Modeling and Simulating Asymmetrical Conductance Changes in Gramicidin Pores

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Collaborators

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Outline

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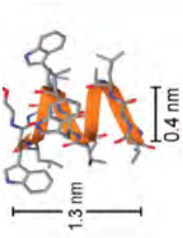
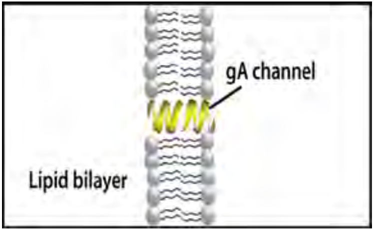
Gramicidin A Channel

Gramicidin A (gA) Channel

- gA is a short polypeptide with a helix structure.
- Upon head to head dimerization, gA forms an channel in lipid bilayers.
- gA is permeable to cations.
- In experiments, with the application of a voltage difference across the lipid bilayer, current and conductance of the channel can be measured.

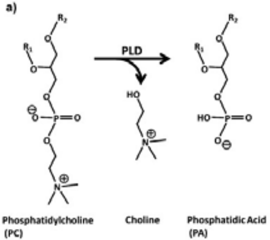


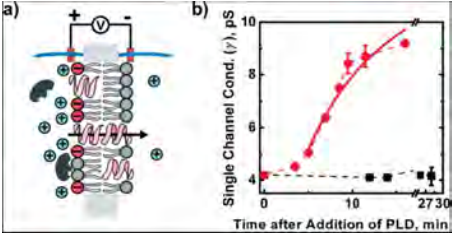


Asymmetrical conductance change

The current and the conductance of the channel are greatly affected by the environment near the entrance of the gA pores and not by that near its exit. Many experiments were designed to control the conductance of gA pore change asymmetrically by modifying the local charge densities around the channel.

- $phospholipaseD(PLD) + phosphatidylcholine(PC) \Rightarrow$ negatively charged phosphatidic acid PA on the membrane

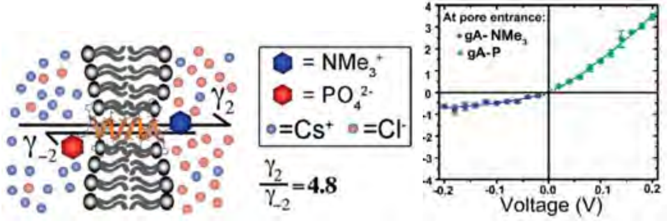




Sheereen Majd et al. J. Am. Chem. Soc., 131 (2009)

Asymmetrical conductance change

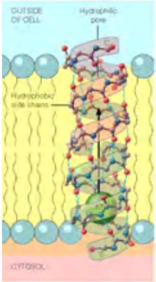
- Attach modified charged groups at the tails of gAs.

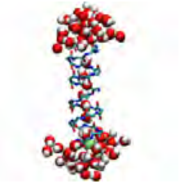
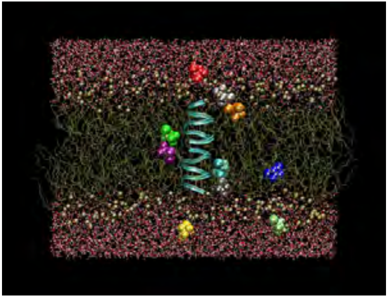


Jerrey Yang et al. J. Am. Chem. Soc., 2010, 132 (6)

Outline

Molecular structure of Gramicidin A pore



www.pearsonhighered.com, www.irelandboinc.com, www.psc.edu

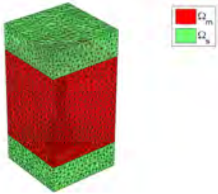
Mesh difficults

- Mesh should keep the topology of the channel.
- Surface mesh is a manifold. A manifold mesh means that the surface formed by all the elements of the mesh is also a manifold.
- Mesh is easy for adaptive meshing strategy.

Minxin Chen, Benzhuo Lu, TMSmesh: A robust method for molecular surfac mesh generation using a trace technique, J. Chem. Theory Comput., 7:203-212, 2011.

Minxin Chen, Bin Tub, Benzhuo Lu, Triangulated Manifold Meshing Method Preserving Molecular Surface Topology, Journal of Molecular Graphics and Modelling, 38: 411-418, 2012

Mesh generated by TMS (Chen&Lu)

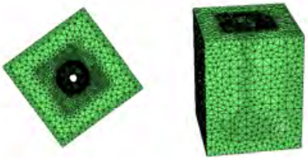


(a)

(b)

Mesh generated by TMS (Chen&Lu)

(c) Ω_s



(d) Ω_m

History

- Molecular dynamics (MD): D. Marx and J. Hutter (2000)...,
- Brownian dynamics (BD): S. Li M. Hoyles S. Kuyucak and S. Chung (1998), Z. B. N. Schuss & R. S. Eissenberg (2001)...,
- Continuous model: Poisson Boltzmann model (C. L. Rice and R. Whitehead), Poinson Nernst Planck model (Eissenberg) Laplace-Beltrami Poinson Nernst Planck model (W. G. Wei)

Poisson-Nernst-Planck equation

model

$$n_t = \nabla \cdot (D_n(\nabla n - \frac{ze}{K_B T} n \nabla \phi) = -\nabla \cdot J_n \quad \text{in } \Omega_s, \tag{1}$$

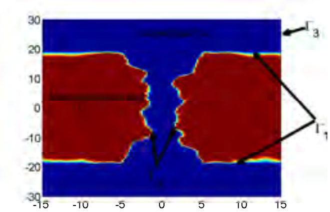
$$p_t = \nabla \cdot (D_p(\nabla p + \frac{ze}{K_B T} p \nabla \phi)) = -\nabla \cdot J_p \quad \text{in } \Omega_s, \tag{2}$$

$$-\nabla \cdot (\varepsilon \nabla \phi) = (p - n)ze + \sum q_i \delta(\vec{x} - \vec{x}_i) \quad \text{in } \Omega. \tag{3}$$

$$\varepsilon(\vec{x}) = \begin{cases} \varepsilon_m \varepsilon_0 & \vec{x} \in \Omega_m \\ \varepsilon_s \varepsilon_0 & \vec{x} \in \Omega_s \end{cases}, \tag{4}$$

where Ω_m is the macro molecular part including the GA and membrane, Ω_s is the solvent part; $\varepsilon_0 = 8.85 \times 10^{-12} C^2/(N \cdot m^2)$ is the dielectric constant of vacuum, $\varepsilon_m = 2$ is the relative dielectric constant of macromolecule, and $\varepsilon_s = 80$ is relative dielectric constant of solvent. $D_p(D_n)$ is the diffution coefficient which is much smaller in the channell than in the bulk solution.

Boundary conditions and Initial Value



(e)

$$\begin{cases} J_n \cdot \nu = J_p \cdot \nu = 0, & \text{on } \Gamma_1 \bigcup \Gamma_2; \\ n = n_\infty,\ \ p = p_\infty, & \text{on } \Gamma_3; \\ n(.,0) = n_\infty,\ \ p(.,0) = p_\infty, & \\ [\varepsilon \nabla \phi] = -\rho_{m1}, & \text{on } \Gamma_1; \\ [\phi] = 0, [\varepsilon \nabla \phi] = 0, & \text{on } \Gamma_2; \\ \phi(x,t) = -\delta V(x_3 - L)/2L, & \text{on } \partial\Omega, \end{cases}$$

Deal with the Delta function

Dirichlet to Neumann Method (Chern & Liu & Wang 2003)

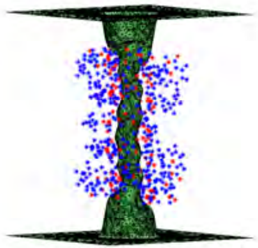
$$\phi = \phi_r + \phi_s + \phi_h, \tag{6}$$

where ϕ_s is the foundemental solution: $\phi_s = \sum_i \frac{q_i}{\varepsilon 4\pi|\vec{x} - x_i|}$; ϕ_h is the solution of homonic problem:

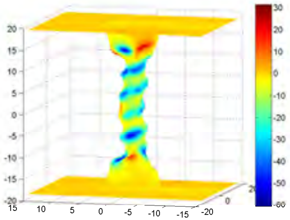
$$\begin{cases} \triangle\phi_h = 0, & \text{in } \Omega_s \\ \phi_h = -\phi_s, & \text{on } \partial\Omega_s. \end{cases} \tag{7}$$

ϕ_r is the solution of following problem

$$\begin{cases} -\nabla\cdot(\varepsilon\phi_r) = (p-n)ze, & \text{in } \Omega \\ [\varepsilon\nabla\phi_r]\cdot\nu = -\rho_1 & \text{on } \Gamma_1 \\ [\varepsilon\nabla\phi_r]\cdot\nu = -[\varepsilon_m\nabla(\phi_s+\phi_m)]\cdot\nu & \text{on } \Gamma_2. \end{cases} \tag{8}$$



(f) interface and fixed charge



(g) ϕ_s

Define space $X = H^1(\Omega) \cap H^3(\Omega_s) \cap H^3(\Omega_m)$ equipped with the norm

$$\|v\|_X = \|v\|_{H^1(\Omega)} + \|v\|_{H^3(\Omega_s)} + \|v\|_{H^3(\Omega_m)}. \tag{9}$$

Regularity Lemma (Babuska1970, Chen1996)

Assume that $p,\ n \in H^1(\Omega_s)$. Then the poisson equation solution $\phi_r \in X$ and satisfies a prior estimate

$$\|\phi_r\|_X \leq C(\|p - n\|_{H^1(\Omega_s)} + |\rho_{m1}| + \|\frac{\partial(\phi_s + \phi_h)}{\partial \nu}\|_{H^{1/2}(\Gamma_1)}). \tag{10}$$

Numerical Method

History

- Finite difference method: M G Kurnikova 1999, W. G. Wei 2011,....
- Spectral element method: D. Chen 2001,...
- Finite element method: B. Z. Lu 2010,...
- Finite volume method: S. R. Mathur 2009,...

FEM Algorithm 1

- step 1: Solve the homonic equation get ϕ_h by mixed element;
- step 2: Compute the value of $[\nabla(\phi_s + \phi_h)] \cdot \nu$ on the interface $\Gamma_1 \cup \Gamma_2$.
- step 3: Use finite element method to compute the ϕ_r, n, p by using the interface boundary condition got in step 2.

FEM Algorithm 2

For the triangulation of domain $\mathcal{T}_h = \{\tau_j\}_{j=1}^{M_h^1} = \Omega_s^h \cup \Omega_h^h$, n and p is approximated by the piecewise linear element is used with the triangulation of domain Ω_s^h, ϕ_r is approximated by piecewise quadratic elements.

Remark

- If $K_1, K_2 \in \mathcal{T}_h$ and $K_1 \neq K_2$, then either $K_1 \cap K_2 = \emptyset$, or $K_1 \cap K_2$ is a common vertex, edge or face of both tetrahedrons.
- For simply, here we assume that the real domain $\Omega_s = \Omega_s^h$, i.e. we take the interface $\Gamma_1 \cup \Gamma_2 = \Omega_s^h \cap \Omega_m^h$.

Semi-discrete form

find $n_h(\cdot,t),\ p_h(\cdot,t) \in (n_\infty \bigoplus S^h_{0,\Gamma_3}(\Omega_s)) \cap V_{\Gamma_3}$, and $\phi^h_r(\cdot,t) \in (-\delta V(x_3 - L)/(2L) \bigoplus S^h_{2,0}(\Omega)) \cap V$ for each $t > 0$, such that

$$\Big\langle \frac{\partial p_h}{\partial t}, v_h \Big\rangle_{\Omega_s} + \Big\langle D_p \nabla p_h + \frac{D_p e}{K_B T} p_h \nabla \phi^h_r, \nabla v_h \Big\rangle_{\Omega_s} = 0, \tag{11}$$

$$\Big\langle \frac{\partial n_h}{\partial t}, v_h \Big\rangle_{\Omega_s} + \Big\langle D_n \nabla n_h - \frac{D_n e}{K_B T} n_h \nabla \phi^h_r, \nabla v_h \Big\rangle_{\Omega_s} = 0, \tag{12}$$

$$\big\langle \varepsilon \nabla \phi^h_r, \nabla u_h \big\rangle_\Omega - \big\langle\ [\varepsilon \nabla \phi^h_r] \cdot \nu, u_h \big\rangle_{\Gamma_1 \cup \Gamma_2} - \big\langle (p_h - n_h) e, u_h \big\rangle_{\Omega_s} = 0, \tag{13}$$

for $\forall\ v_h \in S^h_{0,\Gamma_3}(\Omega_s)$ and $\forall\ u_h \in S^h_{2,0}(\Omega)$, where
$S^h_{0,\Gamma_3}(\Omega_s) = \{\psi \in C(\Omega_s); \psi|_{\tau_j} \in P_1; \psi|_{\partial\Gamma_3} = 0\}$ and
$S^h_{2,0}(\Omega) = \{\psi \in C(\Omega_s); \psi|_{\tau_j} \in P_2; ; \psi|_{\partial\Omega} = 0\}$. $\langle\cdot,\cdot\rangle_\Omega$ and $\langle\cdot,\cdot\rangle_\Gamma$ denote the L_2 inner product over the domain Ω and interface Γ, respectively.

Semi-discrete form

Convergence Theorem

Let ϕ_r, p, n are the solutions of problem (1), (2), (8) and ϕ_r^h, p_h, n_h are the solutions of semi-discrete problem (11)-(13). If $\phi_r(\cdot, t) \in X \cap W^{1,\infty}(\Omega_s) \cap W^{1,\infty}(\Omega_m)$, $p(\cdot, t)$, $n(\cdot, t) \in H^2(\Omega_s) \cap L^\infty(\Omega_s)$, $\mathcal{T}_h$ is quasiuniform, then

$$\|\phi_r - \phi_r^h\|_{H^1(\Omega)} + \|p - p_h\|_{L^2(\Omega_s)} + \|n - n_h\|_{L^2(\Omega_s)} \leq Ch^2, \quad \text{for } 0 < t \leq T$$

$$\|\nabla(p - p_h)\|_{L^2(\Omega_s)} + \|\nabla(n - n_h)\|_{L^2(\Omega_s)} \leq Ch, \quad \text{for } 0 < t \leq T.$$

EAFEM

$$\gamma u - \nabla \cdot (\alpha(\vec{x})\nabla u + \beta(\vec{x})u) = f, \qquad (14)$$

- when $\alpha \ll \beta$, above problem is a convection dominated one.
- In order to keep the discrete maximum principle, the Edge Average Finite Element Method (EAFEM)(Xu & Zikatanov) is used.

J.C. Xu and L. Zikatanov, A monotone finite element scheme for convection- diffusion equations, Mathematics of Computation, 68, (1999), 1429 – 1446.

Algorithm

- step 1: Let $m = 1$, and $p_h^{k_m} = p_h^k$, $n_h^{k_m} = n_h^k$, $\phi_h^{k_m} = \phi_h^k$.
- step 2: solve the following equations for $n_h^{k_{m+1}}$, $p_h^{k_{m+1}}$, with given $n_h^{k_m}$, $p_h^{k_m}$ and $\phi_h^{k_m}$ using EAFEM.

$$\begin{aligned}
\left\langle \frac{p_h^{k_{m+1}} - p_h^{k_m}}{\Delta t}, v_h \right\rangle_{\Omega_s} + \left\langle D_p \nabla p_h^{k_{m+1}} + \frac{D_p e}{K_B T} p_h^{k_{m+1}} \nabla \phi_h^{k_m}, \nabla v_h \right\rangle_{\Omega_s} &= 0, \\
\left\langle \frac{n_h^{k_{m+1}} - n_h^{k_m}}{\Delta t}, v_h \right\rangle_{\Omega_s} + \left\langle D_n \nabla n_h^{k_{m+1}} - \frac{D_n e}{K_B T} n_h^{k_{m+1}} \nabla \phi_h^{k_m}, \nabla v_h \right\rangle_{\Omega_s} &= 0.
\end{aligned}$$

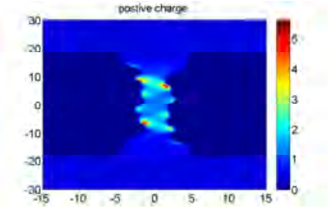
- step 3: Let $p_h^{k_{m+1}} = c p_h^{k_{m+1}} + (1-c) p_h^{k_m}$, $n_h^{k_{m+1}} = c n_h^{k_{m+1}} + (1-c) n_h^{k_m}$, $0 < c \le 1$ and solve Poisson equation

$$\left\langle \varepsilon \nabla \phi_h^{k_{m+1}}, \nabla u_h \right\rangle_{\Omega} - \left\langle\ [\varepsilon \nabla \phi^{k_{m+1}}], u_h \right\rangle_{\Gamma_1 \cup \Gamma_2} - \left\langle (p_h^{k_{m+1}} - n_h^{k_{m+1}}) e, u_h \right\rangle_{\Omega} = 0$$

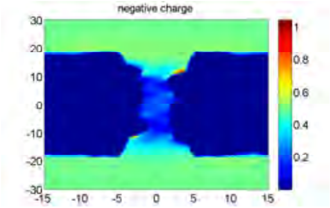
  and then update $\phi^{k_{m+1}} = c\phi^{k_{m+1}} + (1-c)\phi^{k_m}$;
- step 4: if $n_h^{k_{m+1}}$, $p_h^{k_{m+1}}$,$\phi_h^{k_{m+1}}$ are closed to $n_h^{k_m}$, $p_h^{k_m}$, $\phi_h^{k_m}$, then update $n_h^{k+1} = n_h^{k_{m+1}}$, $p_h^{k+1} = p_h^{k_{m+1}}$, $\phi_h^{k+1} = \phi_h^{k_{m+1}}$ and stop. Otherwise let $m = m + 1$ and go to step 2.

Outline

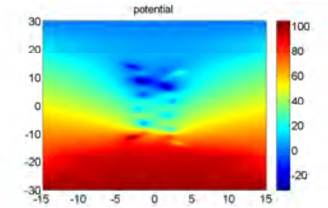
$\delta V = 100mv$, $n_\infty = 0.5M(Kcl)$ results: 2D Cut



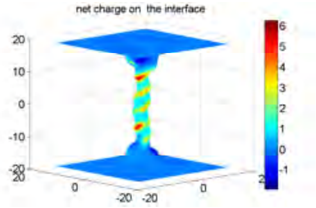
(h) postive charge.



(i) negative charge

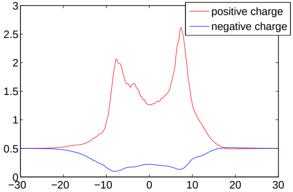


(j) potential

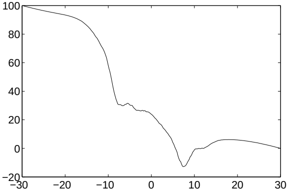


(k) netcharge

$\delta V = 100mv,\ n_\infty = 0.5M(Kcl)$ results: 1D central line

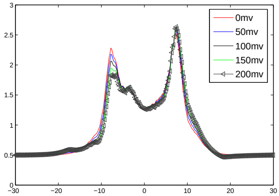


(l) charge

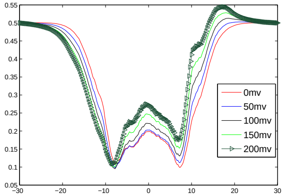


(m) potential

Different potential drop

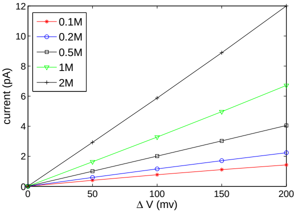


(n) positive charge

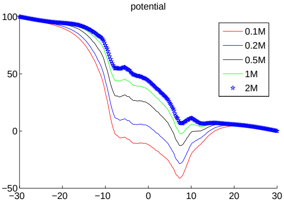


(o) negative charge

Different charge density in the bulk



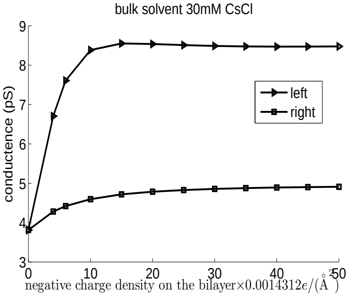
(p) IV curve



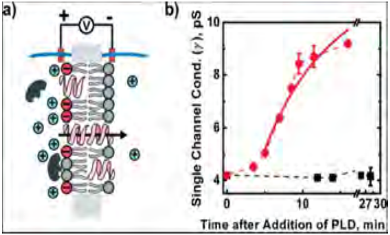
(q) potential ϕ_r at the center line

- I-V statisfies linear relationship;
- For the same potential drop, the higer bulk solvent density is, the larger conductance is, which is obtained by dividing the current by the voltage difference dV added upon the boundaries of the computational domain: $\frac{dI}{dV}$.

Negative charged membrane: conductance

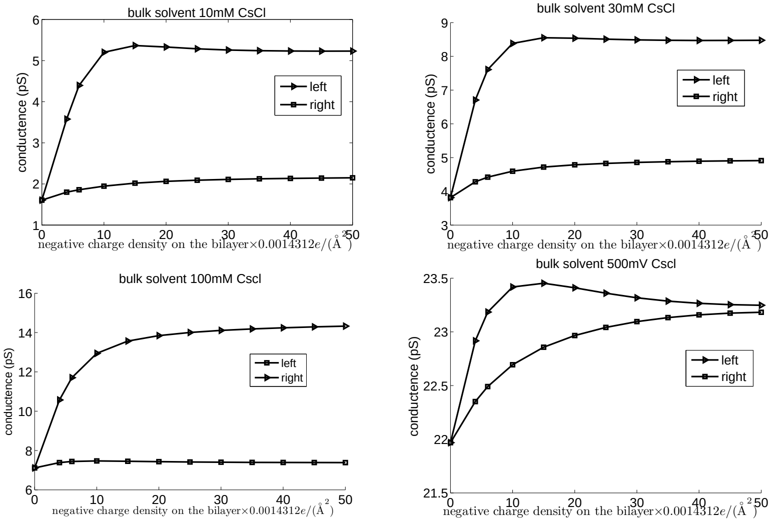


(r) computational result

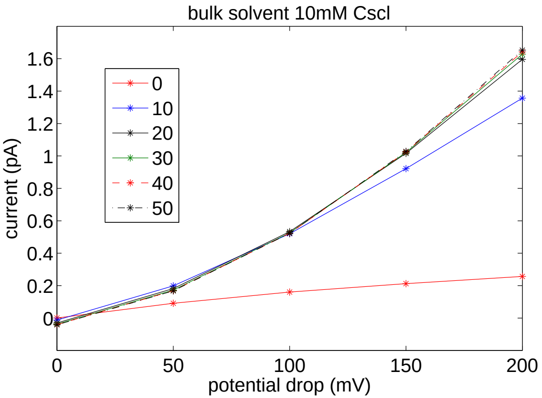


(s) experiment result

Negative charged membrane: conductance

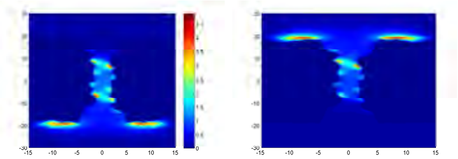


Negative charged membrane: IV curve

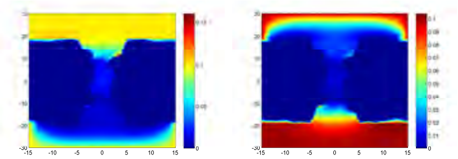


Negative charged membrane:2D cut

$\delta V = 100mv$, $\rho = 1.4312 \times 10^{-2} e/\AA^2$, $n_\infty = 10mM$:



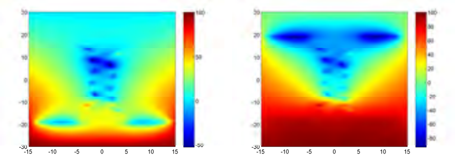
(t) positive charge



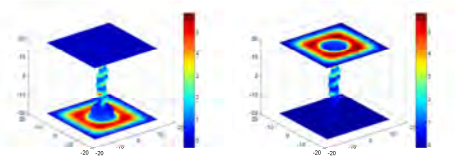
(u) negative charge

Negative charged membrane:2D cut

$\delta V = 100mv$, $\rho = 1.4312 \times 10^{-2} e/\AA^2$, $n_\infty = 10mM$:



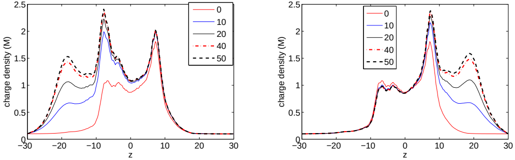
(v) potential



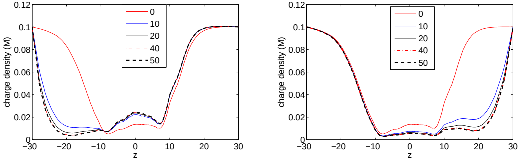
(w) net charge

Negative charged membrane:1D central line

$\delta V = 100mv,\ \rho = 1.4312 \times 10^{-2} e/\mathring{A}^2,\ n_\infty = 10mM$:



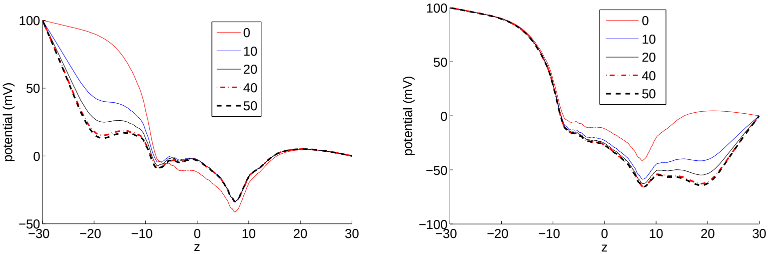
(x) positive charge



(y) negative charge

Negative charged membrane:1D central line

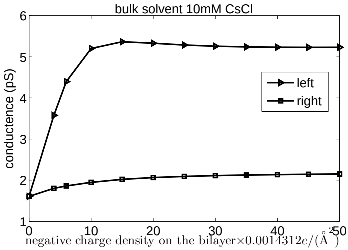
$\delta V = 100mv, \; \rho = 1.4312 \times 10^{-2} e/\AA^2$

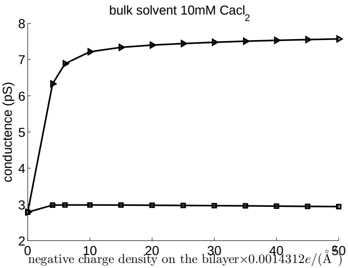


(z) potential

Conductance of different ion

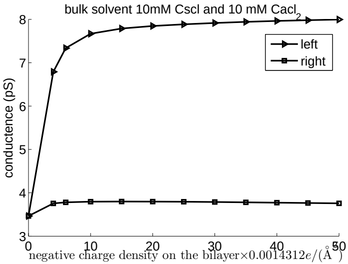
$\delta V = 100mv$, diffusion constant: $Cs^{+} : 2.17 \times 10^{-9} m^2/s$,
$Ca^{2+} : 7.93 \times 10^{-10} m^2/s$





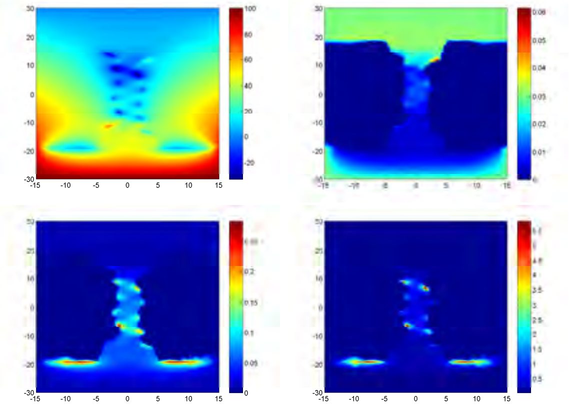
Conductance of different ion

$\delta V = 100mv$, diffusion constant: $Cs^+ : 2.17 \times 10^{-9} m^2/s$, $Ca^{2+} : 7.93 \times 10^{-10} m^2/s$



2d cut

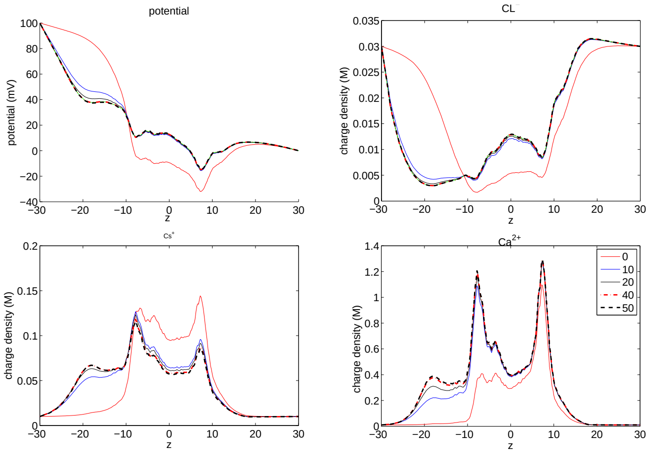
$\delta V = 100mv$, diffusion constant: $Cs^{+} : 2.17 \times 10^{-9} m^2/s$, $Ca^{2+} : 7.93 \times 10^{-10} m^2/s$



upleft: potential; upright: cl^{-}; bottom left: Cs^{+}; bottom right: Ca^{2+}

1d cut

$\delta V = 100mv$, diffusion constant: $Cs^{+} : 2.17 \times 10^{-9} m^2/s$,
$Ca^{2+} : 7.93 \times 10^{-10} m^2/s$



Outline

Conclution

- PNP system is used to model the ion transport in the GA pore;
- By solving PNP, asymmetrical Conductance Changes in GA pore is well simulated;
- The corresponding numercial analysis for the algrithm is proposed.

future work

- Finite size effect: K^+, Cs^+
- Adaptive method and parallel
- Fluid effect
- Different kind of channels

Thank you for your attention!