Differential geometry based ion transport models

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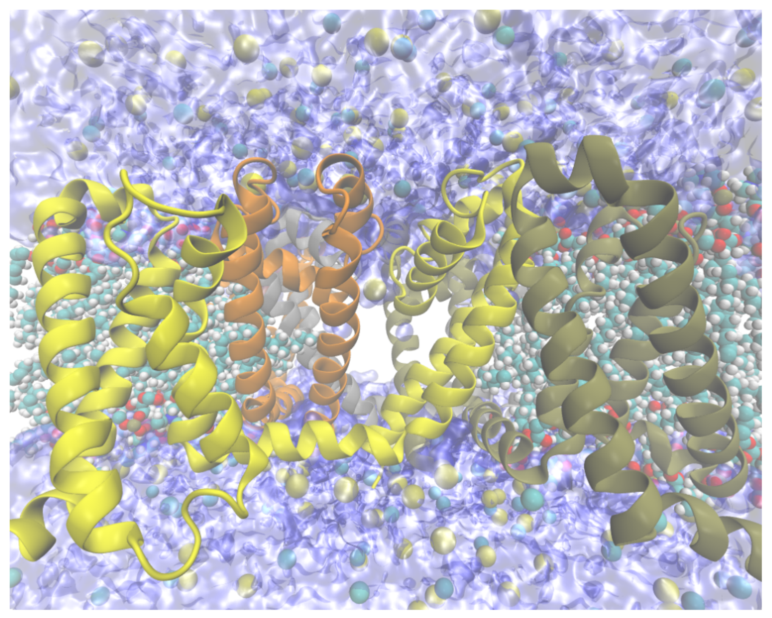
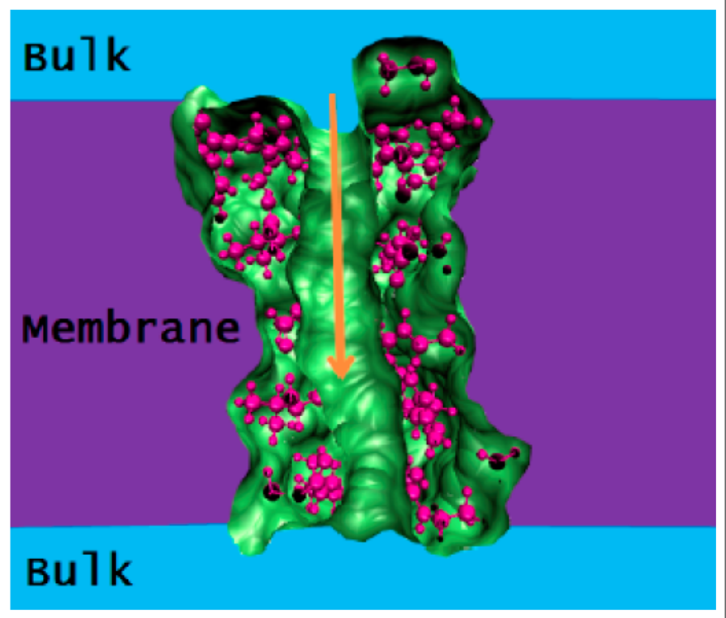
Introduction

Ion channels are pore-forming proteins presented in cell membranes, usually allowing specific ions to pass across membranes and maintaining proper intracellular ion compositions. They are crucial to cell survival and functions, and are key components in many biological processes such as nerve and muscle excitation, resting and action potential generation, sensory transduction, learning and memory, to name a few. Dysfunctional ion channels can cause many diseases: deafness, blindness, migraine headaches, and cardiac arrhythmias. Ion channels are frequent targets for drug design.



(a) Ion channel system



(b) Multiscale model

In order to understand the physiological function of ion channels, a number of theoretical and computational approaches have been developed over the past few decades based on the molecular structures of channel components. In this work, we present a differential geometry based framework for ion transport modeling. Coupling governing equations are derived by variational principle. Furthermore, a number of numerical algorithms are designed and applied to ion channel studies. Our computational results agree well with experimental data.

The mathematical Model

Total energy functional

$$G_{\text{total}}[S,\Phi,n]=\int\{Geometric+Electrostatics+Chemical\}d\mathbf{r}$$

$$Geometric=\gamma\|\nabla S\|+pS+\rho_0(1-S)U_{SS}$$

$$Electrostatics=S\left[-\frac{\epsilon_m(\mathbf r)}{2}|\nabla\Phi|^2+\Phi\sum_j Q_j\delta(\mathbf r-\mathbf r_j)\right]$$

$$+(1-S)\left[-\frac{\epsilon_s(\mathbf r)}{2}|\nabla\Phi|^2+\Phi\sum_\alpha n_\alpha q_\alpha\right]$$

$$Chemical=(1-S)\sum_\alpha n_\alpha\left[\mu_{0\alpha}+k_BT\left(ln\frac{n_\alpha}{n_{0\alpha}}-1\right)-\mu_\alpha\right]$$

- Geometric: Surface energy, mechanical work and solvent-solute interactions.
- Electrostatics: Electrostatic energy in protein and in solvent.
- Chemical: Chemical potential energy.

γ is the surface tension, S is the characteristic function indicates the solvent/solute domain, p is the hydrodynamic pressure, Φ is electrostatics potential, ϵ_s and ϵ_m are the dielectric constants of the solvent and solute, and n_α denotes the concentration of αth ion species.

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Governing Equations obtained by variation

Generalized Poisson-Boltzmann Equation:

$$-\nabla\cdot(\epsilon(S)\nabla\Phi(\mathbf r))=(1-S)\sum_\alpha n_\alpha q_\alpha+S\sum_j Q_j\delta(\mathbf r-\mathbf r_j)$$

$$\epsilon(S)=(1-S)\epsilon_s+S\epsilon_m$$

Electrochemical Potential:

$$\mu_\alpha(\mathbf r)=\mu_{0\alpha}+k_BTln\frac{n_\alpha(\mathbf r)}{n_{0\alpha}}+q_\alpha\Phi(\mathbf r)$$

Nernst-Planck equation:

$$\frac{\partial n_\alpha}{\partial t}=-\nabla\cdot J_\alpha\quad J_\alpha=-D_\alpha n_\alpha\nabla\frac{\mu_\alpha}{k_BT}$$

$$\frac{\partial n_\alpha}{\partial t}=\nabla\cdot\left[D_\alpha\left(\nabla n_\alpha+\frac{q_\alpha n_\alpha}{k_BT}\nabla\Phi\right)\right]$$

Generalized Laplace-Beltrami equations:

$$\frac{\partial S}{\partial t}=\|\nabla S\|\left[\nabla\cdot\left(\gamma\frac{\nabla S}{\|\nabla S\|}\right)+V_{LB}\right],$$

$$V_{LB}=-p+\rho_0U_{SS}+\frac{\epsilon_m(\mathbf r)}{2}|\Phi|^2-\Phi\sum_j Q_j\delta(\mathbf r-\mathbf r_j)$$

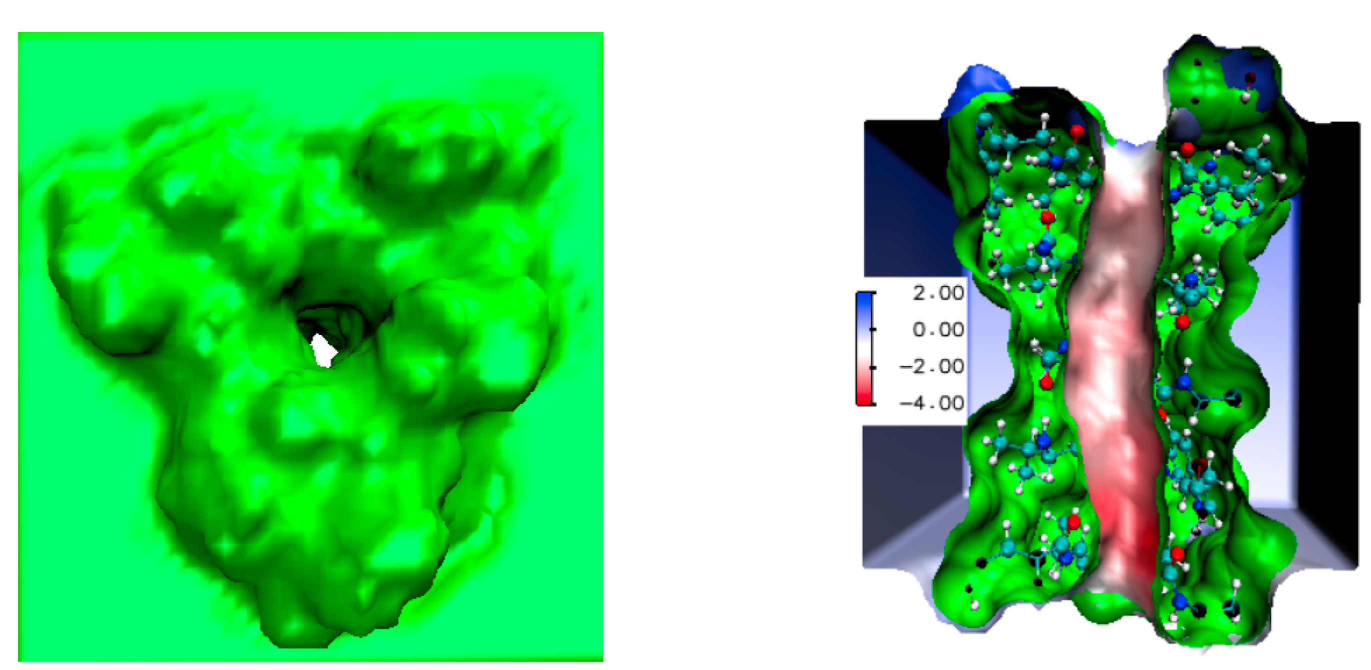
$$-\frac{\epsilon_S(\mathbf r)}{2}|\nabla\Phi|^2-k_BT\sum_\alpha n_\alpha$$

Associated numerical algorithm

- **Dirichlet-to-Neumann mapping(DNM):** Delta function singularities are removed by the Green's function $\Phi^*(\mathbf r)$, which vanishes on the interface Γ by adding a term $\Phi^0(\mathbf r)$, and yields a nonhomogeneous flux on Γ. Only the regular solution needs to be solved.
- **Matched interface and boundary (MIB):** The interface elliptic problem is solved by using the MIB scheme to attain the second order accuracy.
- **Successive relaxation scheme and convergence criteria:** This scheme is employed to achieve the convergence efficiently for the self-consistent outer iterations(surface evolution for S) and inner iterations(coupled equations for ϕ and n_α). The stopping criteria for iterations is by the evaluation of the energy difference, which involves integration evaluation.

Simulation results:I

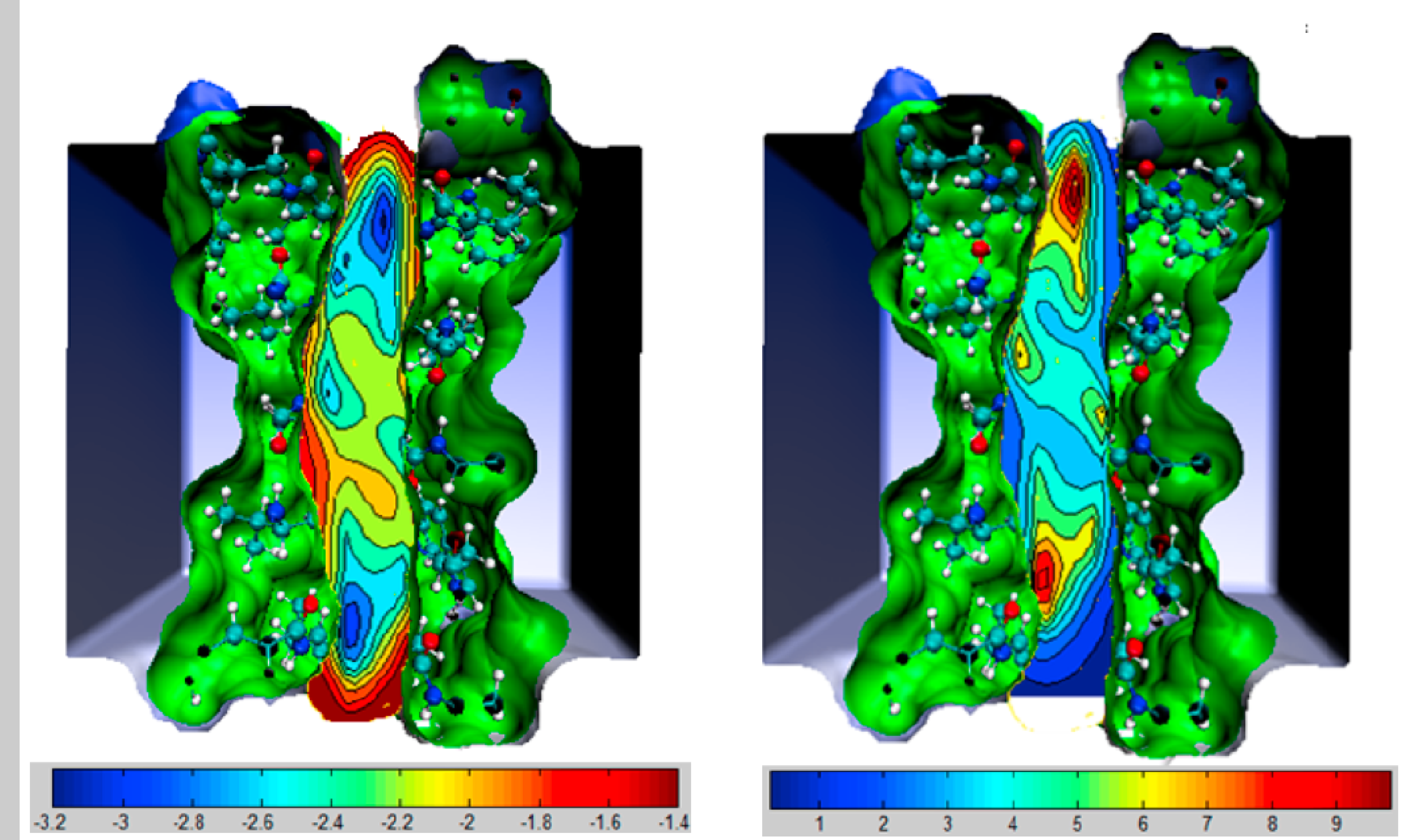
Numerical simulations are carried out based on the molecular structure of Gramicidin A Channel which is one of the most widely studied channels and implicit membrane representation to study the ion transport. The surface defined by S is shown below:



(a) Top view of channel and membrane (b) Side view of the channel pore

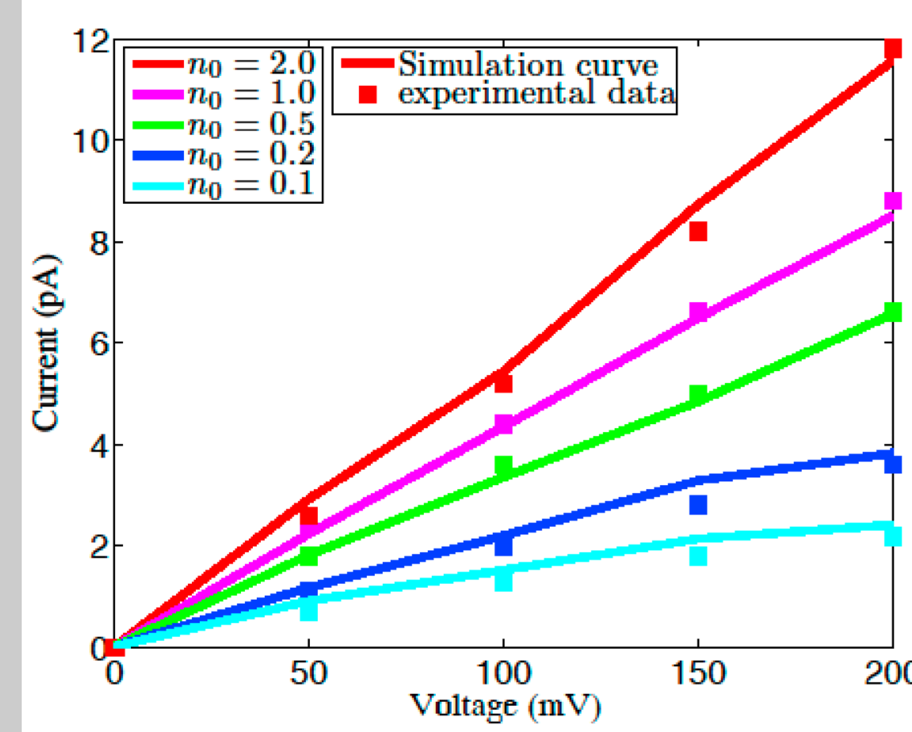
Simulation results:II

The electrostatic potential and ion concentration contours of K^+ along the channel pore direction:



(a) Top view of channel and membrane (b) Side view of the channel pore

I-V curves: Simulation data V.S. Experimental data



Gramicidin is a heterogeneous mixture of six antibiotic compounds, Gramicidin A, B and C, making up 80, 6, and 14 percents respectively, all of which are obtained from the soil bacterial species Bacillus brevis. Gramicidin A ion channel selectively passes monovalent cations. All experimental data are from Cole et al., 2002, *Biophysical Journal*.

Conclusion

The differential geometry based ion transport model is presented and numerical algorithms are developed for solving the coupled equations in the biomolecular context. Numerical convergence is validated and simulation results are compared well with experimental measurements.

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