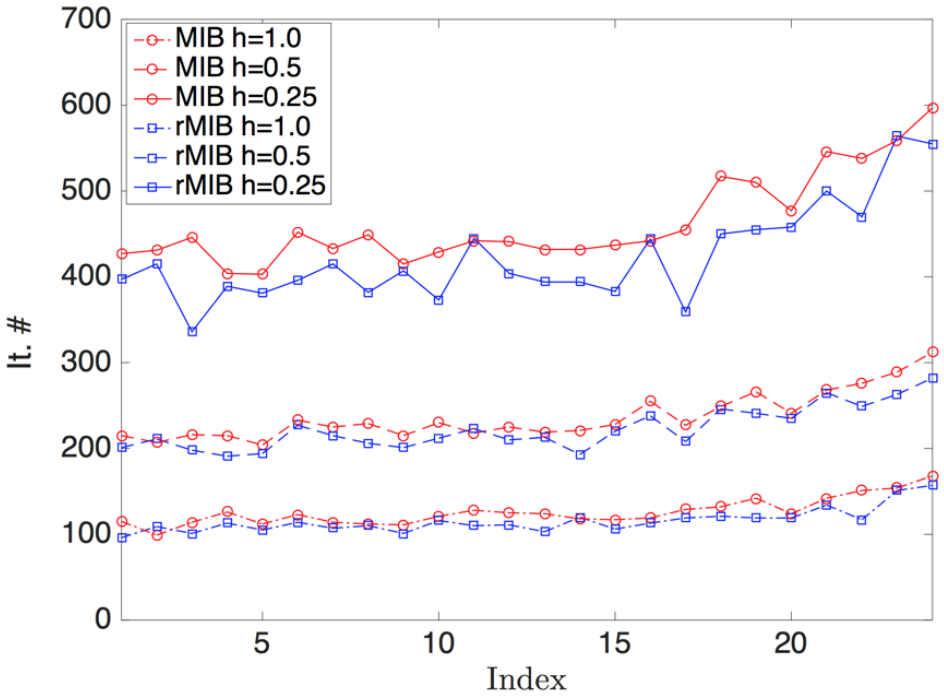
	$\epsilon_1 = 4$				$\epsilon_1 = 8$				$\epsilon_1 = 20$			
h	1.0	0.5	0.25	0.125	1.0	0.5	0.25	0.125	1.0	0.5	0.25	0.125
4pti	-15.8	+1.9	+0.4	-5887.9	-5.6	+1.3	+0.3	-2933.9	-0.4	+0.8	+0.2	-1162.6
err.(%)	0.27	0.03	0.01	–	0.19	0.05	0.01	–	0.03	0.07	0.02	–
2ovo	-13.9	+1.5	+0.3	-4326.3	-5.3	+1.0	+0.2	-2154.4	-0.7	+0.6	+0.1	852.4
err.(%)	0.32	0.03	0.01	–	0.25	0.05	0.01	–	0.08	0.06	0.01	–

Electrostatic free energies E↓sol of proteins 4pti and 2ovo computed with rMIB solver: ϵ↓1 =4,8, 20, ϵ↓2 =80, ion concentration = 0.15M, MSMS density =10, values at h=1, 0.5, 0.25 show difference from values at h=0.125 in kcal/mol.

[Hu, Zhao & Geng, CiCP (2018)]

Solving PB equation on a set of 24 proteins



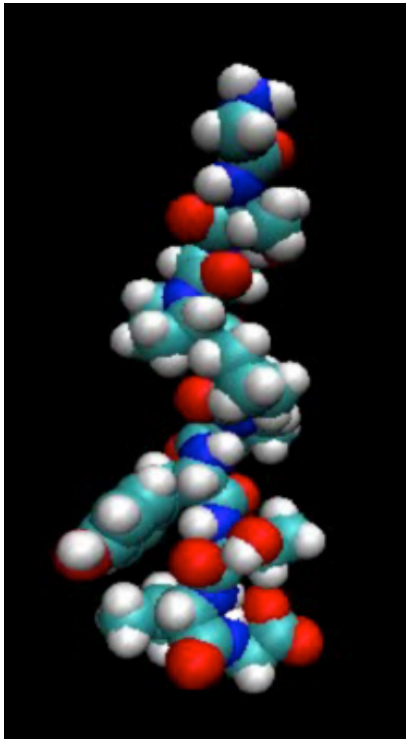


PB Equation Parameters:
$\epsilon\downarrow 1 = 1$, $\epsilon\downarrow 2 = 80$, $\kappa = 1$

[Geng & Zhao, J. Comput. Phys. (2017)]

Molecular Dynamics is the ultimate goal

Potential $\phi(x,y,z)$ → Force $\boldsymbol{F}$ on individual atoms



Not simply the q$\boldsymbol{E}$ term, $\boldsymbol{E}$ is not continuous across interface

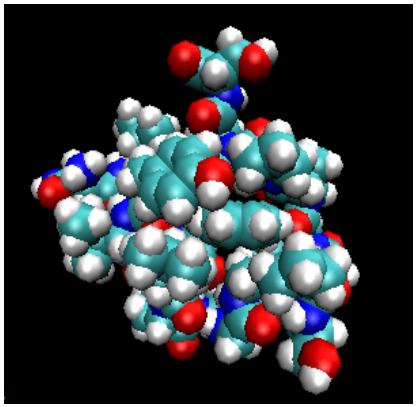
[Gilson et al. J. Comput. Phys. 1993]

$$\mathbf{F} = \int_{\Omega} [\rho_f \mathbf{E} - \frac{1}{2}|\mathbf{E}|^2 \nabla \epsilon - \frac{1}{2}\epsilon \kappa^2 \phi^2 \nabla \lambda] d\Omega$$

reaction force

dielectric boundary force

ionic boundary force



Computing force is an interface problem.

[Geng & Wei, J. Comput. Phys. 2011]

Dielectric Boundary Force

$$\mathbf{F}^{\mathrm{DB}} = \int_{\mathbf{\Gamma}} f^{\mathrm{DB}} d\mathbf{S} = \int_{\mathbf{\Gamma}} \frac{1}{2}(\epsilon^{+}|\mathbf{E}^{+}|^{2}) - \epsilon^{-}|\mathbf{E}^{-}|^{2})d\mathbf{S}$$

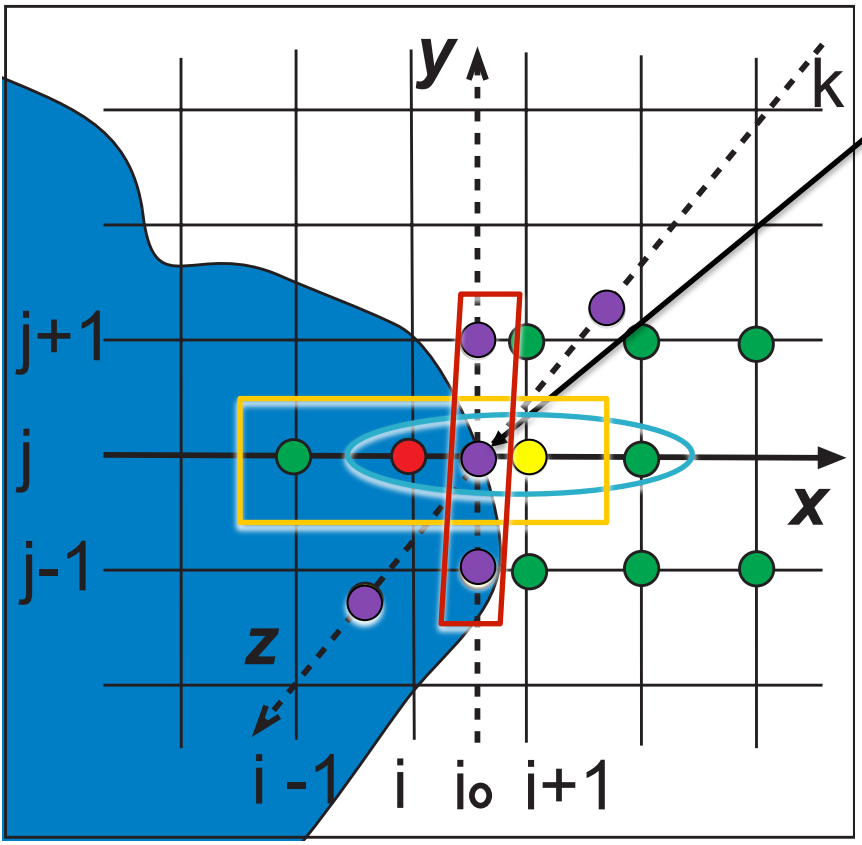
Challenge:

- Find f^{DB} from surface potentials and their gradient
- Numerical Surface Integral
- Distribution of the force to individual atoms

Reference:

Lu et al. (2007), Che et al. (2008), Zhou et al. (2008), Geng et al. (2011), Li et al. (2011), Li et al. (2013)

Gradient of Potential Computed Using MIB



To compute gradient at an interface points, we need [$\phi\downarrow x\uparrow+$, $\phi\downarrow x\uparrow-$, $\phi\downarrow y\uparrow+$, $\phi\downarrow y\uparrow+$, $\phi\downarrow z\uparrow+$, $\phi\downarrow z\uparrow+$]

In MIB scheme,

$$\begin{bmatrix} \xi \\ \eta \\ \zeta \end{bmatrix} = \begin{bmatrix} \sin\psi\cos\theta & \sin\psi\sin\theta & \cos\psi \\ -\sin\theta & \cos\theta & 0 \\ -\cos\psi\cos\theta & -\cos\psi\sin\theta & \sin\psi \end{bmatrix} \begin{bmatrix} x \\ y \\ z \end{bmatrix}$$

From interface jumps,

$$\begin{bmatrix} [\beta\phi_\xi] \\ [\phi_\eta] \\ [\phi_\zeta] \end{bmatrix} = \mathbf{C} \cdot \begin{bmatrix} \phi_x^+ \\ \phi_x^- \\ \phi_y^+ \\ \phi_y^- \\ \phi_z^+ \\ \phi_z^- \end{bmatrix}$$

where

$$\mathbf{C} = \begin{bmatrix} \mathbf{C}_1 \\ \mathbf{C}_2 \\ \mathbf{C}_3 \end{bmatrix} = \begin{bmatrix} p_{11}\beta^+ & -p_{11}\beta^- & p_{12}\beta^+ & -p_{12}\beta^- & p_{13}\beta^+ & -p_{13}\beta^- \\ p_{21} & -p_{21} & p_{22} & -p_{22} & p_{23} & -p_{23} \\ p_{31} & -p_{31} & p_{32} & -p_{32} & p_{33} & -p_{33} \end{bmatrix}$$

Validation of Gradient (Normal Derivative)

N	IIM				MIB			
	$E\downarrow\infty$ (u)	order	$E\downarrow\infty$ ($u\downarrow n\uparrow-$)	order	$E\downarrow\infty$ (u)	order	$E\downarrow\infty$ ($u\downarrow n\uparrow-$)	order
32	3.1e-3		1.6e-2					
64	7.0e-4	2.2	4.5e-3	1.8				
128	1.2e-4	2.6	1.1e-3	2.0				
256	2.8e-5	2.1	2.9e-4	1.9				
512	6.2e-6	2.2	7.3e-5	2.0				

$$u(\mathbf{x}) = \begin{cases} \sin(x+y) & \text{in } \Omega^-, \\ \log(x^2+y^2) & \text{in } \Omega^+, \end{cases} \qquad \beta(\mathbf{x}) = \begin{cases} \sin(x+y)+2 & \text{in } \Omega^-, \\ \cos(x+y)+2 & \text{in } \Omega^+, \end{cases}$$

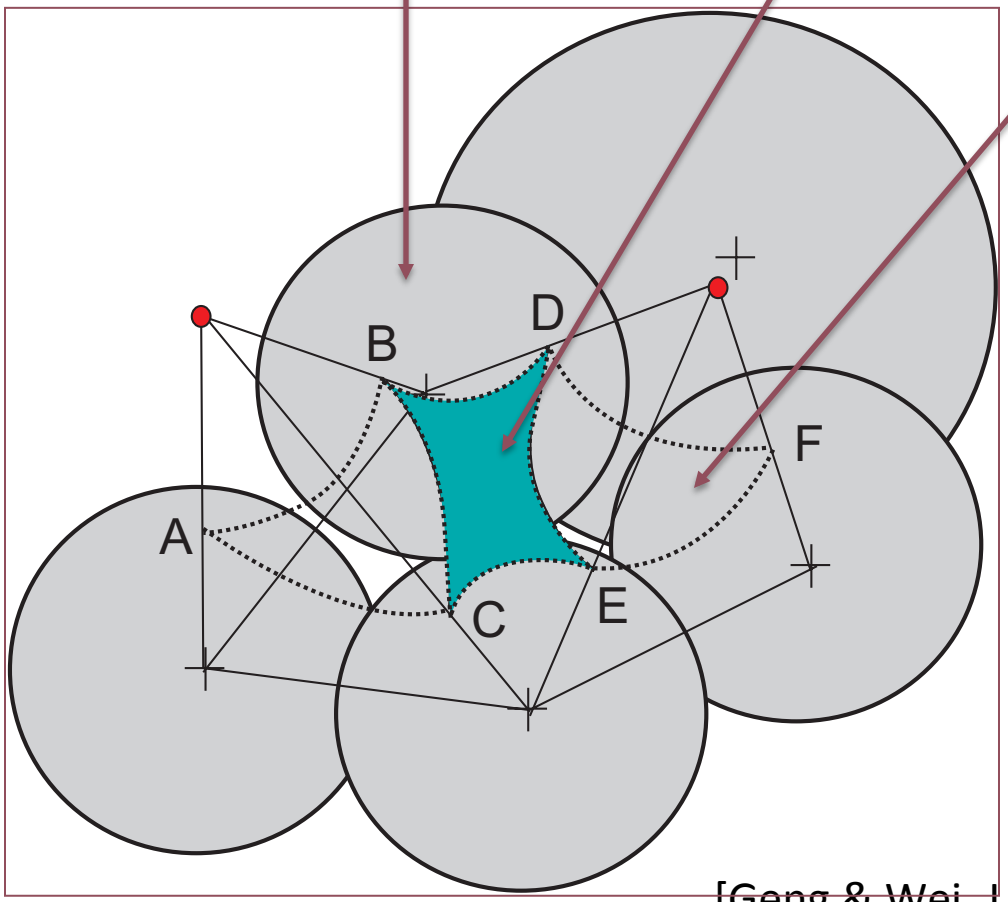
Interface: circle with radius ½ centered at (0,0)

IIM Data: [Li et al., SIAM Numer. Analy., 2017]

Validation of Forces

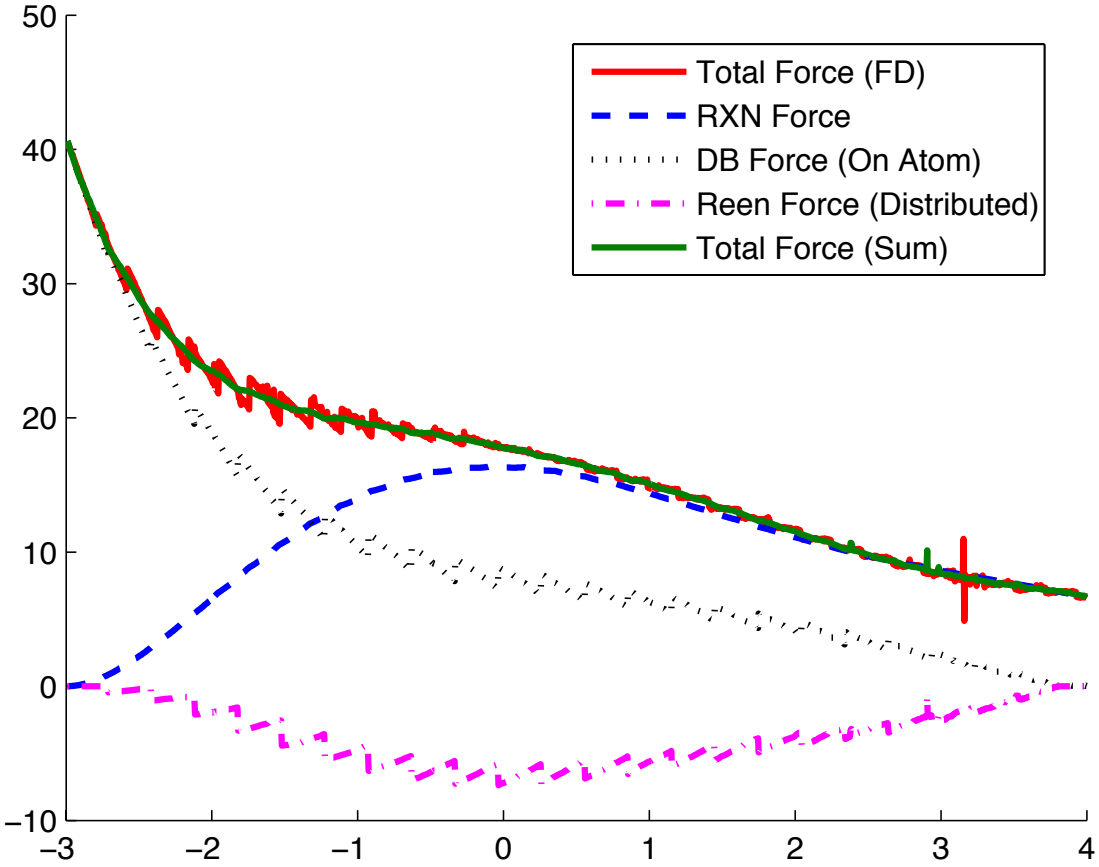
$$F_{x,i}^{\mathtt{FD}} = \frac{\Delta G(x+\delta h) - \Delta G(x-\delta h)}{2\delta h}$$

$$F_{x,i}^{\mathtt{sum}} = F_{x,i}^{\mathtt{RXN}} + F_{x,i}^{\mathtt{contact}} + F_{x,i}^{\mathtt{toric}} + F_{x,i}^{\mathtt{reen}}$$



[Geng & Wei, J. Comput. Phys. 2011]

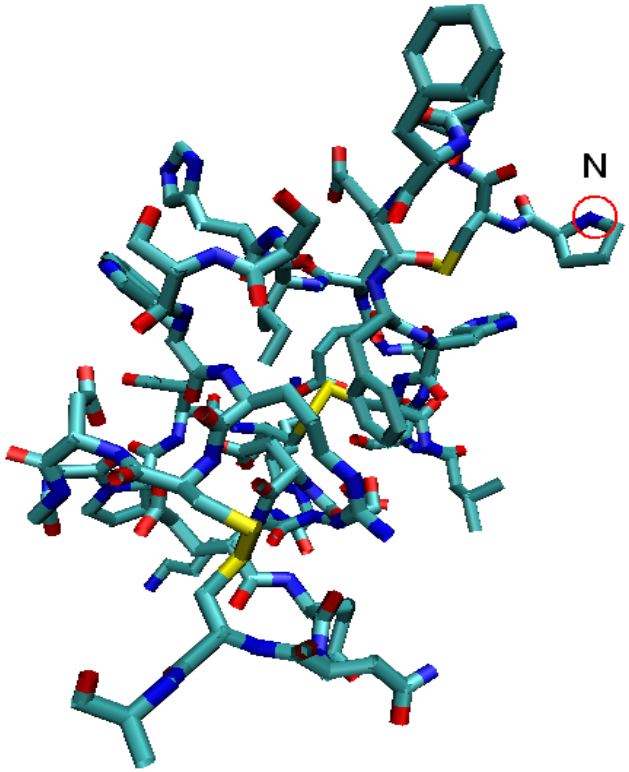
Validation: two-atom system

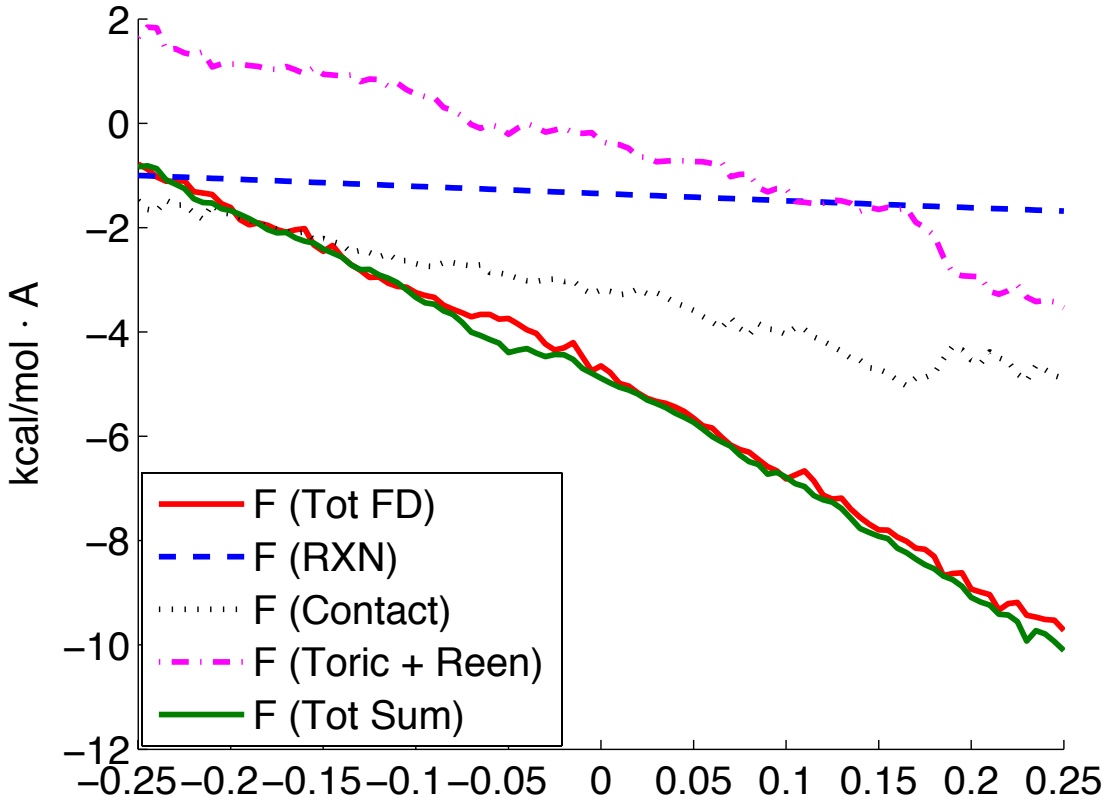


Two spherical atoms with radius 2.0 Å and centered
charge 1.0e,
one is fixed at (-3,0,0), the other moves from (-3,0,0) to (4,0,0)

[Geng & Wei, J. Comput. Phys. 2011]

Validation: Protein 1ajj

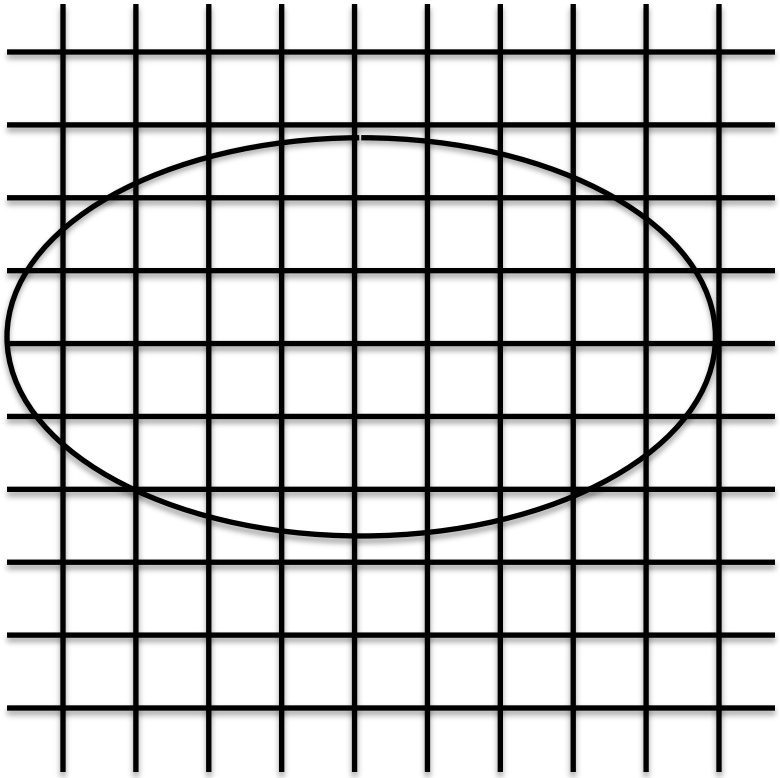




Protein 1ajj with 519 atoms; one nitrogen atom is moved from -0.25 to 0.25 from its original location.

[Geng & Wei, J. Comput. Phys. 2011]

Fields and Forces Computed Using rMIB



Summary of Future Work

- Summary
  - 2^{nd} order MIB returns 2^{nd} order Gradient?
  - MIB force for PB equation is qualitatively verified
- Future work
  - rMIB implementation
  - Improve the speed (mesh generator, linear algebraic solver, assignment of boundary condition)
  - Improve the robustness
  - Molecular simulation on larger proteins

Thank you