A non-canonical voltage-sensing mechanism in K2P channels

Investigation of non-canonical voltage-sensing mechanism in K2P channels using Molecular Dynamics simulations

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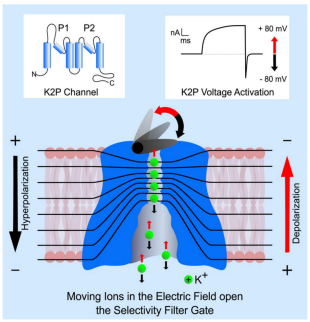
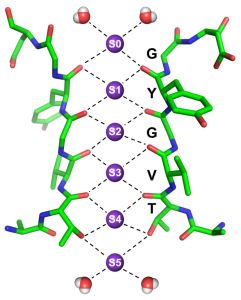
In Short

- Two-pore domain K^+ (K2P) channels are major regulators of cell excitability and play an important role in a wide range of physiological functions
- Many K2P channels sense transmembrane voltages, even though they do not have voltage-sensing domains
- A non-canonical voltage-sensing mechanism within the selectivity filter (SF) was proposed to explain the voltage-sensitivity in many K2P channels, but mechanistic understanding at atomistic level is still lacking
- This study aims to investigate the molecular mechanism of the non-canonical voltage-gating in K2P channels using Molecular Dynamics (MD) simulations.



Adapted from [1]



Selectivity filter

Figure 1: *(Left) An illustration of a non-canonical voltage-sensing mechanism within the selectivity filter (SF) that controls gating in many K2P channels (adapted from [1]). (Right) A SF structure of a K^+ channel with a signature sequence of amino acids, TVGYG. The SF has six ion binding sites labeled from S0 to S5.*

Two-pore domain K^+ (K2P) channels play a crucial role in regulating the resting membrane potential and are highly expressed in various tissues, including the brain, peripheral nervous system, heart, and muscles. These channels are regulated by many stimuli, such as pH level, mechanical stretch, temperature, and transmembrane voltage. Notably, the regulation of K2P channels by transmembrane voltages raises many questions, since they lack the typical voltage sensing domains found in other voltage-gated channels. A non-canonical voltage-sensing mechanism within the selectivity filter (SF) has been proposed to explain this behavior [1], but experimental and/or computational evidence supporting this mechanism is currently missing (see Figure 1). This study aims to address this issue through comprehensive computational electrophysiology [2] investigations conducted by Molecular Dynamics (MD) simulations (see Figure 2).

Interestingly, K2P channels are the only members of a big K^+ channel family that are voltage-gated by the SF. This is surprising considering that the SF structure is the same across all K^+ channels. The difference comes only in the sequence of amino acids that make the SF. In K2P channels a K^+ channel signature sequence, TVGYG, is altered at valine and tyrosine positions, but the implications of these sequence changes on the SF properties remain poorly understood. Additionally, it was shown by Schewe et al. [1] that a mutation of a highly conserved threonine residue completely abolishes the voltage-sensitivity, but the atomic-level changes caused by this mutation are unknown.

Furthermore, 15 member proteins of a K2P channel family can form channels not only as homodimers but as well as heterodimers, which significantly contributes to their functional and regulatory diversity. However, the SF gating properties of heteromeric channels have not been characterized yet, and it remains unclear whether they exhibit voltage-gating behaviour similar to homodimeric channels. Of particular interest are heterodimeric channels involving a subunit from TWIK-1 channel, since TWIK-1 is a distinct K2P channel with low intrinsic activity and linear current-voltage characteristics [1].

By employing large-scale all-atom MD simulations, we aim to elucidate the molecular mechanism underlying the non-canonical voltage-gating in K2P channels. Our study will provide insights into the unique gating mechanisms and ion permeation pathways that endow K2P channels with the voltage-gating property. We will investigate the implications of amino acid sequence variations on the SF properties and also look at novel heterodimeric K2P channels, which are vastly unexplored. The findings of this research will enhance our understanding of the functional roles and pharmacological regulation of K2P channels, contributing to future studies in rational drug design targeted at these channels.

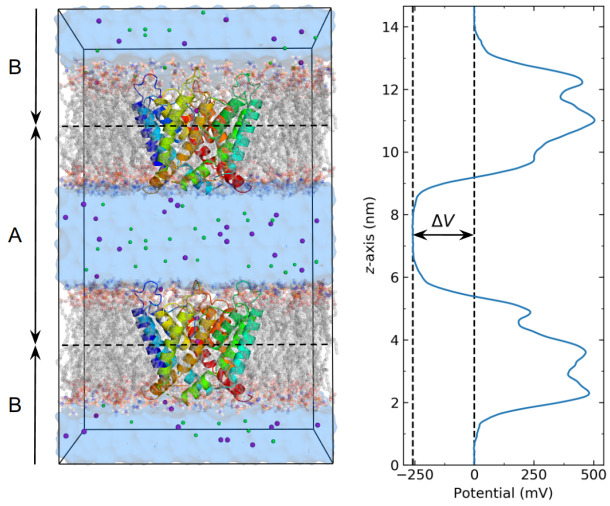


Figure 2: *(Left) A double bilayer system for computational electrophysiology [2] investigations conducted by Molecular Dynamics (MD) simulations. The system is divided into compartments A and B with boundaries highlighted with dashed lines. Structure of MthK is embedded into POPC lipid bilayers, water molecules are shown as a transparent volume for clarity, and K^+ and Cl^- ions are shown as purple and green spheres, respectively. (Right) Electrostatic potential profile along z-axis. Transmembrane voltage is generated by introducing K^+ charge imbalance between comparments A and B.*

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More Information

[1] M. Schewe et al., A Non-canonical Voltage-Sensing Mechanism Controls Gating in K2P K+ Channels, *Cell* **164**, 937-949 (2016). doi: 10.1016/j.cell.2016.02.002

[2] C. Kutzner et al., Computational Electrophysiology: The Molecular Dynamics of Ion Channel Permeation and Selectivity in Atomistic Detail, *Biophys. J.* **101**, 809-817 (2011). doi: 10.1016/j.bpj.2011.06.010

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