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Recreating Ion Channel IV Curves using Specific Frequency Components
John Rigby, Steven Poelzing.
INTRODUCTION: Impedance spectroscopy cannot distinguish between ion channel families. We hypothesized that amplitudes of specific characteristic frequencies will correlate with the current amplitude passed by a specific ion channel families. Previously, we demonstrated the feasibility of this technique using the inward rectifying potassium channel, $K_{IR}2.1$. In this study, $Na_V1.5$ is used to demonstrate that the technique is applicable to other families of ion channels.
METHODS: IV curves were generated using a standard voltage step protocol performed in whole-cell voltage clamp mode on HEK293 cells transiently transfected with SCN5A (encodes $Na_V1.5$). Noise functions containing 1-50 kHz frequencies were inserted into each voltage step. The real component of the Fast Fourier transform (FFT) was then calculated for each trace. Each frequency magnitude as a function of voltage step was correlated with the IV curve.
RESULTS: The magnitude of 22.5 and 24.5 kHz correlated well with the IV curve of $Na_V1.5$ in the presence of the noise function ($R>0.8$), and poorly in the absence of noise ($|R|<0.3$). Two nodes of zero correlation were also found (11.36 +/- .08 kHz and 36.23 +/- 4.79 kHz. For $K_{IR}2.1$, current and frequency amplitudes did not correlate well between 11 and 36 kHz, suggesting that this correlation may be unique to $Na_V1.5$. On the other hand, frequencies were identified below 10 kHz whose amplitudes highly correlate with either one or both channels.
CONCLUSIONS: These data suggest that specific frequencies exist which can re-create the shape of both $K_{IR}2.1$ and $Na_V1.5$ IV curves. Furthermore, the correlation at some frequencies is channel specific, while others are not. This methodology could be a powerful tool for assessing the behavior of multiple ionic currents simultaneously during a freely running action potential.

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Mapping the Importance of 4 factors in Creating Monovalent Ion Selectivity in Biological Molecules
Michael Thomas, Dylan Jayatilaka, Ben Corry.
The ability of macrocycles, enzymes, ion channels, transporters and DNA to differentiate between ion types is often crucial to their function. Using molecular dynamics simulations on both detailed systems and simple models we quantify the importance of four factors which affect the ion selectivity, including the number of coordinating ligands [1], their dipole moment [2], the cavity size [3] and their vibrational motion. The information resulting from our model systems is distilled into a series of 'selectivity maps' that can be used to 'read off ' the relative free energy associated with binding of different ions, and to provide an estimate of the importance of the various factors. While our maps cannot capture all elements of real systems, it's remarkable that our simple model produces differential site binding energies in line with experiment and more detailed simulations for a variety of systems. This makes our maps a very useful tool for assisting in understanding the origins of selective binding and transport. Our studies show that the various suggested mechanisms of ion selectivity can be important in various situations. The chemical nature of the coordinating ligands is essential for creating thermodynamic ion selectivity in flexible molecules, but as the binding site becomes more rigid the number of ligands and the reduction of thermal fluctuations can become important.
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Testing the Applicability of Nernst-Planck Theory in Ion Channels
Chen Song, Ben Corry, Bert de Groot.
The question of whether Nernst-Planck (NP) theory, which is a macroscopic method for calculating ion flux, is still valid in microscopic narrow ion channels has been remaining a mystery for some years. Recently, we tested the ability of the NP theory to accurately predict channel currents by combining and comparing the results with those of Brownian dynamics (BD) simulations. The extensive tests for simplified and realistic ion channels indicate that the NP theory is still applicable in narrow ion channels provided that accurate concentrations and potentials can be input into the NP equation properly, as the currents obtained from the combination of BD and NP match well with those obtained directly from BD simulations. Here, we show first results comparing NP calculations and molecular dynamics (MD) simulations that show promising agreement, further confirming the validity of the NP theory at the microscopic scale. This finding opens a door to utilizing the results of microscopic simulations in continuum theory which can provide an efficient way to calculate the ion flux in ion channels, and might stimulate further effort in this direction.

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A New Poisson-Nernst-Planck Equation (PNP-FS-IF) for Charge Inversion Near Walls
YunKyong Hyon, James E. Fonseca, Bob Eisenberg, Chun Liu.
The plasmas of biology are interacting mixtures of ions - often charged spheres - that do not behave like the ideal solutions of textbooks. Interactions are always present because of strong electrical forces. Flows are usually present. Life without flow is death. We analyze ionic solutions as complex fluids with an approach that has successfully analyzed complex systems like liquid crystals that are dominated by interactions between composite components. The finite size of ions is particularly important in biology in crowded environments like channels, active sites of enzymes, or charged surfaces. We here deal with surfaces and try to capture the essential features of charge inversion (layering) near a charged wall. Charge inversion (layering) near walls is a characteristic phenomenon resulting from the electrostatic interactions in systems with charged walls. The mathematical model is derived by the energy variational approach (*EnVarA*) – J.Chem.Phys. (2010) 133:104104 – that combines the action of conservative (Hamiltonian) systems and the dissipation of Onsager and Rayleigh. Both are written in the same laboratory coordinates after variational derivatives of variables are taken. The generalized energy and dissipation include entropic and electrostatic components, and repulsion between spheres. An interfacial electroneutrality constraint between bulk and charged wall captures some essential features of charge inversion. Taking variational derivatives yields a field theory of partial differential equations and boundary conditions that are appropriate for life's solutions – that interact and flow – as well as thermodynamic equilibrium. The new equations, PNP-FS-IF, include (1) a nonlocal contribution of finite size (FS) and (2) an interfacial constraint (IF) of electroneutrality. PNP-FS-IF produces charge inversion near walls. We compare the charge inversion seen with PNP-FS-IF and Monte-Carlo simulations.

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How Interactions Control Molecular Transport in Channels
Anatoly B. Kolomeisky, Karthik Uppulury.
The motion of molecules across membrane channels and pores is critically important for understanding mechanisms of many cellular processes. Here we investigate the mechanism of interactions in the molecular transport through nanopores by analyzing discrete stochastic models. According to this approach the channel transport is viewed as a set of chemical transitions between discrete binding sites along the pore. It is shown that the strength and spatial distribution of molecule/channel interactions can strongly modify the molecular fluxes. Our analysis indicates that the most optimal transport is achieved when the binding sites are near the entrance or exit from the channel depending on the sign of the interaction potential. This observation allows us to explain recent single-molecule experimental results on translocation of different polypeptides. It also agrees with available information on distribution of binding sites in many membrane channels. In addition, we studied the role of intermolecular interactions during the channel transport, and it is argued that an increase in the flux can be observed for some optimal interaction strength. The mechanisms of these phenomena are discussed.

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Investigating Co-Transport Mechanisms in the AmtB Ammonium Transporter using QM/MM Molecular Dynamics
Shihao Wang, Sefer Baday, Simon Bernèche, Guillaume Lamoureux.
AmtB from Escherichia coli is a transmembrane protein with an important role in ammonium transport, especially at low external ammonium concentrations. However, whether AmtB is a channel that permeates NH_3 or an NH_3/H^+ co-transporter is still an open question. An extensive series of hybrid Quantum Mechanical(QM)/Molecular Mechanical(MM) simulations has been performed to investigate the mechanism of ammonium transport through AmtB. Focus has been placed on the deprotonation of ammonium and the possible co-transport of H^+ and NH_3. Constraint dynamics simulations have been used to obtain the potentials of mean force for the possible NH_4^+ deprotonation paths involving water molecules and/or protein side chains. Further investigations on the transport pathways of H^+ and NH_3 have shown the details of the co-transport mechanism. The distribution of solvent and ammonia inside the pore is also analyzed