

Models, Electrostatics and Molecular Dynamics of the Na⁺/K⁺-ATPase

J. Fonseca, R. F. Rakowski*, and S. Kaya

School of EECS, Russ College of Eng & Tech, Ohio University, Athens, OH 45701, USA

* Dept. of Biological Sciences, Ohio University, Athens, OH 45701, USA

e-mail:kaya@ohio.edu, fax: (740) 593-0007

Abstract—The present work establishes a unique framework for the simulation study of ion-motive pumps in general and the Na⁺/K⁺-ATPase, or sodium pump, in particular. We shall discuss the implications of electrostatic analysis, molecular surface determination, molecular dynamics simulations, and valence calculations on the structure-function relationship of Na⁺/K⁺-ATPase. These approaches will be used to investigate atomic-level characteristics such as ion binding and accessibility that remain undetermined.

Keywords—Na⁺/K⁺-ATPase; homology modeling; molecular dynamics; electrostatics

An ongoing convergence of bio- and nano-engineering has focused interest on ion transport through trans-membrane proteins. Ion transport takes place either through *passive* (ion channels) or *active* (ion pumps) proteins, which have innate properties such as selectivity and gating that allow them to be classified as bioelectric devices. Contrary to ion channels that have attracted attention from the device community recently [1], ion-motive pumps are still largely unexplored [2].

The Na⁺/K⁺-ATPase, or sodium pump, is a voltage-gated membrane transport protein found in most higher order eukaryotic cells and is essential for life. The sodium pump is vital to maintaining a transmembrane voltage and regulating cellular volume. Even though electrophysiological studies have contributed the vast majority of information on the sodium pump's function in the last century, it has been only in recent years that molecular-level understanding has been forthcoming [3,4]. Still, many structure-function aspects, such as ion binding, ion permeation, conformational changes, and gating processes, essential to the full understanding of the sodium pump, remain elusive. We seek to use a variety of modeling and simulation tools to investigate the effects of electrostatic and steric changes on the properties of ion binding sites as well as ion and water pathways.

Recent successes in crystallography of the calcium pump by Toyoshima and others have given structures [3] of different conformations of the related Ca²⁺-ATPase, SERCA, which have a high degree of similarity with the sodium pump in the transmembrane helices, especially in residues that are believed to coordinate ion binding [5,6]. After inclusion of the model in a lipid bilayer, electropotential maps, site valence information, and the molecular surface can be combined with molecular dynamics (MD) simulations to investigate regions in which ion binding and permeation is believed to occur.

Site valence data has been calculated to determine putative sites in the pump's binding cavity. Electropotential maps can be augmented with protein surface/cavity calculations to show possible binding locations as well as ion/water permeation pathways between these sites and the exterior of the protein. MD simulations have been used to explore water and ion accessibility and permeation pathways through simulations of the >500,000 atom protein-lipid-water-ions system. This is the first attempt to perform molecular dynamics simulations of a homology-modelled sodium pump and bilayer system, a task that has been considered only for the H⁺/K⁺-ATPase previously [7].

The Na⁺/K⁺-ATPase has been introduced and the diversity of structural and functional characteristics that remains undetermined has been outlined. Many details of essential properties such as conformational changes, gating processes, ion binding and water accessibility remain unresolved. We have created multiple homology models of the sodium based on different conformations of SERCA and have begun investigations using several tools to acquire a variety of information, such as valence calculations, molecular surface determination, electrostatic isopotential profiles, and molecular dynamics trajectories.

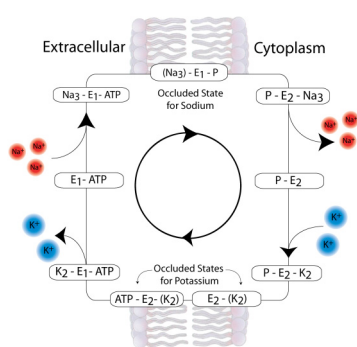


Figure 1. The Post-Albers cycle above indicates the main stages of conformational changes (E₁-E₂), ion binding, release and occlusion, and ATP hydrolysis. Potassium is released and sodium bound on the intracellular side and this process is reversed on the extracellular side. The arrows indicate the forward pump cycle.

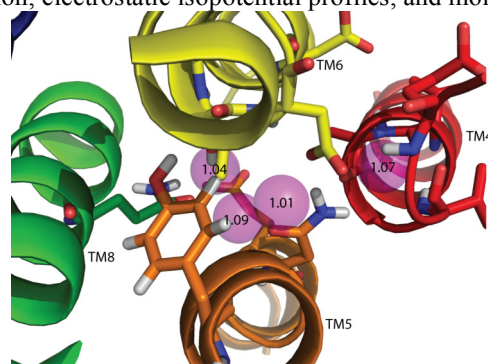


Figure 2. Cytoplasmic-side view of the homology model of Na⁺/K⁺-ATPase based on SERCA E1•2Ca²⁺. Four putative sites (shown with valences) were found in the cavity created by the transmembrane segments. Residues that are predicted to bind Na⁺ are shown in stick representation.

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