Electro-Chemical Modeling Challenges of Biological Ion Pumps

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There are two major classes of proteins that control the movement of ions across biological membranes: channels and transporters. Ion channels allow the passive movement of ions down their electrochemical gradients whereas transporters power uphill movements. Two major questions have challenged channel biophysicist for nearly a half-century: permeation (selective passage of ions through an open channel) and gating (channel opening and closing). A major advance in the understanding of permeation and gating of K^+-selective channels has been made by the publication of atomic resolution structures of a bacterial K^+ channel by the laboratory of Roderick MacKinnon who received the Noble prize in Chemistry in 2003 for this body of work. The availability of detailed atomic structure allows the classical problems of permeation and gating to be addressed by interdisciplinary teams and techniques. Recent examples of the application of transport modeling to permeation through biological channels include both the Poisson-Nernst-Planck electrodiffusion approach and structurally based Brownian dynamic simulations [1, 2]. Channel gating, however, involves changes in the structure of the protein. A detailed understanding of channel gating is hindered by the computational limitations of molecular dynamic simulations and the lack of structural information about intermediate conformations between the closed and fully open states.

The class of transporters known as ion-motive ATPases have a number of features similar to ion channels, but they are more complex proteins since they require coupling of the free energy change associated with ATP hydrolysis with the uphill movement of the actively transported substance. Rather than simply acting as selective channels for passive ion movements, ion motive ATPases are molecular batteries suitable for bio-electro-chemical applications that require the establishment or maintenance of an electrochemical gradient. P-type ATPases are a major class of ion pumps that hydrolyze intracellular ATP and change their structure by phosphorylation reactions at various stages of the transport cycle as diagrammed in Fig.1. Recently an atomic resolution structure of several conformations of a P-type ATPase (SERCA, the Ca^{2+} pump of skeletal muscle), have been published [3, 4]. Homology modeling based on the structure of SERCA has been used to predict the structure of the closely-related Na^+, K^+-ATPase (sodium pump) [5, 6]. The most-likely mechanism of active transport is an "alternating access" model in which the transported ions are bound at one face of the membrane, "occluded" in a state not directly accessible to either side, and released to the opposite side of the membrane as a consequence of changes in protein conformation and changes in the ion binding affinity of the transport sites. A molecular model of the major structural changes associated with the Na^+ bound and K^+ bound states is shown in Fig. 2. A detailed understanding of the mechanism of ion translocation will require knowledge of the structure of additional intermediate states of the enzyme and molecular dynamic simulations of the transitions between these states. Several aspects of the overall problem, however, are approachable by a combination of modeling and molecular biological techniques. For example, we propose to investigate the geometry of the binding sites and the pathway for ion binding and release by site directed mutagenesis of sodium pumps that can be expressed in the surface membrane of frog eggs (*Xenopus laevis*). Studies have also been performed that allow resolution of the rate of release of each of the 3 Na^+ ions at the outside of the membrane of voltage-clamped giant axons of squid (*Loligo pealei*) [7]. We will review the current state of knowledge concerning ion pumps and discuss various modeling opportunities and challenges presented by this important class of biological molecules. The Na^+-K^+ ATPase will be the principal focus of our discussion.

A full journal publication of this work will be published in the Journal of Computational Electronics.

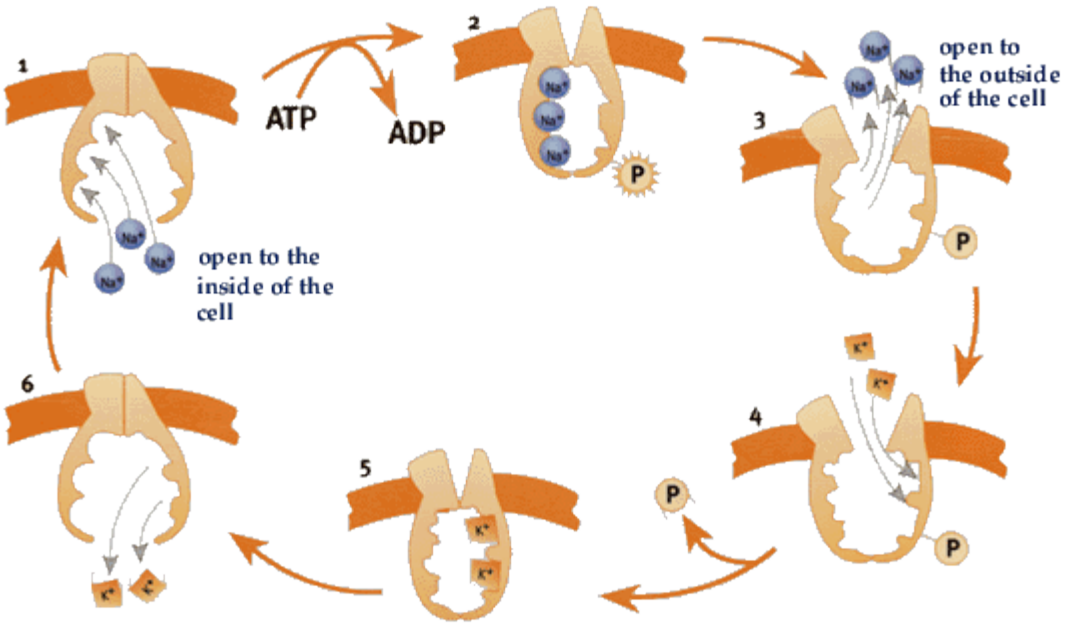

FIGURE 1. The basic operation cycle of the Na^+, K^+- ATPase. Three Na^+ ions are bound from the inside of the cell, the enzyme is phosphorylated and the ions are occluded within the protein. They are subsequently released to the outside of the cell, followed by binding of 2 K^+ ions. This allows the enzyme to be dephosphorylated and the K^+ ions to be released to the inside of the cell. From: http://www.nobel.se/chemistry/educational/poster/1997/skou.html.

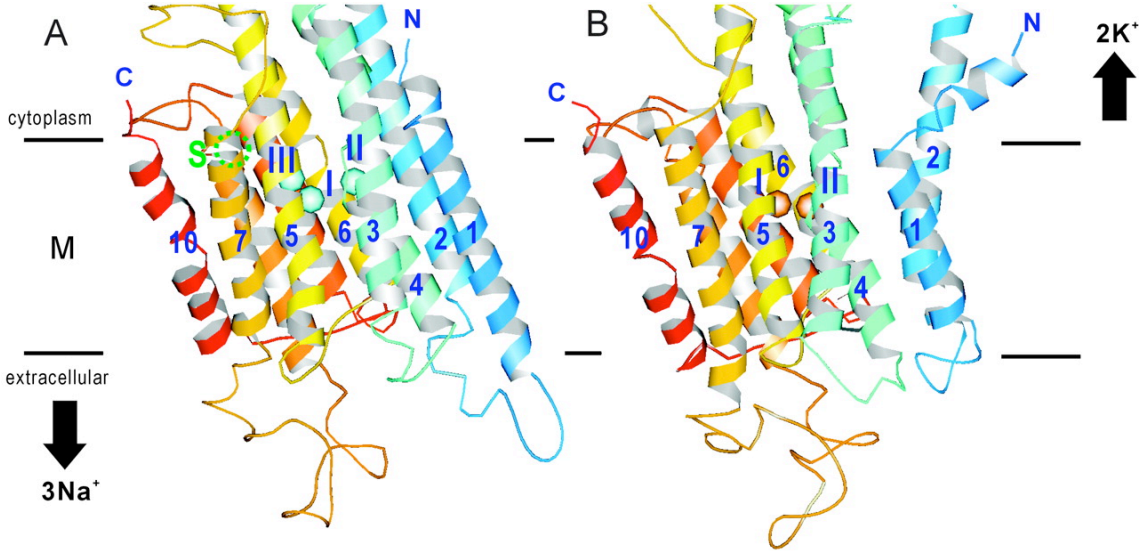

FIGURE 2. Ribbon representation of the transmembrane part (M) of the homology model of the Na^+K^+-ATPase in Na^+- (A) and K^+-bound (B) forms. α-Helices are numbered. Horizontal bars represent the boundaries of the hydrophobic core of the lipid bilayer. Spheres in A represent Na^+ ions (I–III), and in B represent K^+ ions (I and II). From [5].

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