Water Molecular Distribution and Hydration Studies of a Voltage Gated Potassium Channel or Nanopore

Introduction

Nature provides us with a very large number of channels or nanopores embedded in cell membranes. The function of channels is to allow selectivity and specificity for a variety of molecular species transport across the cell membrane. These channels include:

1. Ligand-gated channels
2. Voltage-gated channels
3. Second messenger gated channels
4. Mechanosensitive channels
5. Gap junctions: porins not gated

Our rationale for studying nature's nanopores include:

1. Their functional mechanisms are not well understood.
2. Better understanding may lead to the development of novel nanochannel devices or "biomimicry."

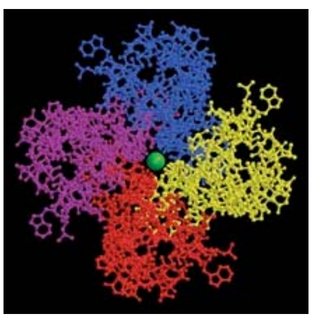

Figure 1: The voltage-gated potassium channel shown here is one of the few channels where a complete 3-D molecular structure has been obtained. (Ref: MacKinnon et al., *Science*, Vol. 309, 897, 2005.)

Modeling

We have selected the voltage-gated potassium channel as our model system because of its biological importance and the fact that its full molecular structure has been determined recently (Fig. 1, above).

The first step in understanding the physical mechanism of potassium transport through this protein nanopore is the determination of the water molecular distribution along the axial length of the pore. To accomplish this, we utilized a full-scale molecular dynamics calculation as described previously [Zhang, Y., Peters, M.H., and Li, Y., 'Nonequilibrium Multiple Time Scale Dynamic Simulation of Receptor-Ligand Interactions in Structured Protein Systems', *Proteins, Structure, Function and Genetics*, **52**, 339-348 (2003).]

Some minor updates in our previous study include:

1. All force field constants are taken from the Cornell et al Amber Force Field Constants (*J. Am. Chem. Soc.*, 117, 5179-5197, 1995).

2. Hydrogen atoms were added to the protein channel using Accelyrs Viewer Pro.

Results

Initial hydration of the voltage-gated potassium channel has been accomplished using our previous techniques referenced above. The simulation box, complete with the hydrated potassium channel, is shown below.

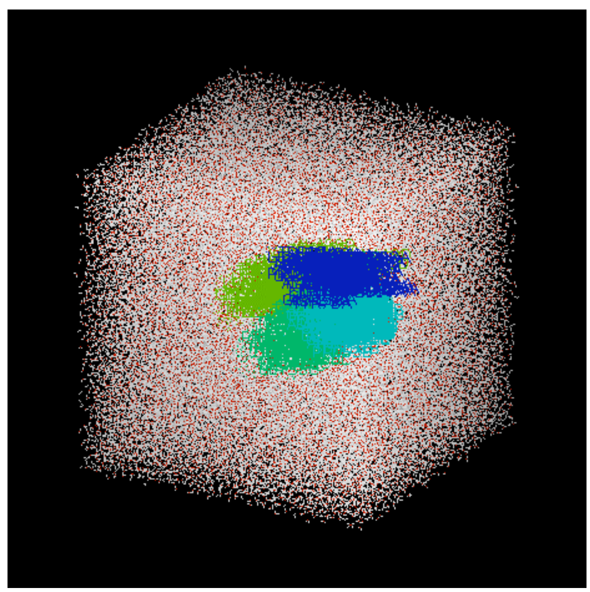

Figure 2: Hydrated voltage-gated potassium channel. The box length was selected as 120A and resulted in 54,062 water molecules.

mpeters@vcu.edu

Utilizing canonical ensemble molecular dynamics simulations, we are conducting detailed simulations of the expected water molecular distribution inside and proximal to the nanopore of this channel.

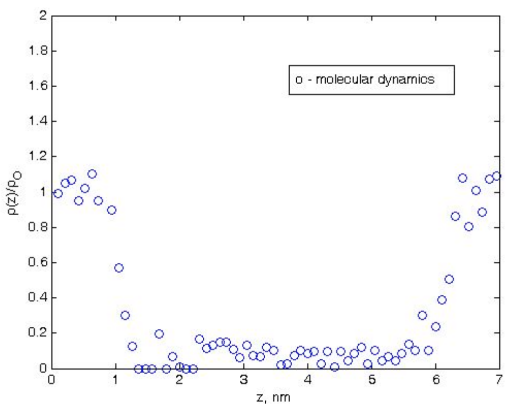

Figure 3. Water molecular distribution function inside nanopore.

Current studies are focused on the transport of potassium ions through the nanochannel, including the external electrical potential or cell membrane potential (~-60mV) .

A hypothesis of selective ion transport through a potassium channel has been presented by T.W. Allen, S. Kuyucak, and S.-H. Chung based on the K+ channel of *Steptomyces lividans* [*Biophysical Journal*, **77**, 2502-2516 (1999)]. The K+ channel in the open position acts as a selectivity filter in exchanging the K+ions hydration layer in favor of carbonyl oxygen atoms associated with particular amino acid groups along the lining of the pore. Na+ ions that are also present are too small to shed their hydration layers in an energetically favorable way. With the additional feature of a hydrophobic region within the channel, the Na+ion-water complex cannot pass through the pore.

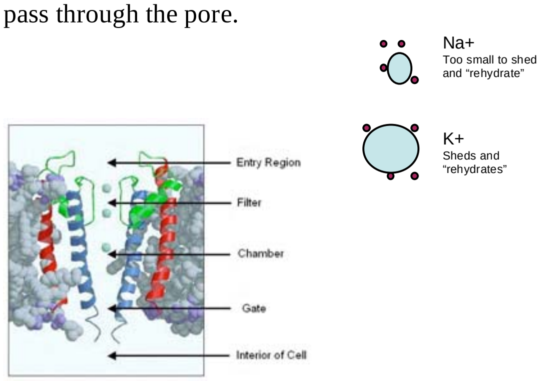

Figure 4. Hypothesized selective ion transport mode in a K+ channel.

To test this hypothesis, we will place potassium ions at the end of the channel and at random locations and random velocities (Maxwellian sample). The ensemble will involve hundreds of such random initial ion assignments. Each ion or ensemble member will be tracked in time, and the net potential experienced by potassium ions as they interact with the channel pore will be recorded.

A complete mechanistic picture of ion transport in the nanopore will be developed. Results from this study will have general applicability to the transport of ions in nanopores by providing a "nano-blueprint" for the design of synthetic nanopores for a variety of applications.

mpeters@vcu.edu