

Organization: Rush Medical Center / University of Illinois at Urbana-Champaign



Title: Computational, Experimental, and Engineering Foundations of Ionic Channels, as Miniaturized Sensors, Devices and Systems

MTO Simbiosys

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Project Goals

Develop an integrated theoretical and experimental approach to investigate ionic channels as bio-sensors

Technical Approach

- Construct mean field model of gramicidin
- Construct mean field model of porin.
- Develop Monte-Carlo model of ion dynamics in gramicidin and porin, including the effects of finite ion size
- Show sensitivity of gramicidin to experimentally alterable parameters
- Show sensitivity of porin to experimentally alterable parameters
- Measure properties of single channels of porin
- Measure sensitivity of single channels of porin to experimentally alterable parameters

Recent Accomplishments

- Current-voltage relations, ion occupancies and selectivities were computed for wild-type porin *ompF* and its mutant *G119D* in a range of concentrations of KCl and CaCl₂, using a drift-diffusion model with a spatially uniform diffusion coefficient, implemented using the PROPHET simulator.
- Current-voltage relations were computed for 100mM KCl in *ompF* using several spatially varying profiles of diffusion coefficient, including (i) estimates obtained from Molecular Dynamics (MD) simulations and (ii) predictions from a one-dimensional drift-diffusion model based on a reverse-engineering approach.
- Monte-Carlo (MC) code runtime was reduced by approximately two orders of magnitude. A model of ionic core repulsion has been included to account for the finite ion size. Comparison with earlier models based on point charges indicates that the ion size plays an important role in the selectivity of the gramicidin channel.
- *IV* relations were experimentally measured for *ompF* and *G119D* in a range concentrations of KCl and CaCl₂.
- Meshless drift-diffusion solver was implemented and used to simulate the gramicidin channel.
- Clear experimental evidence of the difference a change in fixed charge makes (produced by a mutation) in selectivity to Ca²⁺ vs. K⁺ in porin.
- The first theory of chloride channels using a combination of Density Functional and drift-diffusion theory.
- Mutations are under way to make a synthetic calcium channel.
- Direct calculations are in progress comparing ensemble Monte Carlo and Molecular Dynamics calculations of pair correlation functions.

Six-Month Milestones

- Improve the performance of meshless drift-diffusion solver – extend application to the porin channel.
- Use the drift-diffusion model to (i) compute the *IV* relations of *ompF* and *G119D* in mixed solutions of CaCl₂/KCl and (ii) investigate further the role of the permanent charge density on the protein and the ion diffusion coefficient on the channel conductance.
- Extend the drift-diffusion model to include effects of excess chemical potential.
- Verify the MC code by computing the Nernst potential. Implement two grids – a coarse grid for Poisson and fine grid for ion trajectories.

Team Member Organizations

University of Illinois at Urbana-Champaign & Rush Medical Center

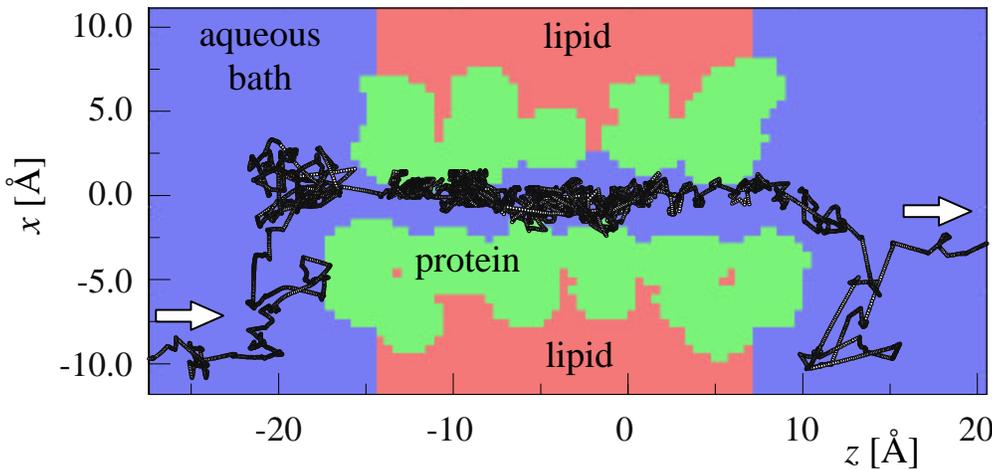


Figure 1. Geometric representation of gramicidin channel used in the 3D Monte Carlo transport model. The successful trajectory of a single Na^+ ion with a finite ionic radius traversing the channel from one electrode to the other is shown. The ionic radius of Cl^- is commensurate with the channel radius, rendering anion permeation extremely unlikely.

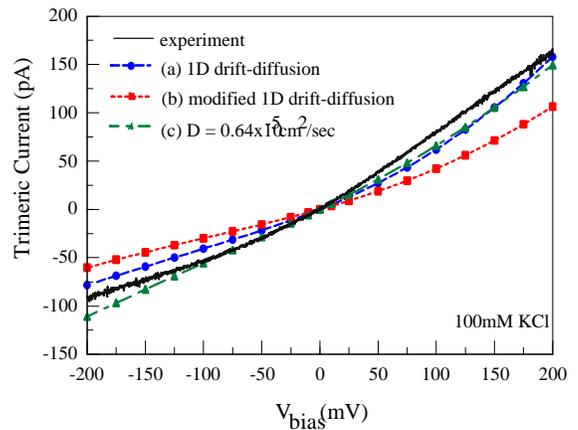
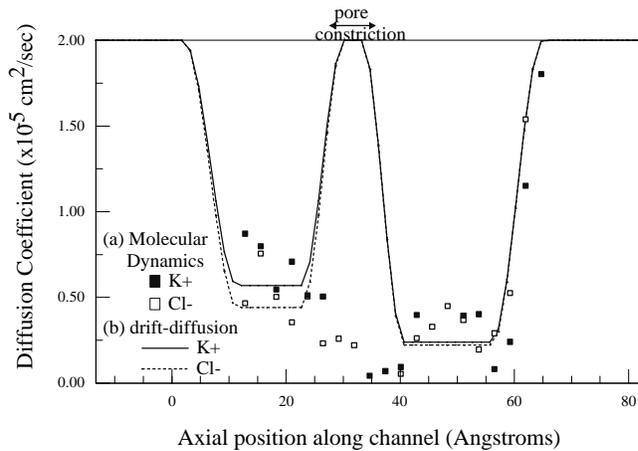


Figure 2 (a) Diffusion coefficient as a function of axial position in the *ompF* porin channel computed by MD and reverse-engineering 1D drift-diffusion theory to fit experimental data. (b) Measured and computed *IV* curves for *ompF* in 100mM KCl, for the diffusion coefficient profiles shown in (a), and with a single spatially uniform diffusion coefficient.

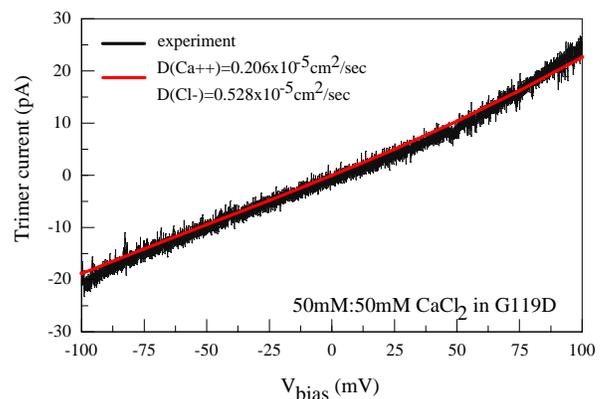
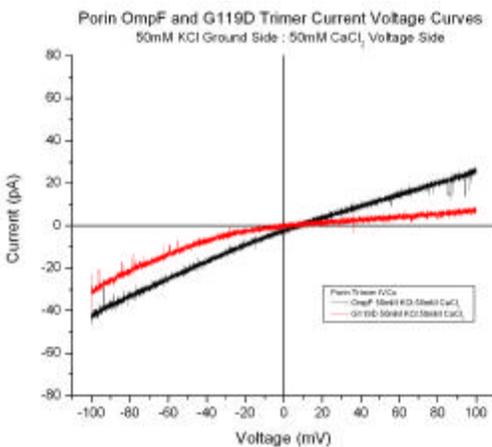


Figure 3 (a) Experimentally measured *IV* relations for 50mMKCl/50mM CaCl₂ in *ompF* (black) and G119D (red) (b) Measured *IV* relations for 50mM CaCl₂ in G119D compared with curves computed using the drift-diffusion theory with uniform diffusion coefficients.