Simulating Electrostatics and Diffusion Processes at the Molecular Level

Benzhuo Lu

Institute of Computatuonal Mathematics and Scientific/Engineering Computing, China

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Outline

- **Introduction**
- **Continuum models and numerical solutions for**
  - **Equilibrium electrostatics**
  - **Electro-Diffusion-reaction**
  - **Model extensions**
- **Summary**
- **Future work**

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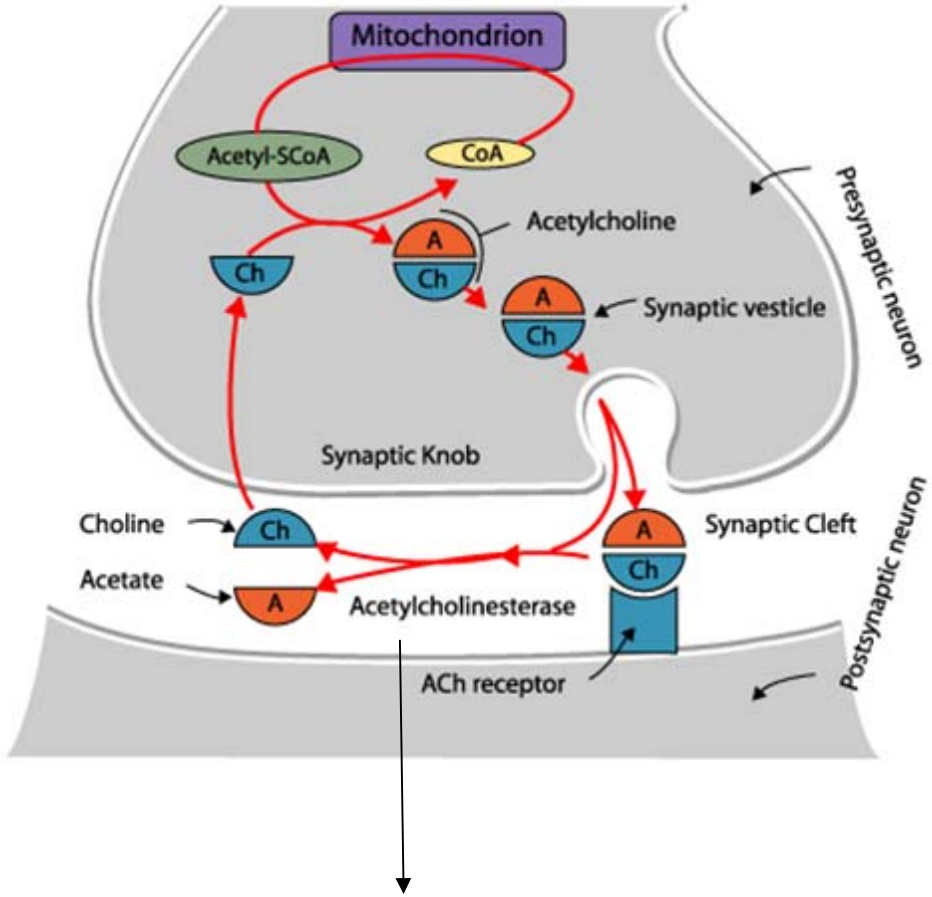
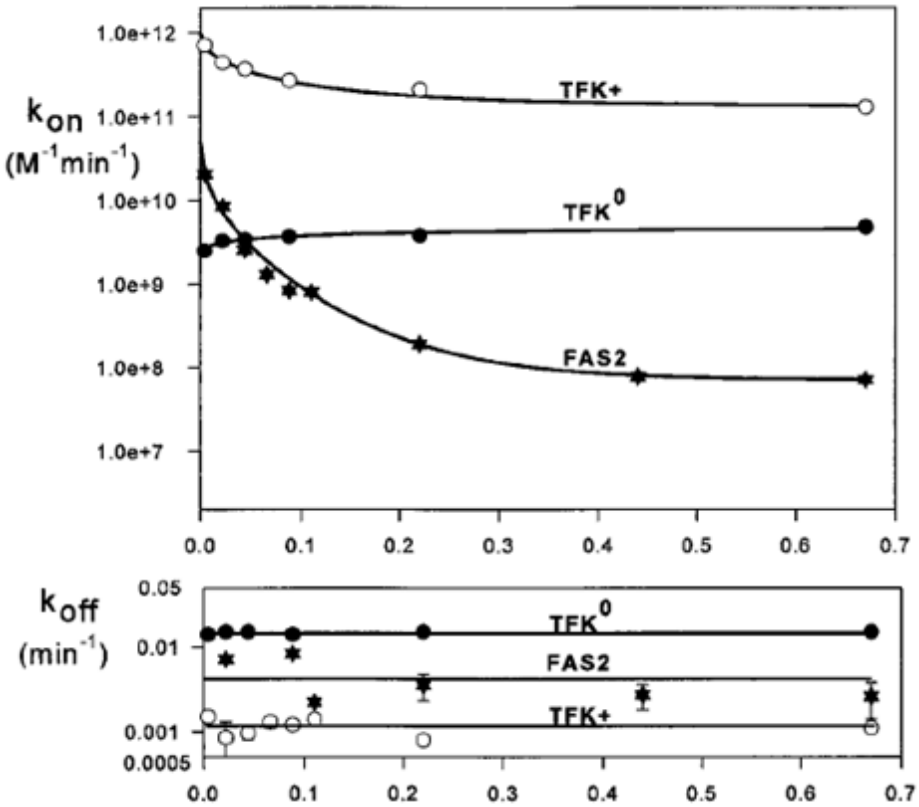
An example: neurotransmission in synapse



Substrate consumption

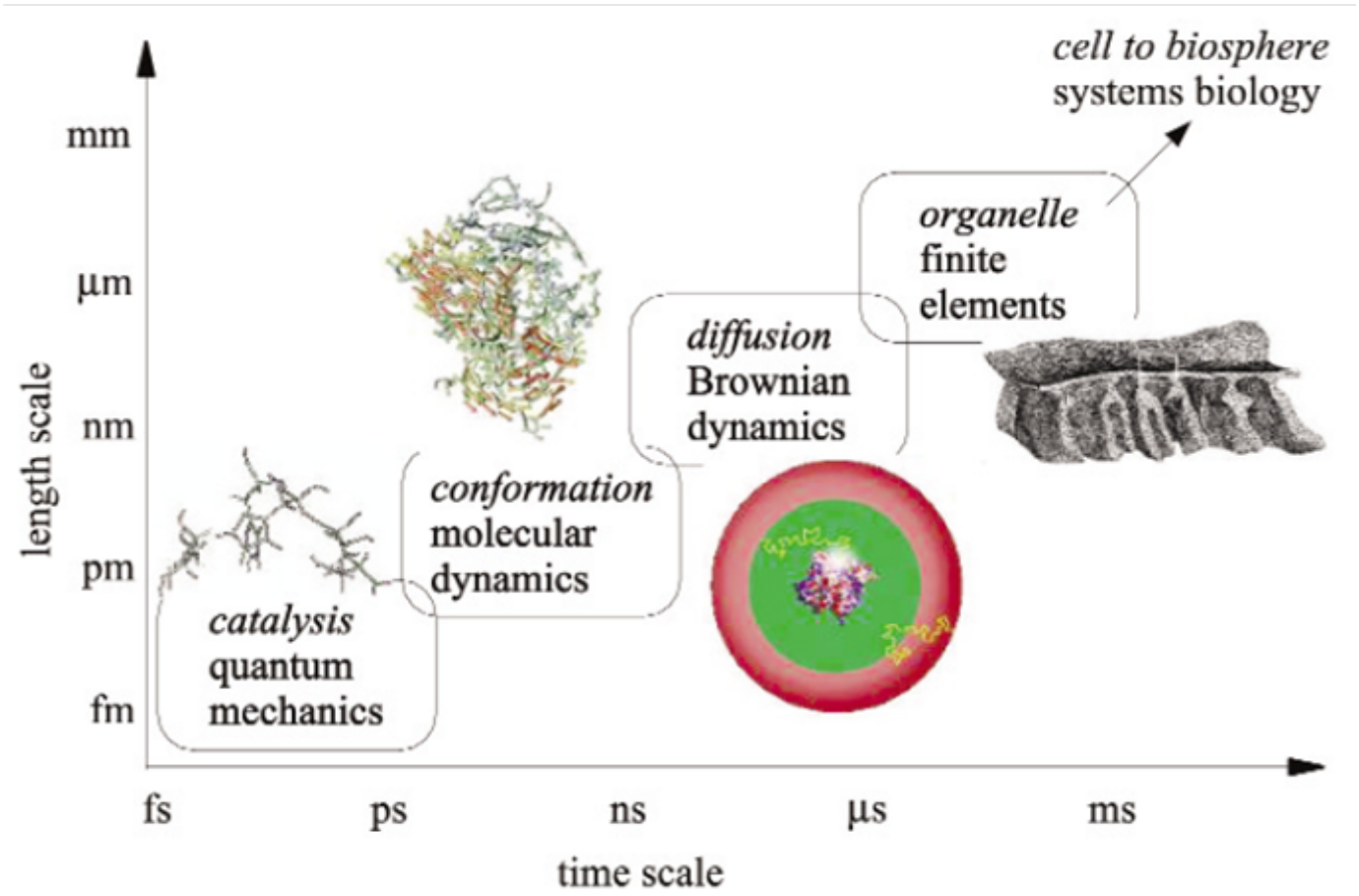
electrostatic steering



Rate and binding affinity decrease with [NaCl] has been attributed to screening effects.

Radic Z, et al. 1997. *J Biol Chem* **272**: 23265.

Scales and models



Granularity

Solution system: free energy and kinetics

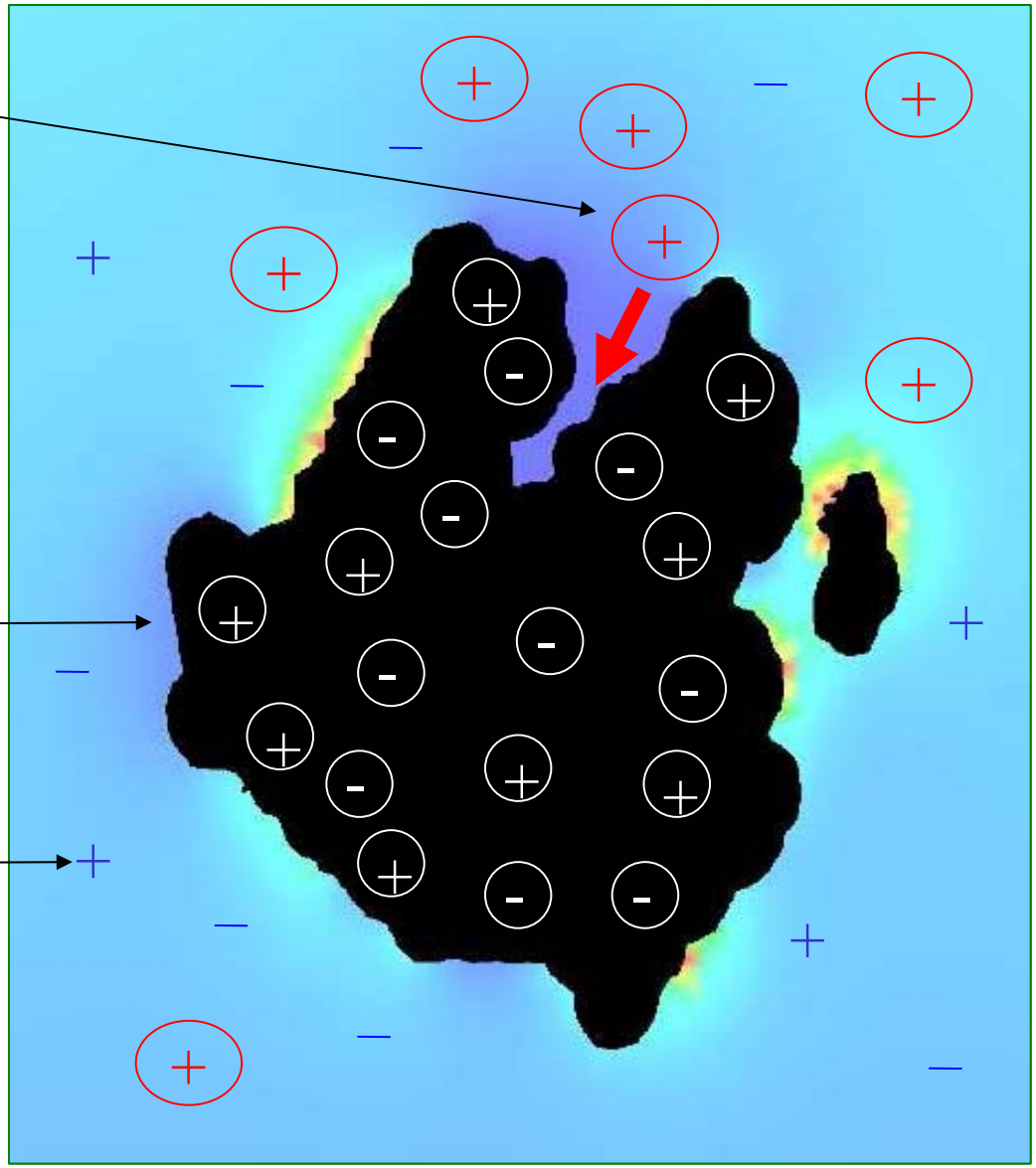
Diffusive/reactive particles

Solute charges

fixed ρ^f, ε_{in}

+/- salt

Density p^i, ε_{out}



Interactions:

Electrostatics

van der Waals

Electro-diffusion

- **Equilibrium**

  -- Electrostatics: Poisson-Boltzmann equation

  * Computational efficiency and accuracy
  * Post-processing: energy and force calculations

- **Non-equilibrium**

  -- Diffusion-reaction process: Poisson-Nernst-Planck model

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Electrostatics:

Poisson equation

$$-\nabla \varepsilon \nabla \phi - \lambda \rho^{ion} - \rho^{f} = 0$$

ρ^{ion} → Boltzmann distribution → **Poisson-Boltzmann equation**

$$-\nabla \varepsilon \nabla \phi - \lambda \sum_{j} c_j q_j e^{-\beta q_j \phi} - \rho^{f} = 0$$

Linearized PBE

$$-\nabla \cdot \epsilon \nabla \phi + \kappa^2 \phi = \rho^f$$

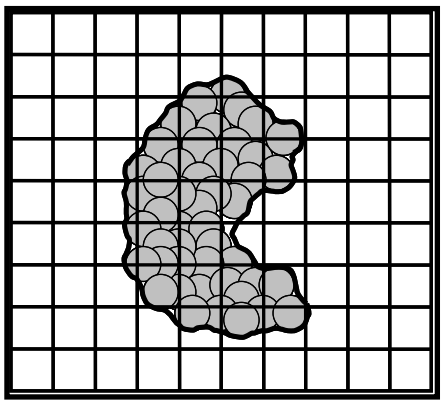
Issues

- Singular charge distribution within the molecule
- Discontinuous dielectric at the molecular surface
- Highly irregular molecular surface

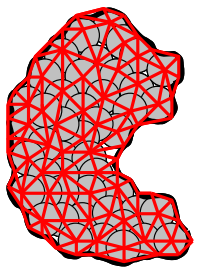
- Currently, efficiency is the main issue in PB applications.

Numerical methods

- **Finite difference**
  - **-- Grid ~ N^3**
  - -- Operations ~ N^3
  - -- Less accurate



- **Boundary element method (LPBE)**
  - -- Grid ~ N^2 ☺
  - -- Operations ~ N^2*N^2 ☹ -> challenge!



- **Finite element method**
  - -- Grid ~ N^3
  - -- Operations ~ N^3
  - -- Not easy to setup

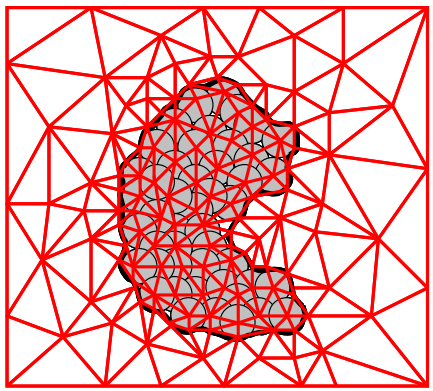


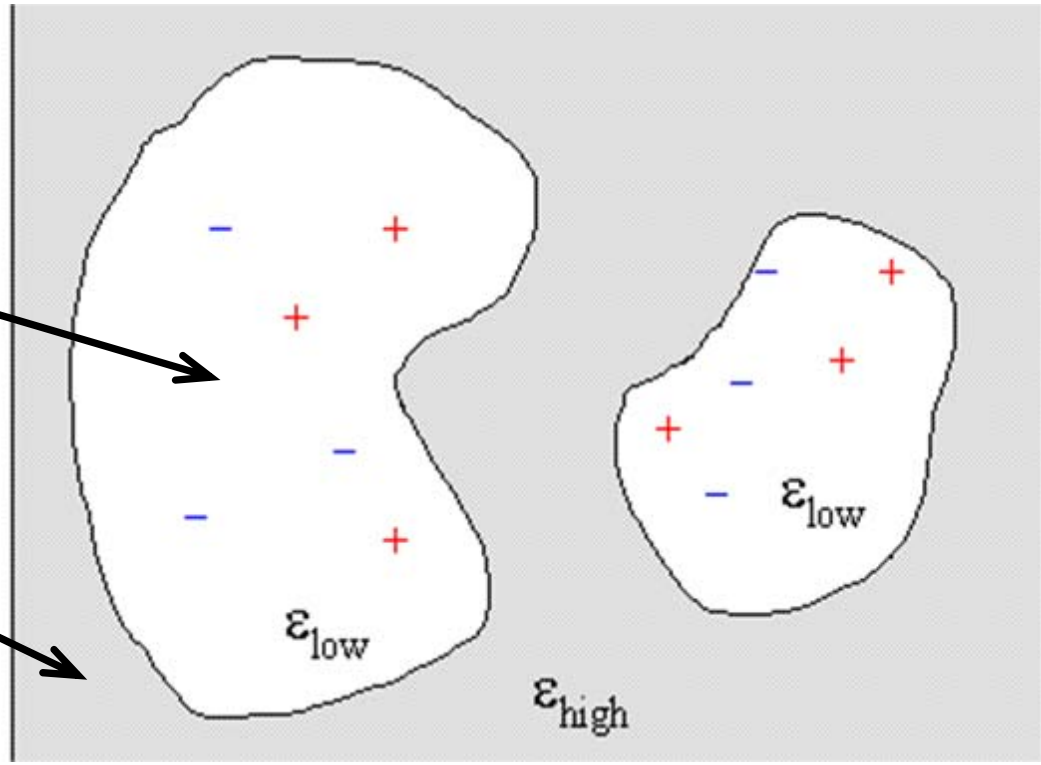
Figure borrowed from Nathan's talk

Boundary integral equations (BIE)

The linearized PB equation:

$$\nabla^2 \phi_p^{int} = -\frac{1}{D_{int}} \sum_k q_k \delta(r - r_k)$$

$$\nabla^2 \phi^{ext} = \kappa^2 \phi^{ext}(r)$$



Using Green's second identity for a single molecule

$$\int_V (\phi \nabla^2 \psi - \psi \nabla^2 \phi) dV = \int_S (\phi \nabla \psi - \psi \nabla \phi) \cdot dS$$

Boundary integral equations for LPBE

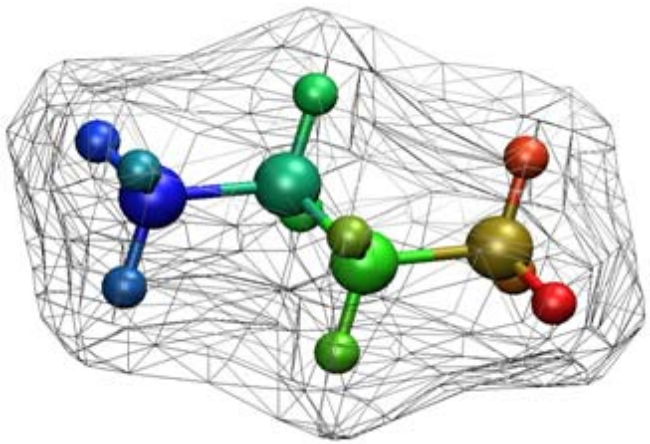
Using Green's theorem to recast the PBE to an integral form:

$$\frac{1}{2}\phi_p^{\text{int}} = \oint_S^{PV} [G_{pt}\frac{\partial \phi_t^{\text{int}}}{\partial n} - \frac{\partial G_{pt}}{\partial n}\phi_t^{\text{int}}]dS_t + \frac{1}{D_{\text{int}}}\sum_k q_k G_{pk}, \quad p \in S, \tag{1}$$

$$\frac{1}{2}\phi_p^{\text{ext}} = \oint_S^{PV} [-u_{pt}\frac{\partial \phi_t^{\text{ext}}}{\partial n} + \frac{\partial u_{pt}}{\partial n}\phi_t^{\text{ext}}]dS_t, \quad p \in S, \tag{2}$$

$$G_{pt} = \frac{1}{4\pi|r_t - r_p|} \text{ and } u_{pt} = \frac{\exp(-\kappa|r_t - r_p|)}{4\pi|r_t - r_p|}$$

Discretize: integral --> summation !

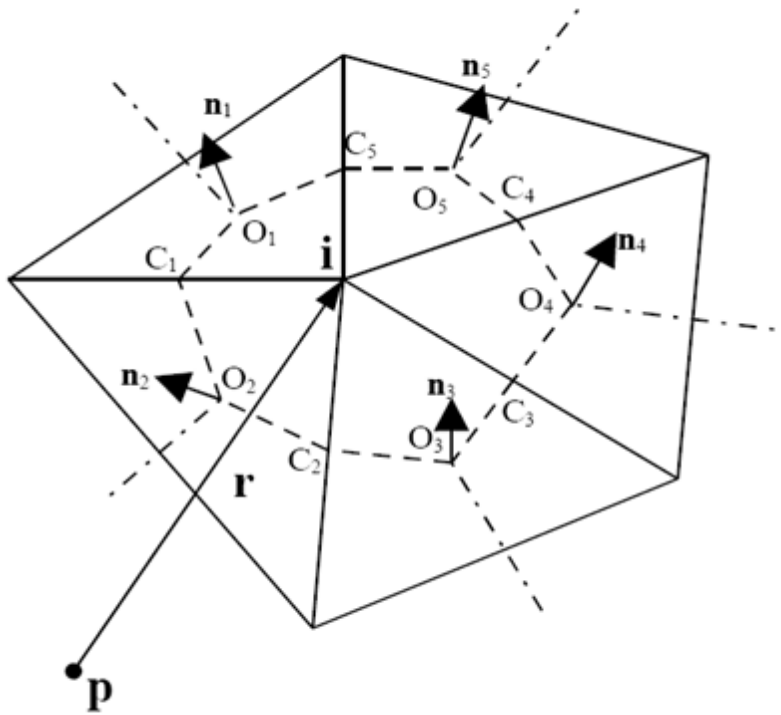
Discretize ⟹  ⟹ $Ax = b$

BEM bottleneck: computations ~ $N_{element}^2$!

Two techniques to accelerate the solution

- "Node patch" BEM
- "New Version Fast multipole method" and adaptive FMM
  Computations ~ N

“Node patch” BEM
-- most efficient low order BEM (?)



Advantages:

- Reduces the linear system size by half without losing accuracy
- Saves time when storing the matrix coefficients
- Source = target, nearly optimal in current AFMM calculations

Lu, B. Z. and McCammon, J. A. . *J. Chem. Theory. Comput*. 3:1134, 2007

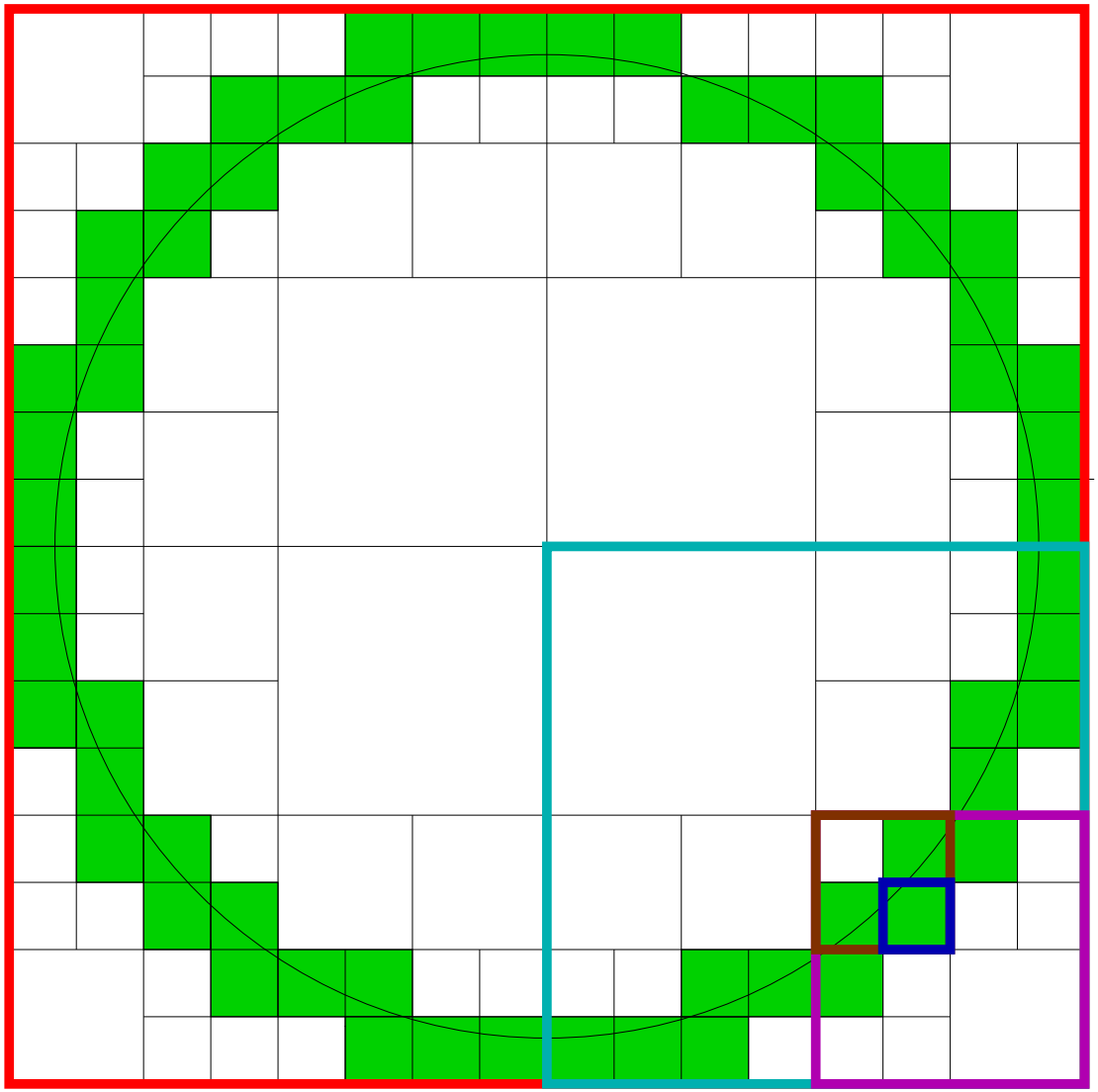
Fast multipole method

- Top 10 Algorithm of the 20th Century !
  Dongarra and Sullivan, *Computing in Science and Engineering*, Jan./Feb., 2000.

Complexity ~ O(N)

Greengard, Rokhlin, 1987, 1997;
Greengard, LF, Huang, JF, 2002

A 2D adaptive tree structure
-- AFMM



4 levels

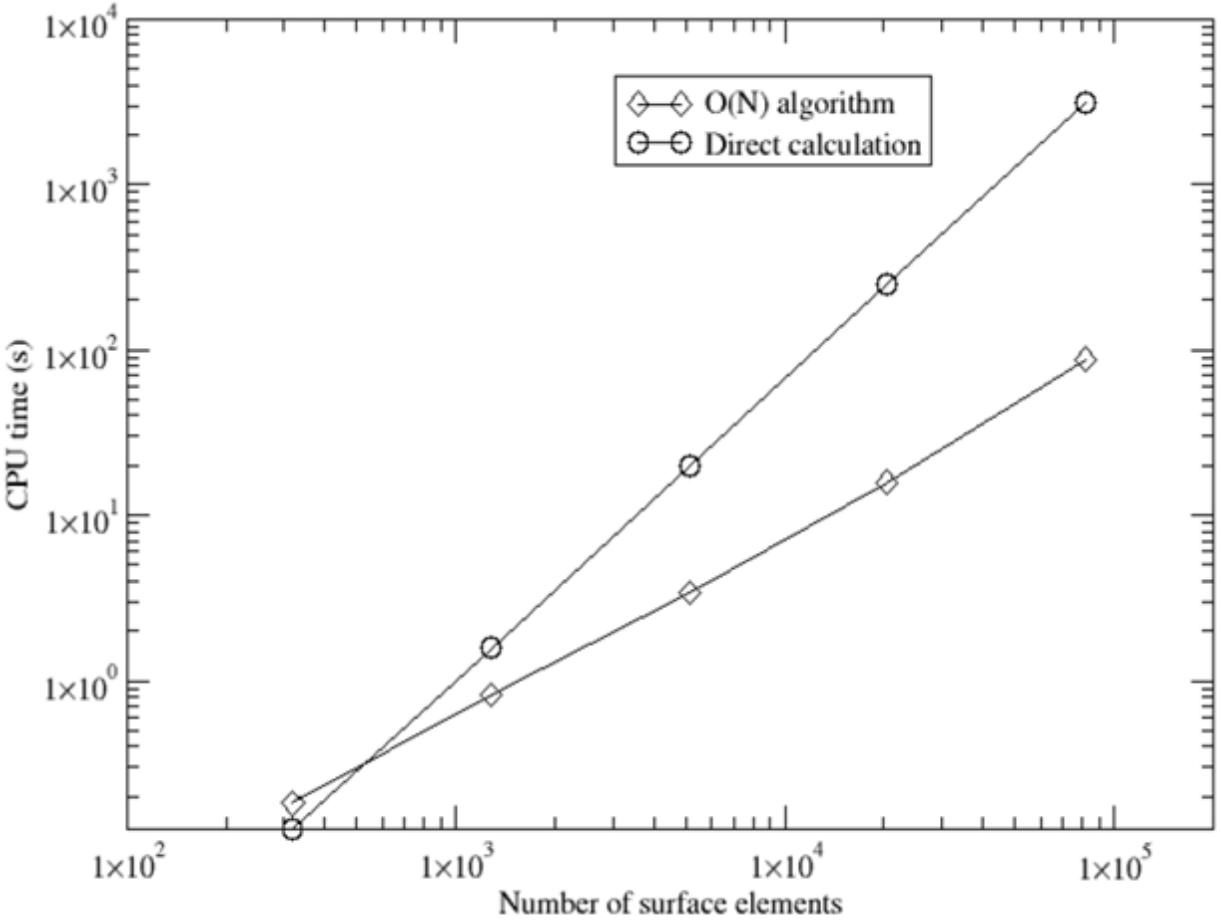
256 smallest cells

64 used cells

Cheng, H, Greengard L, Rokhlin V, 1999. (for kernel 1/r)

Current collaborate work AFMPB with J. F. Huang **(**for kernel e^{-kr}/r)

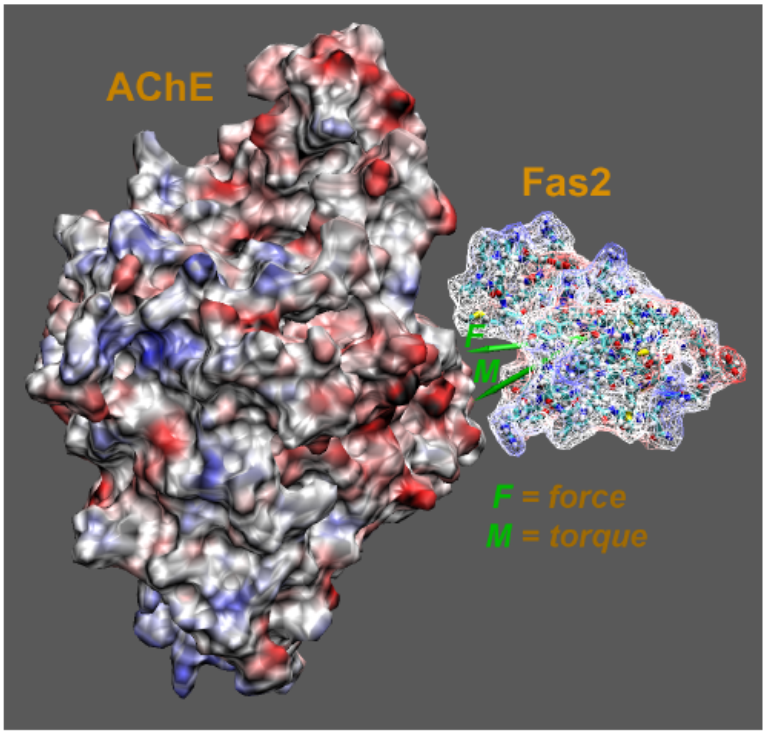
Computational performance



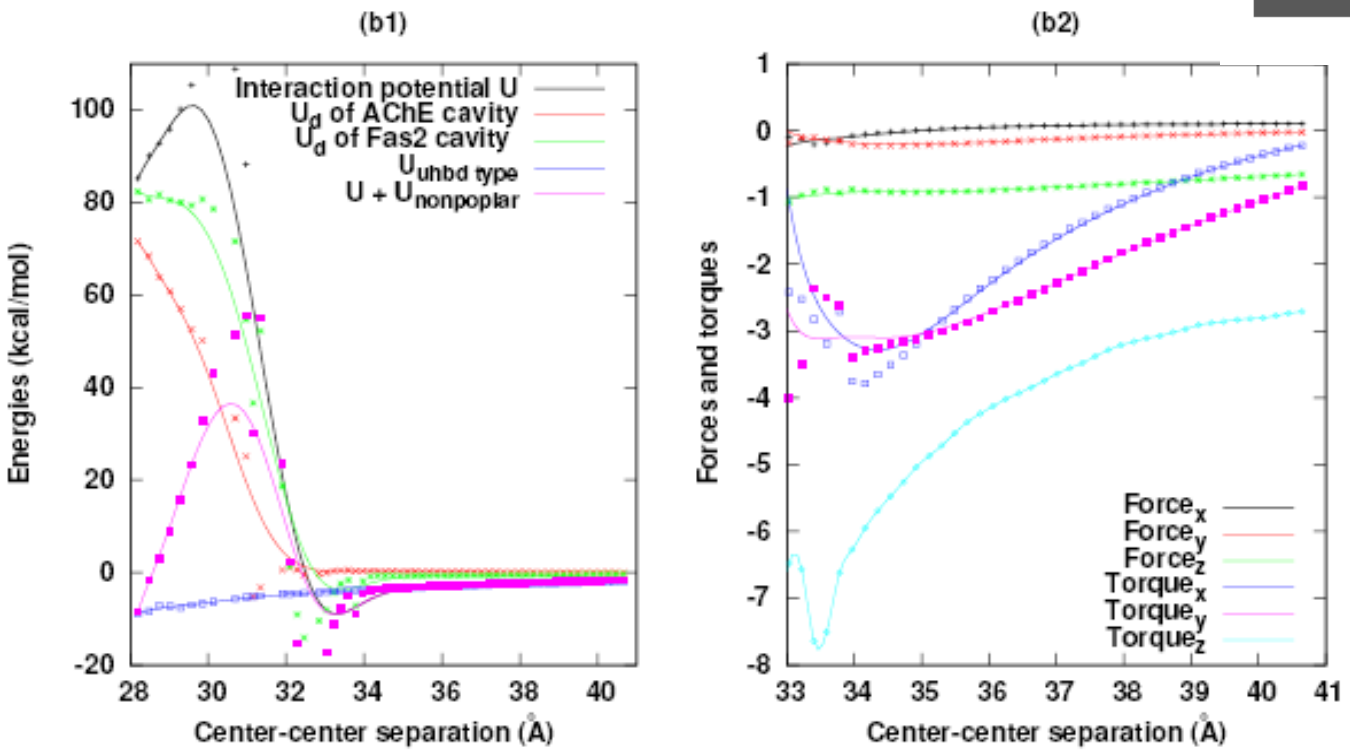
In 2006,
For 81920 BEs
~ 40 folds speed up

Now, 2009, AFMPB
> 100 folds speed up

Energy, force and torque between proteins: acetylcholinesterase (AChE) and fasciculinII (Fas2)



(a)



Lu, BZ, Cheng, XL, Huang, JF, and McCammon, JA. *Proc. Natl. Acad. Sci. U. S. A.* 103: 19314, 2006.

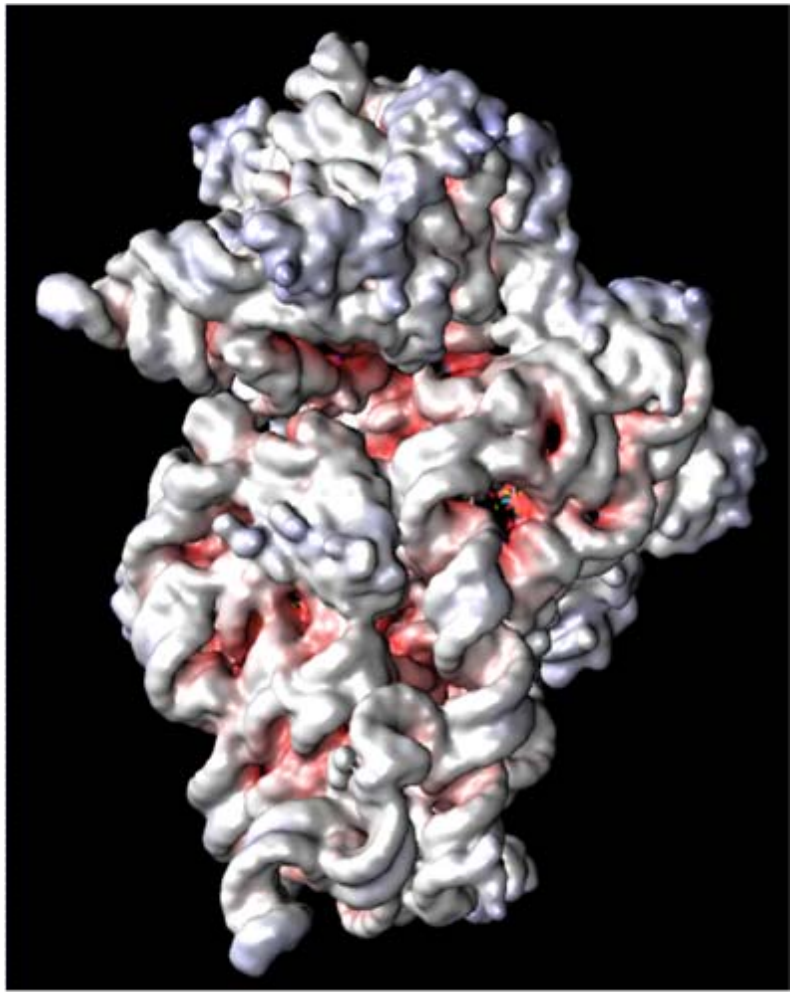
AFMPB: Adaptive Fast Multipole PB Solver

Ribosome(30S)

21 peptides and a 1540 nucleotides RNA subunit

Atoms: 88431

Size: 211 × 177 × 200 A



B. Lu, XL Cheng, JF Huang, JA McCammon, *J Comput. Theor Chem*, 2009

We achieved tens of fold speedup.

Can we make it a hundred fold faster?

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Electrodiffusion process

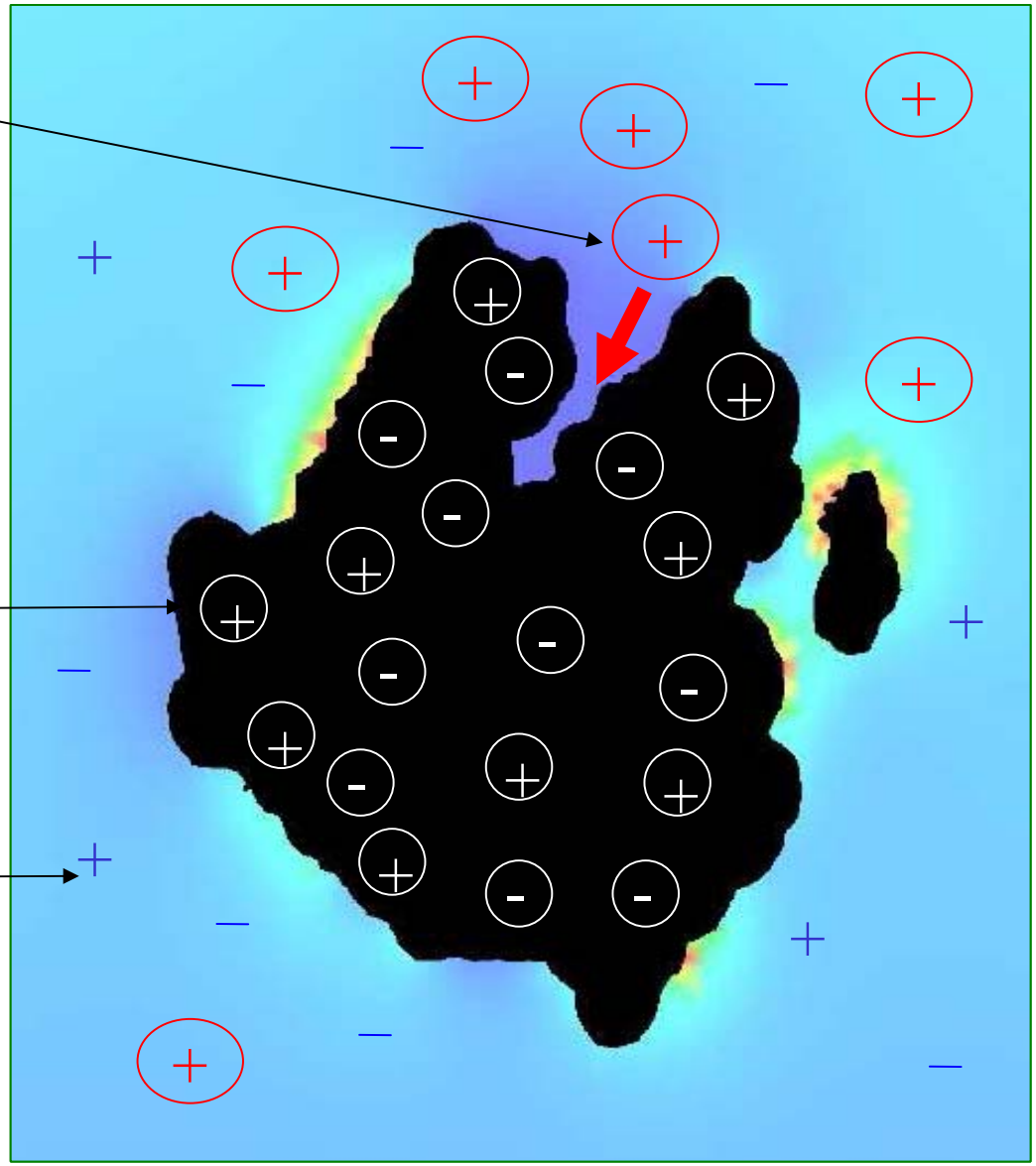
Diffusive/reactive particles

Solute charges

fixed ρ^f, ε_{in}

+/- salt

Density p^i, ε_{out}



Poisson-Nernst-Planck equations

PNPE

$$\begin{cases} \dfrac{\partial p^i(r,t)}{\partial t} = \nabla \cdot \{D^i(r)(\nabla p^i(r,t) + \beta \nabla (q^i \phi(r,t)) p^i(r,t))\}, \quad r \in \Omega_s, \quad i = 1, \ldots, K, \\ \nabla \cdot \varepsilon(r) \nabla \phi(r,t) = -\rho^f(r) - \sum_i q^i p^i(r,t), \quad r \in \Omega \end{cases}$$

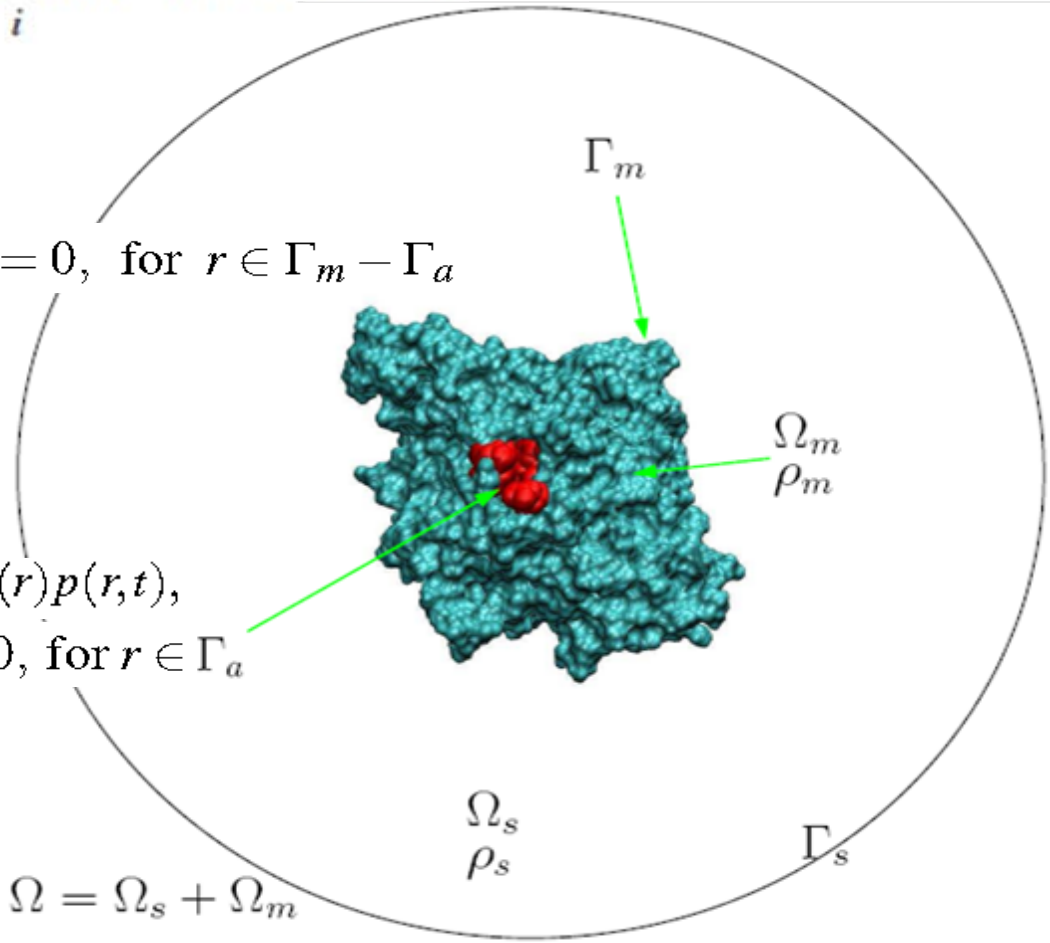
boundary conditions

$$n(r) \cdot j = 0, \quad \text{for } r \in \Gamma_m - \Gamma_a$$

$$\begin{cases} n(r) \cdot j = -k(r) p(r,t), \\ \text{or } p(r,t) = 0, \text{ for } r \in \Gamma_a \end{cases}$$

rate coefficient:

$$k = \frac{-\int_{\Gamma_a} n \cdot j ds}{p_{bulk}}$$



Lu BZ, Zhou YC, Huber G, Bond S, Holst M, McCammon JA. *JCP*, 2007

Special cases

- Flux $J = -D^i(\nabla p^i + \beta q^i p^i \nabla\phi) = -D^i(e^{-\beta q^i \phi}\nabla e^{-\beta q^i \phi} p^i) = 0, \rightarrow p^i = p_o^i e^{-\beta q^i \phi}$,

  PNPE --> nonlinear Poisson-Boltzmann equation

- Pure diffusion equation

- Partially coupled case (Smoluchowski equation): PBE + NP

  Tai, KS, et al., 2003; Song, YH, et al, 2004;

Mesh generation

MSMS
Surface triangular mesh

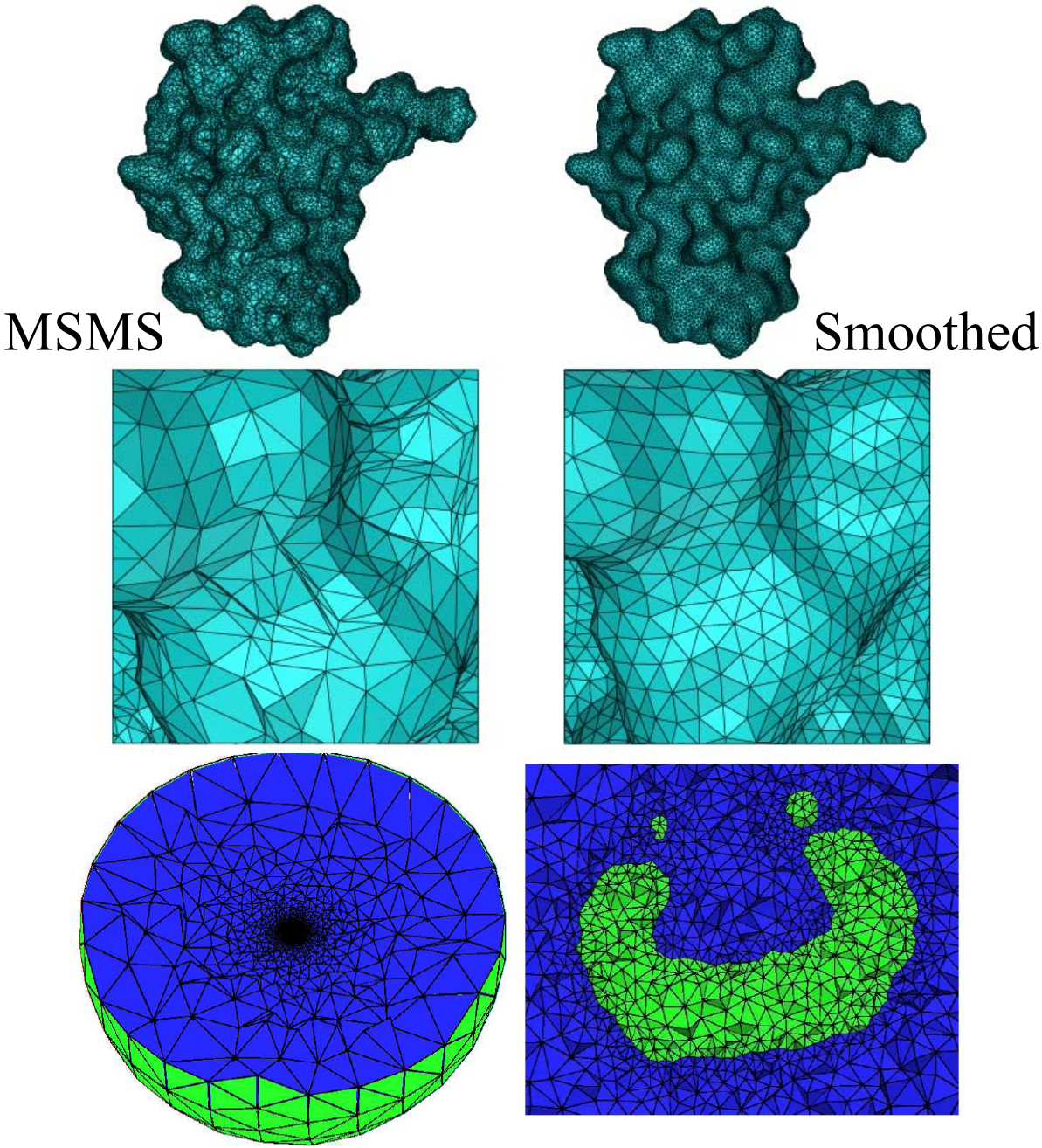
↓

ADVENTURE_TetMesh
Surface mesh smoothing

↓

TetGen
Volume tetrahedral mesh

Sanner et al., 1996; Yagawa et al., 1995; Si and Gaertner, 2005.



Lu BZ, Zhou YC, Huber G, Bond S, Holst M, McCammon JA. 2007

Solution of the Poisson equation -- Regularization scheme I

$$\nabla \cdot \varepsilon(r)\nabla\phi(r,t) = -\rho^f(r) - \sum q^i p^i(r,t), \quad r \in \Omega, \quad i = 1...K,$$

Decompose ϕ into singular and regular parts: $\phi = \phi^s + \phi^r$

$$\nabla \cdot \varepsilon(r)\nabla\phi^s(r) = -\rho^f(r), \quad r \in \Omega,$$

$$\nabla \cdot \varepsilon(r)\nabla\phi^r(r) = \begin{cases} 0, & r \in \Omega_m, \\ -\sum_i q^i p^i(r), & r \in \Omega_s, \quad i = 1...K. \end{cases}$$

The singular part is easy to solve using boundary element method

Hybrid FD/BEM for nonlinear PBE, Boschitsch and Fenley, 2004

Hybrid FEM/BEM Lu BZ, Zhou YC, et al, 2007

Solution of the Poisson equation -- Regularization scheme II

Decompose $\phi = \phi^s + \phi^h + \phi^r$

The singular part

$$\phi^s = G|_{\overline{\Omega}_m} \text{ in } \overline{\Omega}_m,$$

$$\phi^s = 0 \text{ in } \Omega_s,$$

The harmonic part

$$\Delta\phi^h = 0 \text{ in } \Omega_m,$$

$$\phi^h = -\phi^s \text{ on } \Gamma.$$

The regular part

$$-\nabla\cdot(\varepsilon\nabla\phi^r) - \lambda\sum q^i p^i = 0 \text{ in } \Omega,$$

$$[\phi^r] = 0, \quad \left[\varepsilon\frac{\partial\phi^r}{\partial n}\right] = -\varepsilon_m\left(\frac{\partial\phi^s}{\partial n} + \frac{\partial\phi^h}{\partial n}\right) \text{ on } \Gamma.$$

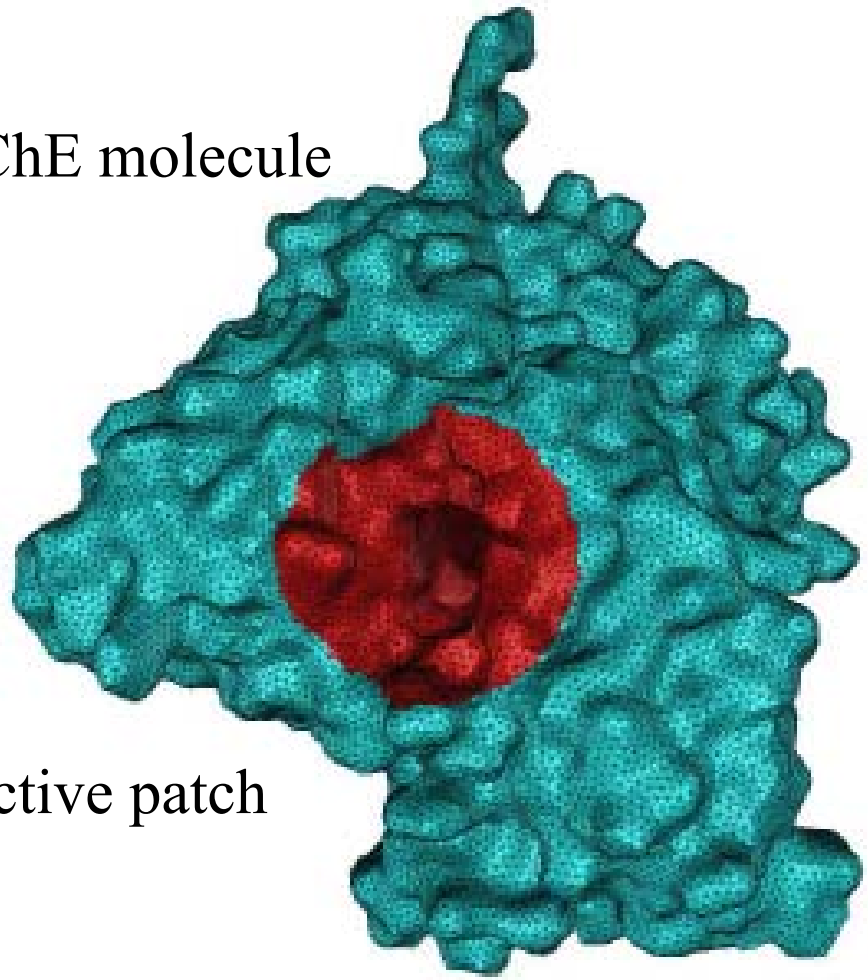
Chern IL, Liu JG, Wang WC, 2003

Application: ACh consumption by AChE

System:

ions, a swam of ACh (+), one AChE molecule

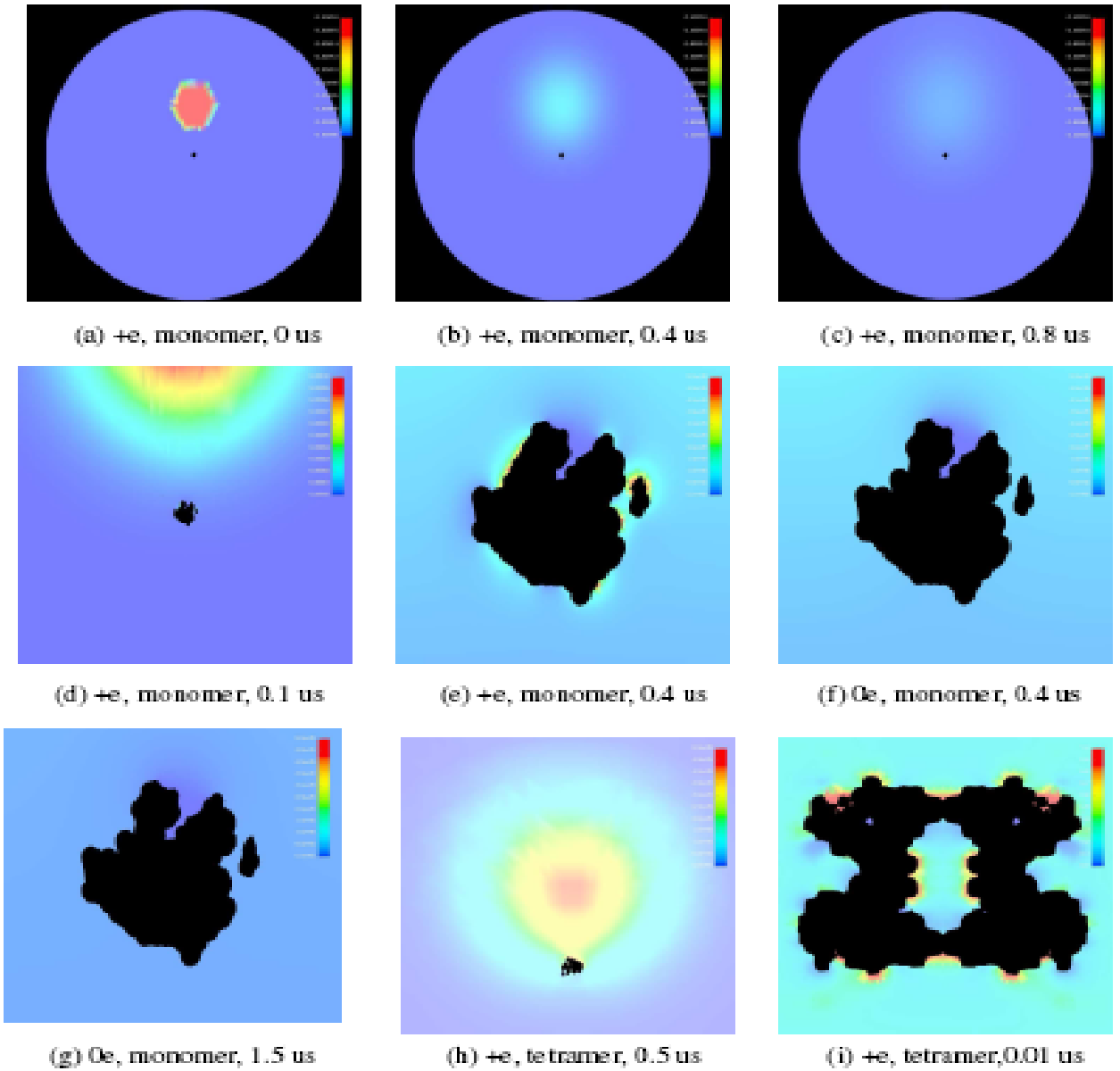
ACh $\xrightarrow{\text{AChE}}$ acetate + choline



AChE with a reactive patch

Lu BZ, Zhou YC, Huber G, Bond S, Holst M, McCammon JA. *J. Chem. Phys.*, 2007
Zhou YC, Lu BZ, Huber G, Holst M, McCammon JA. *J. Phys. Chem. B*, 2008

A time-dependent diffusion-reaction process



Lu BZ, Zhou YC, Huber G, Bond S, Holst M, McCammon JA. *JCP*, 2007

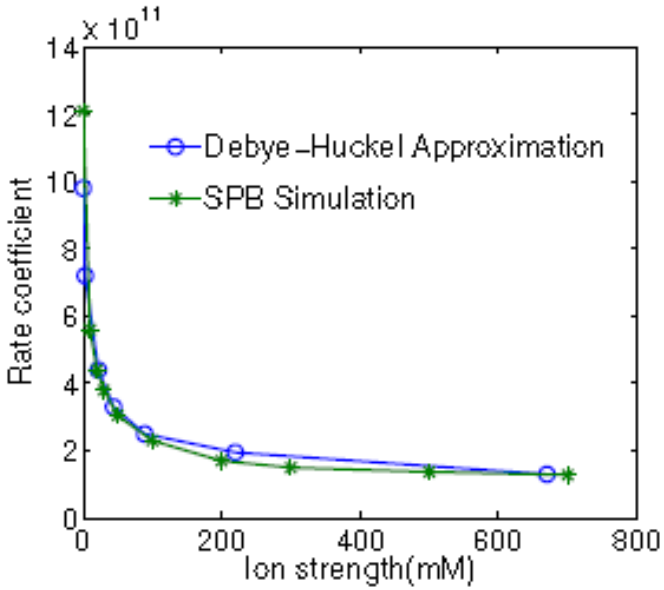
Rate coefficients for AChE monomer
-- Modification on Debye-Huckel limiting law (?)

- LPB + NP (uncoupled)

  Debye-Huckel limiting law:

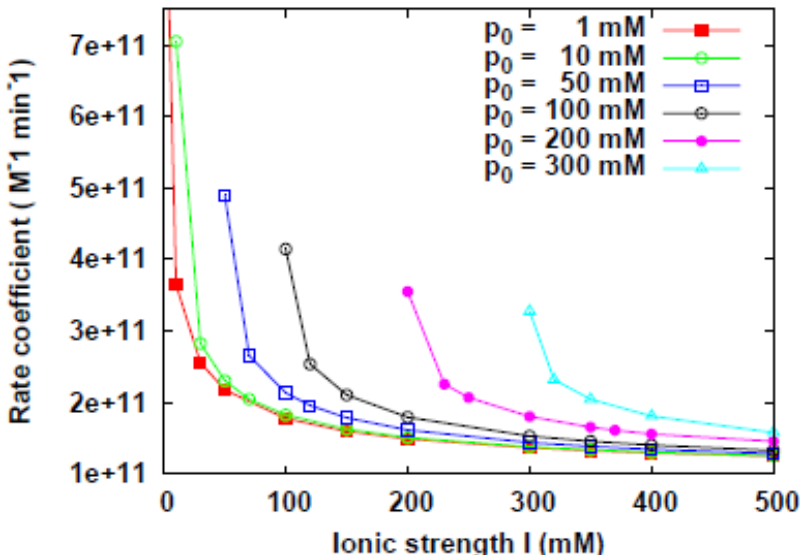
$$k_{on} = (k_{on}^{0} - k_{on}^{H})10^{-1.18(z_E z_S)\sqrt{I}} + k_{on}^{H}$$

Radic Z, et al. 1997.



Zhou YC, et al. *JPCB*, 2008

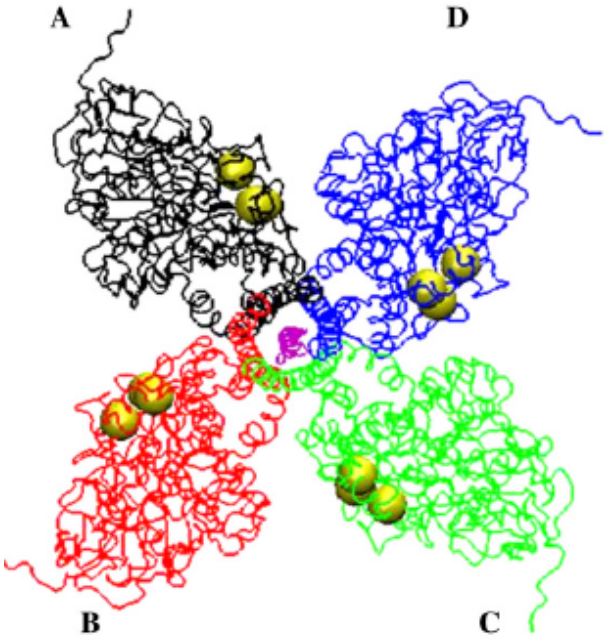
- PNP

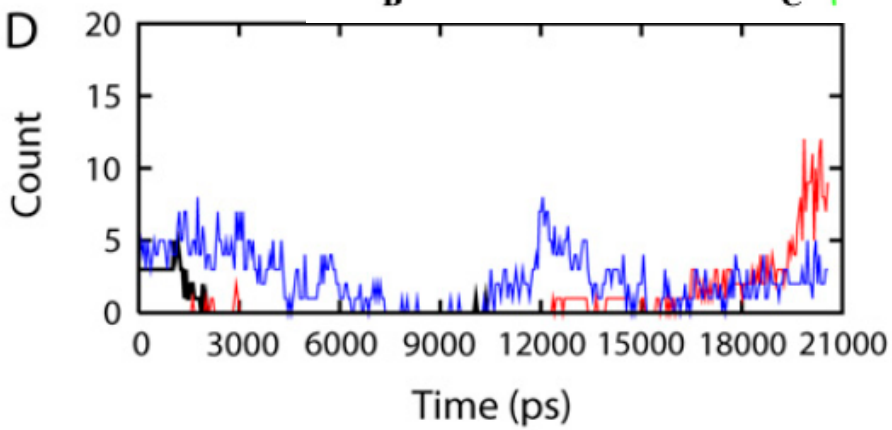


Lu et al. submitted

Enzymatic activity versus structural dynamics

AChE tetramer

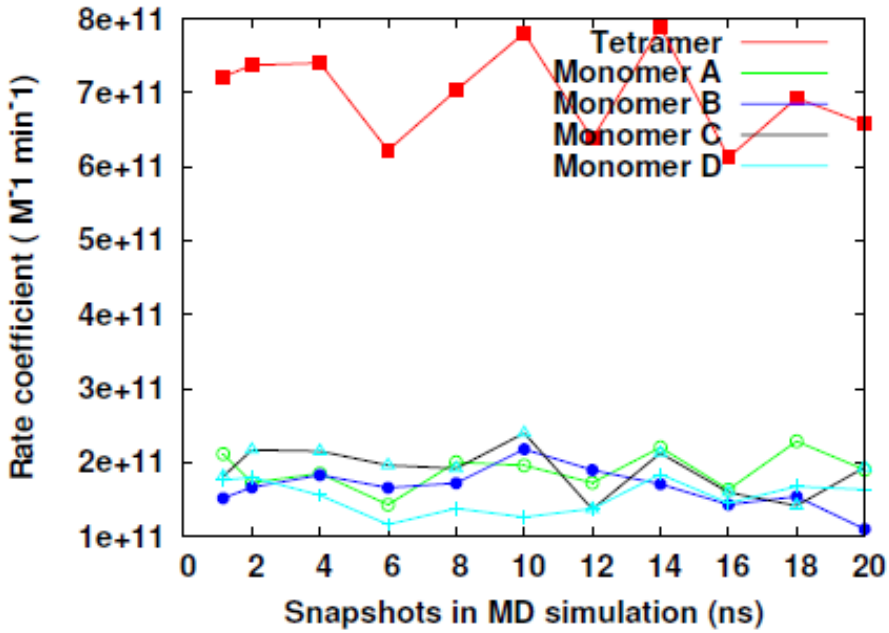




Occlusion count for each subunit.
A (black), B (red), C (green), and D (blue).

Gorfe A, Chang C, Ivanov I, McCammon JA, *Biophysical J.* 2008

Varying rate coefficients of different snapshots from MD simulation trajectory



Gorfe A, B. Lu, McCammon JA,
Biophysical J. 2009

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Extensions of the standard PNP model

- vdw interaction

  A main nonpolar interaction

  → Molecular surface-free model

- Size effects

Incorporating van der Waals interaction --- Molecular surface-free method

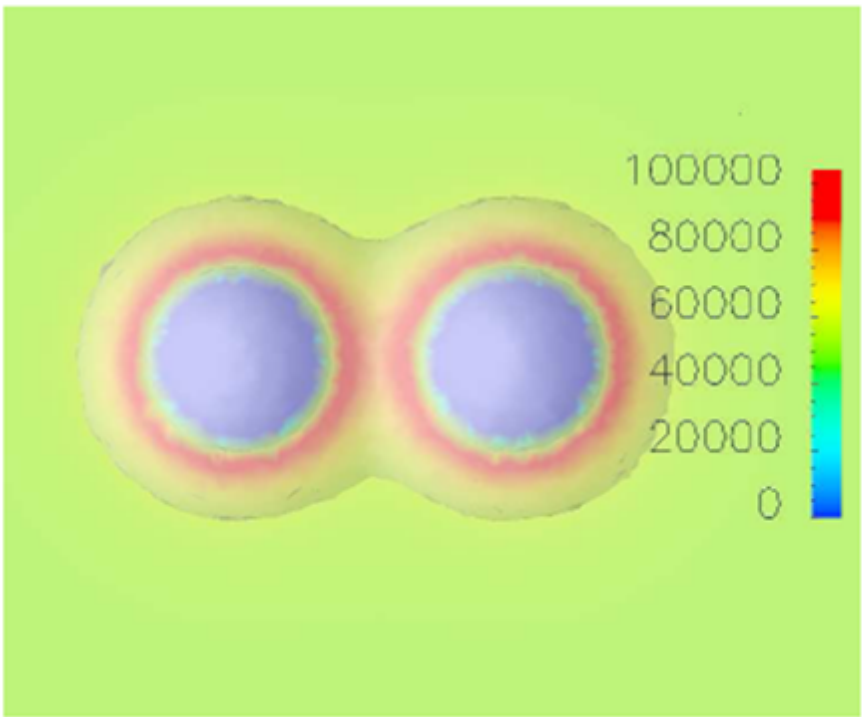
Modified diffusion equations

$$\frac{\partial p^i(r,t)}{\partial t} = \nabla \cdot \{D^i(r) e^{-\beta V^i(r,t)} \nabla (e^{\beta V^i(r,t)} p^i(r,t))\} + k^i(r) p^i(r,t), \quad r \in \Omega, \quad i = 1 \ldots K,$$

where $V^i = q^i \phi + V^i_{\mathrm{vdw}}$

One species is water!

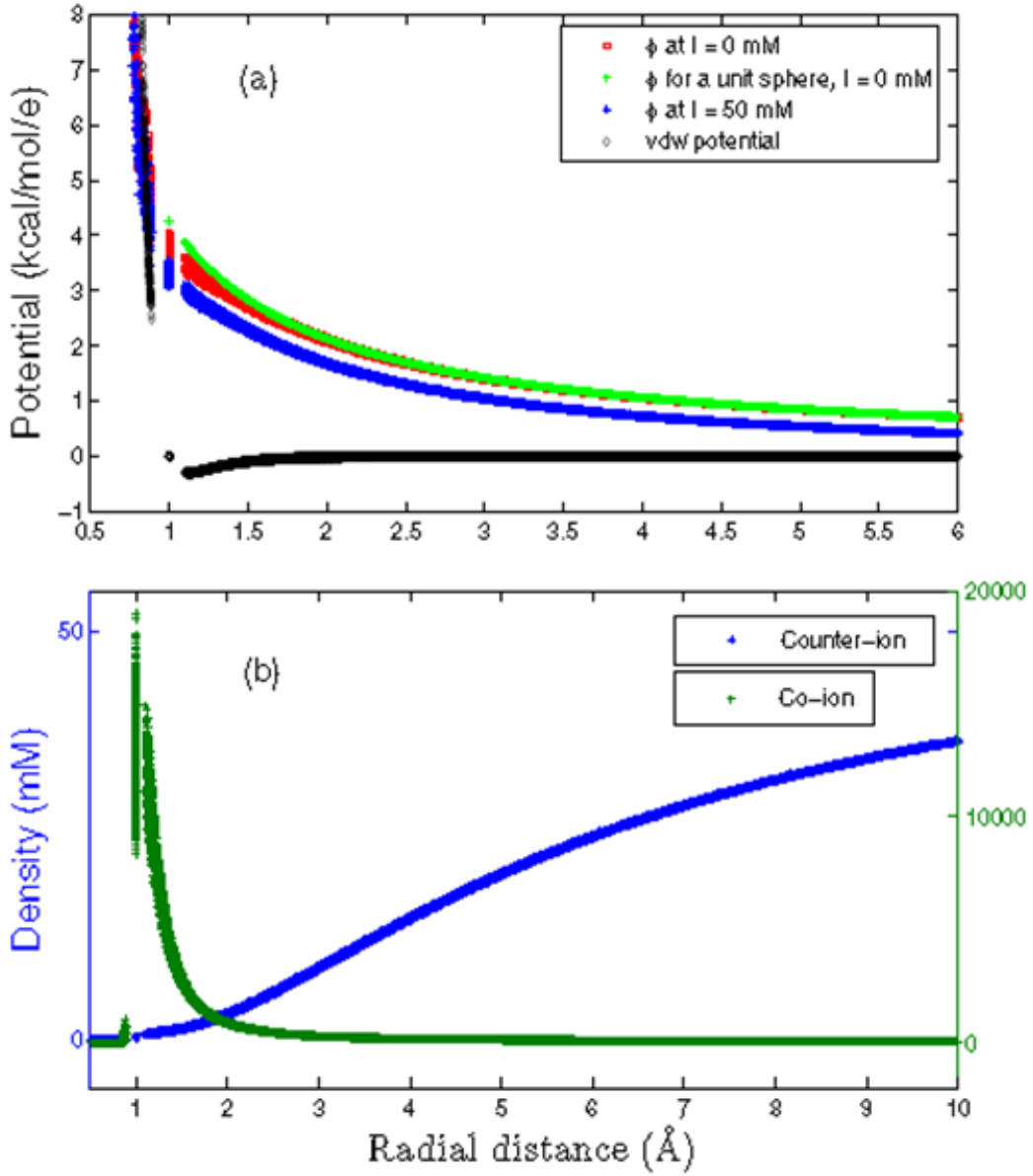
Water density around two atoms



Water density around two atoms. The isosurface value is 60000 mM.

Lu BZ, McCammon JA, *Chem. Phys. Lett.* 2008

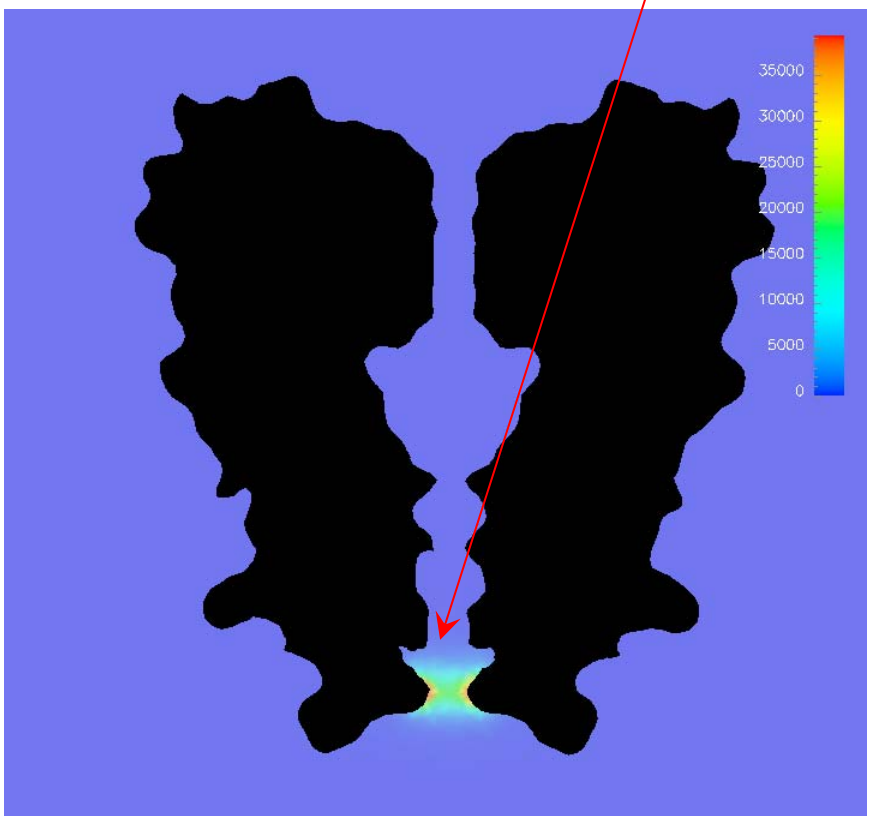
Potentials and ionic densities around a model atom

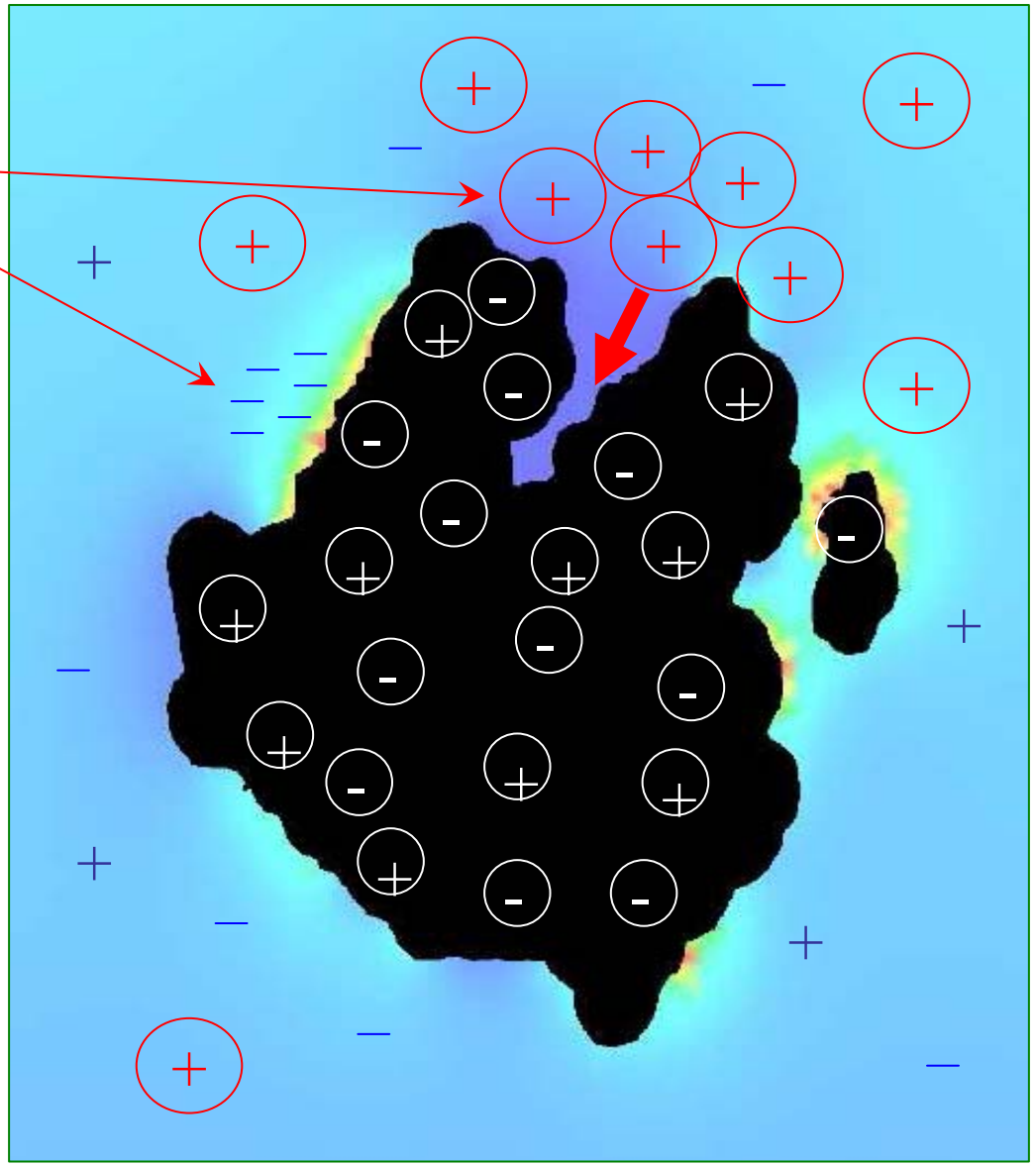


Lu BZ, McCammon JA, *Chem. Phys. Lett*. 2008

Size effects on potential and diffusion process

unreasonable packing X





Size modified PNP model

- Add a solvent entropy term

$$F_0 = F_{\text{ele}} + k_B T \int \left[\sum_i \rho_i (\ln(\rho_i \lambda_i^3) - 1) - \rho_0 (1 - \rho_i a_i^3) \ln(\rho_0 (1 - \rho_i a_i^3) \lambda_0^3 - 1) \right] dx$$

Borukhov, D. Andelman, and H. Orland, *PRL*, 1997
Chu V. et al., *Biophysical J.*, 2007

- A modified PNP model

$$-\nabla \cdot \{D^i(r) \nabla p^i(r) + \frac{D^i(r) c^i p^i(r)}{1 - \sum_k a_k^3 p^k(r)} \sum_k a_k^3 \nabla p^k(r) + \beta D^i(r) p^i(r) q^i \nabla \phi(r)\} = 0, \quad r \in \Omega_s, \quad i = 1 \ldots K, \tag{1}$$

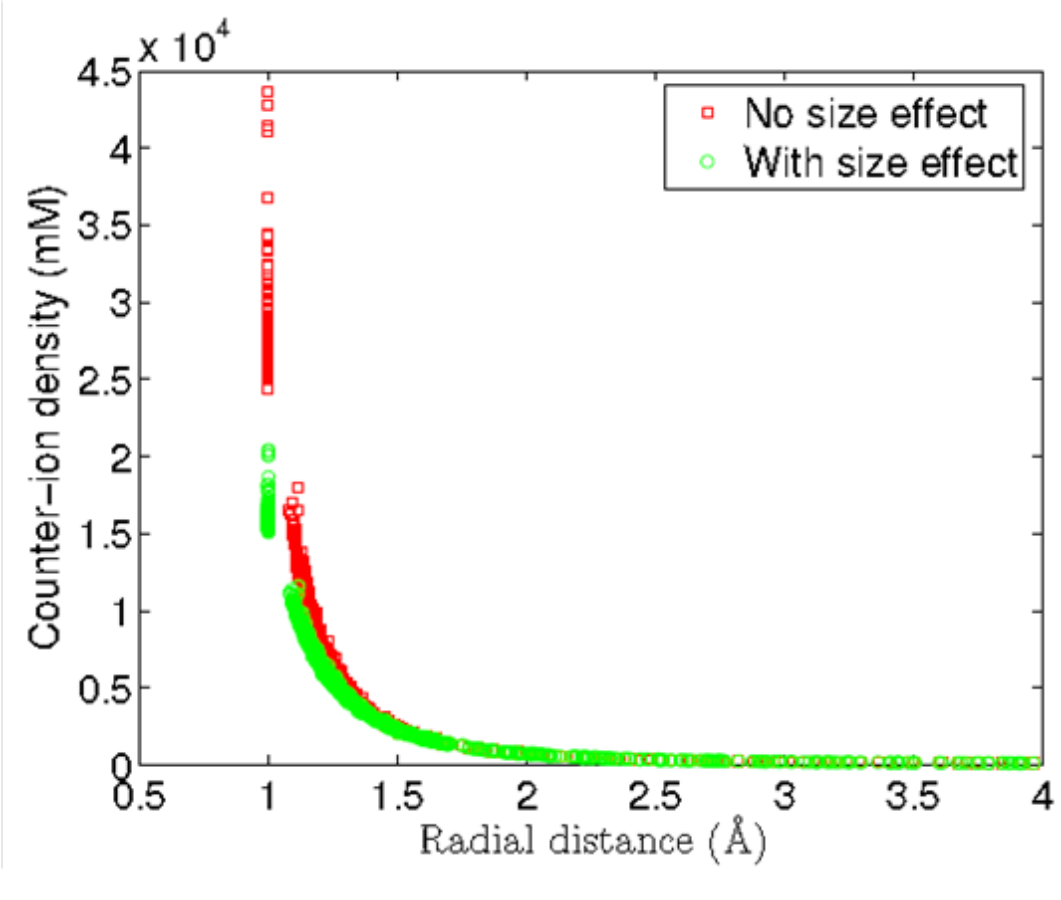
$$-\nabla \cdot \varepsilon(r) \nabla \phi(r,t) - \rho^f(r) - \sum_i q^i p^i(r,t) = 0, \quad r \in \Omega, \tag{2}$$

Lu BZ, Zhou YC, et al. in preparation

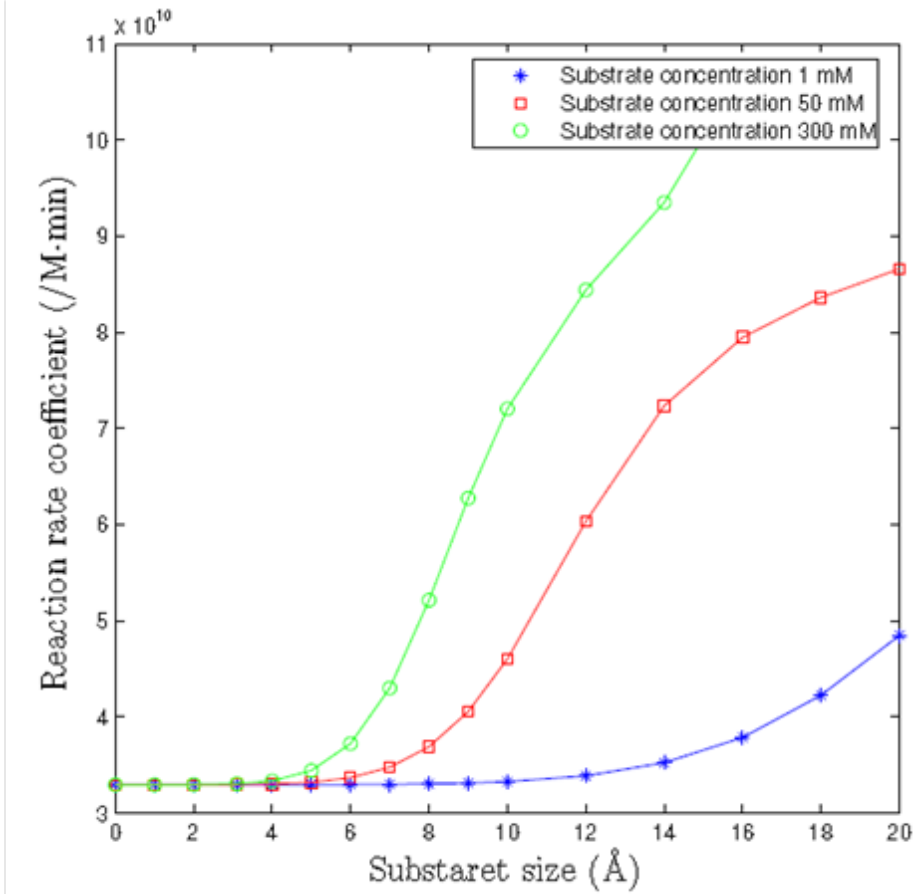
- The size effect is easier to be formulated in PNP model for multiple species with different sizes, but difficult in modified PBE,

Size effects from modified PNP

Ionic density around a charged cavity



Reaction coefficient



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Outline

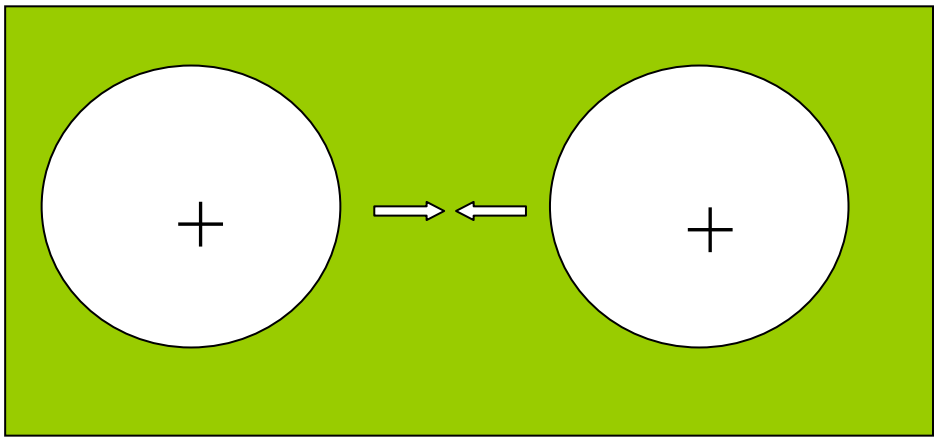
- Introduction
- Continuum model and numerical solutions for
  - Equilibrium electrostatics
  - Electro-Diffusion-reaction
  - Model extensions
- **Summary**
- **Future work**

Future work

- Mesh generation
- Faster, converged and stable algorithms/solvers

  for continuum model
- More accurate model →beyond the mean-field theory

Like-charge attraction



Larsen AE and Grier DG, 1997

- Other continuum models: electro-elastics, hydrodynamics

Electro-elastic deformation

Electro-hydrodynamics and more …?

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