

# Commentary on Unidirectional Fluxes of Monovalent Ions in Human Erythrocytes Compared with Lymphoid U937 Cells: Transient Processes after Stopping the Sodium Pump and in Response to Osmotic Challenge

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## Commentary

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## ABOUT THE STUDY

Biological processes occurring in nature are complex and diverse, and it is often difficult to understand their mechanisms. Sometimes simplified models help to understand the causes of a certain phenomenon. Since all living organisms are composed of cells, it is important to understand the mechanism of their functioning in order to withstand various unfavorable factors that lead to disruption of their work and cause various diseases. Based on an animal cell model Vereninov A. A. and his colleagues developed an original software supplied by a simple executable file for calculating the fluxes of monovalent ions in cells of various types, with membrane potentials from -5 to -90 mV and the intracellular  $K^+/Na^+$  ratios between 0.2 and 9, i.e., for the entire range of values found in native animal cells [1-7]. In the proposed model, a living animal cell is represented as an electrochemical cell, surrounded by a highly water permeable membrane and in osmotic equilibrium with the external medium. Inside such a cell there are polyvalent anionic macromolecules impermeable through the membrane. The electrochemical steady state of the cell is provided by the transmembrane transfer of ions, primarily the main monovalent ions  $K^+$ ,  $Na^+$  and  $Cl^-$ , resulting in an electrical potential difference across the membrane. The main pathways for transporting ions across the cell membrane are represented by three groups (pumps, ion channels and cotransporters), which differ in the nature of the forces that move ions across the membrane. The movement of each ion in the mathematical description of the model is determined thermodynamically. The driving force that determines the movement of ions through electrically conductive channels has traditionally been considered to be the difference in the electrochemical potentials of a single ion on both sides of the membrane, and in the case of coupled ion transfer through cotransporters, the sum of the differences in the

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electrochemical potentials of the ions involved in the transfer. For simplicity, each ion pathway, i.e., the Na/K pump, the K<sup>+</sup>, Na<sup>+</sup> and Cl<sup>-</sup> channels and each of the cotransporters are characterized by one integral rate coefficient. These are apparent coefficients, which ignore molecular mechanisms of ion transfer and do not depend on any hypotheses regarding these mechanisms. The authors propose a computer program convenient for calculating ion fluxes through the cell membrane both in an equilibrium state and in transient processes. It should be noted that direct measurement of ion fluxes is a very difficult task and even impossible.

Calculations using the developed program show what changes in cell functioning can be caused only by simple electrochemical processes, and make it possible to distinguish mechanisms, highlighting those that are controlled by complex signaling pathways. Previous publications have demonstrated the use of model calculations to analyze lymphoid proliferating U937 cells at balance state and during transient processes after stopping the Na/K pump by ouabain, for staurosporine-induced apoptosis and in response to osmotic challenge [8-11]. The presented results showed that this model can be successfully applied to various types of cells that differ significantly in functional and structural characteristics, not only for continuously proliferating cells, but also for differentiated cells, such as human erythrocytes, characterized by extremely low permeability to monovalent cations and rather low membrane potential. The presented approach demonstrates the close relationship between the movements of the main monovalent ions through the cell membrane and makes it possible to highlight the influence of each of the computation parameters on the ion-water homeostasis of the system under study.

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