on three factors; the dipole moment of the coordinating ligands [1], the number of coordinating ligands [2] and the cavity size of the coordination site [3]. By using free energy methods in molecular dynamics simulations to study model systems as well as a range of biological molecules including channels, transporters and enzymes, we are able to determine the contribution of each of these factors to the overall ion selectivity of the molecule. Varying contributions of each give rise to the richness in ion selectivity we see.
By mapping out the importance of these factors in various cases, an estimation of the degree of selectivity of an ion selective biological molecule can be made given its structure. These results also assist in predicting the nature of a binding site of an unknown structure and have the potential to aid in the design of novel synthetic ion selective molecules.
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3412-Pos Board B459
Hydrophobic Selectivity And Electrostatic Gating In Narrow Ion Channels
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Previous studies have shown that some ion channels, such as the nicotinic acetylcholine receptors (nAChR), have a hydrophobic region lining the pore in the transmembrane domain (TM-domain) that is responsible for gating the channel, and a charged ring at the extracellular entrance of the TM-domain which is important for ion selectivity. Our recent studies show that the hydrophobic effect can also contribute to the ion selectivity, and the electrostatic effect can also play a role in the gating behavior.
1) Hydrophobic selectivity: Singe walled carbon nanotubes (SWNTs) are selected as the model of the hydrophobic pores and potential of mean force calculations are performed for Na^+, K^+ and Cl^- respectively. The results show that for the (8,8) and (9,9) SWNTs which ions can pass through under biological driving forces, the free energy difference between types of ions can exceed 2 kcal/mol. This difference arises mainly from the differing dehydration energies and this hydrophobic selectivity may complement electrostatic origins of selectivity.
2) Electrostatic gating: Preliminary electrostatic calculation results on the TM-domain of the nAChR in the closed state show that a ring of charged residues can tightly bind an ion preventing conduction. A small conformational change of the protein that increases pore radius by only 0.5 Å can reduce the binding by ~6 kcal/mol and allow permeation.

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The Anomalous Mole Fraction Effect in Calcium Channels: The Ryanodine Receptor Case Study
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The origin of the anomalous mole fraction effect (AMFE) in calcium channels is explored with an ion permeation model of the ryanodine receptor (RyR) calcium channel. This model predicted and experiments verified new AMFEs in RyR. In mole fraction experiments, conductance is measured in mixtures of two ion species (X and Y) as their relative amounts (mole fractions) vary. This curve can have a mimimum (an AMFE). The traditional interpretation of the AMFE is that multiple ions move through the pore in a single file. Nonlinear mole fraction curves without minima are generally interpreted as X displacing Y from the pore in proportion larger than its bath mole fraction (preferential selectivity). We find that the AMFE is also caused by preferential selectivity of X over Y if they have similar conductances. This is a prediction for any channel. Preferential selectivity causes the resistances to current flow in the baths, channel vestibules, and selectivity filter to change differently with mole fraction. This resistors-in-series model provides a fundamentally different explanation of the AMFE that does not require single filing or multiple occupancy. The success of the resistors-in-series model to predict AMFEs in RyR shows that the traditional model should be reconsidered for calcium channels.

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Energetics of Calcium Selectivity: A Three-Dimensional Classical Density Functional Theory Approach
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Selectivity of a calcium channel is explored with three-dimensional density functional theory of fluids (DFT). The model pore has millimolar Ca2+ affinity similar to the ryanodine receptor calcium channel. The four flexible aspartate side chains in the selectivity filter are modeled as four carboxyl groups (each as two independent, half-charged oxygen atoms) that are free to move within the selectivity filter, but cannot leave it. These oxygens coordinate the permeating ions. We examine how the ions are coordinated by computing radial correlation functions around the permeating ions. We also examine how this coordination changes in wide and narrow selectivity filters. The energetics of selectivity are computed and their components (e.g., electrostatics, excluded volume) show that the coordination of the ions by the oxygens determines the Ca2+ selectivity of the pore by the charge/space competition mechanism. In this mechanism, selectivity is determined by a balance of electrostatic and steric interactions of ions and amino acid side chains in the crowded selectivity filter. Our approach of combining three-dimensional DFT with state of the art computational techniques is unique in channel selectivity. Moreover, the DFT approach allows a natural decomposition of the energies involved in selectivity. The convolution-type calculations at the heart of the DFT are computed using a combination of fast transforms and analytical results. The software itself is built upon the PETSc framework from Argonne National Laboratory.

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H+ Permeation in Hv1 Voltage-gated Proton Channels
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Voltage-gated H^+ channels are structurally homologous to the voltage sensor domain of K_v, Na_v and Ca_v channels but, despite the lack an ion-selective pore domain, conduct robust H^+ current without apparent need for an accessory protein. Recent evidence indicates that although H_v1 is dimeric, each subunit contains a separate H^+ permeation pathway that can be abrogated by amino acid mutation and chemical modification. However, the molecular mechanism of H^+ permeation in H_v1 is unknown.
Previous studies suggested that H^+ permeation in voltage-gated proton channels is likely to employ a Grötthus-type H^+-hopping mechanism involving one or more protonatable amino acids. We hypothesized that residues which are required for H^+ permeation in H_v1 should be identifiable by loss of function phenotype in a mutagenesis screen. Candidate H^+-acceptor residues within the voltage sensor were selected from those conserved in H_v1 species orthologues and by examination of homology models based on H_v1 structure based on known K_v channel protein structures and refined by molecular dynamics simulations. We used site-directed mutagenesis to neutralize candidate residues by substitution to Ala or Asn. Mutated GFP-H_v1 channels were expressed in mammalian culture cells and whole-cell H^+ currents at fixed pipette pH and varying bath pH were elicited by depolarizing voltage steps. Although the apparent threshold for voltage-dependent activation of H_v1 current was altered by as much as −120 mV in certain mutants, the charge-neutralizing mutations we tested were insufficient to entirely abrogate expressed H^+ current. Mutagenesis data and molecular models were used to generate a molecular model of H^+ permeation through H_v1.

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Ion Transport through OmpF in Molecular Dynamics Simulations and Experiments
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The outer membrane pores F (OmpF) of E. coli bacteria is a diffusion channel which has a wide range of functions and properties of biological relevance. The temperature-dependent ion conductance in OmpF is measured in a wide range of electrolyte concentrations and compared with molecular dynamics simulations. The agreement between experiment and theory is very good. In the experiment single OmpF channels are reconstituted into planar lipid bilayers. In test studies, bulk electrolyte simulations and experiments showed that the simulations are accurate for salt concentrations up to 1 molar. Comparing the temperature dependence of the OmpF channel conductance with that of the bulk conductivity in the range from 0 to 90 degree Celsius revealed that at low salt concentrations the transport is mainly driven along the pore surfaces. Increasing the salt concentration saturates the surface charge transport and induces ion transport in the center of the nanopore. The confinement of the nanopore then favors the formation of ion pairs.