High Structural Homology but Low Electrophysiological Similarity

Investigation of Ion Selectivity and Conduction in CNG and HCN Channels using Molecular Dynamics Simulations

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In Short

- Analyse ion binding profiles of different ions such as Na^+, K^+ and Ca^{2+} in CNG channels
- Understand the difference between homotetramer CNGA1 and heteromeric CNGA1/CNGB1 channels in gating and permeation
- Investigate the ion conduction difference between CNG and HCN channels

Mammalian cyclic nucleotide-gated (CNG) channels are crucial components of numerous signal transduction pathways, most classically in the visual and olfactory sensory systems [1]. Although classified as members of the voltage-gated ion channels, CNG channels are mostly gated by ligands rather than voltage. So far, we performed simulations of Na^+ and K^+, respectively, in the homotetramer CNGA1 [2] using Amber99sb and Charmm36m force field. The results in Charmm36m force field showed considerably higher conductance than the experimental value [3].

Hyperpolarization-activated cyclic nucleotide–gated (HCN) channels are involved in the generation of rhythmic activity in heart and brain [4]. Although HCN channel are members of the voltage-gated potassium channel (Kv) superfamily, they differ from Kv channels in three important ways. First, they are opened by hyperpolarization, not by depolarization. Second, they discriminate relatively poorly K^+ from Na^+. Third, their opening is facilitated by binding of cyclic nucleotides to a C-terminal cytosolic cyclic nucleotide binding domain (CNBD). The cryo-EM structures of HCN4 in the presence or absence of bound cAMP, representing the pore domain in closed and open conformations, became available in 2021. The preliminary MD simulation results also identified the open state is conductive [5].

Although HCN and CNG channels share strong homologue in their structures, but their ion selectivity and conductivity are considerably different. To study the detailed mechanism governing non-selective cation permeation in these channels, molecular dynamics (MD) simulations are used to provide microscopic and quantitative insights, thereby obtaining the specific structural mechanisms of the relevant interactions. Molecular dynamics based computational electrophysiology [6] is employed to establish transmembrane potential gradients on duplicated channels simulation box (Figure 1).

Within this project, we have overall four aims: (i) We will extend our current simulations of Na^+ and K^+ on homotetramer CNGA1 to 1µs using Charmm36m force field. With sufficient equilibration of the system, we hope to better reproduce experimental conductance. (ii) We will perform simulations with mixed ions of Na^+, K^+ and Ca^{2+}, mimicking the physiological condition. From these simulations, we expect to derive the selectivity of K^+, Na^+ and Ca^{2+} and analyse ion binding profiles of different ion types regarding to their thermodynamic and kinetic properties. (iii) By comparison of the simulations of heteromeric CNGA1/CNGB1 and homomeric CNGA1 simulations, we aim to understand their difference in gating and permeation. (iv) We will conduct the simulations on HCN4 channels to investigate the structural mechanism of low conductance by comparing with the CNG channels.

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https://leibniz-fmp.de/research/research-section/chemical-biology/han-sun

More Information

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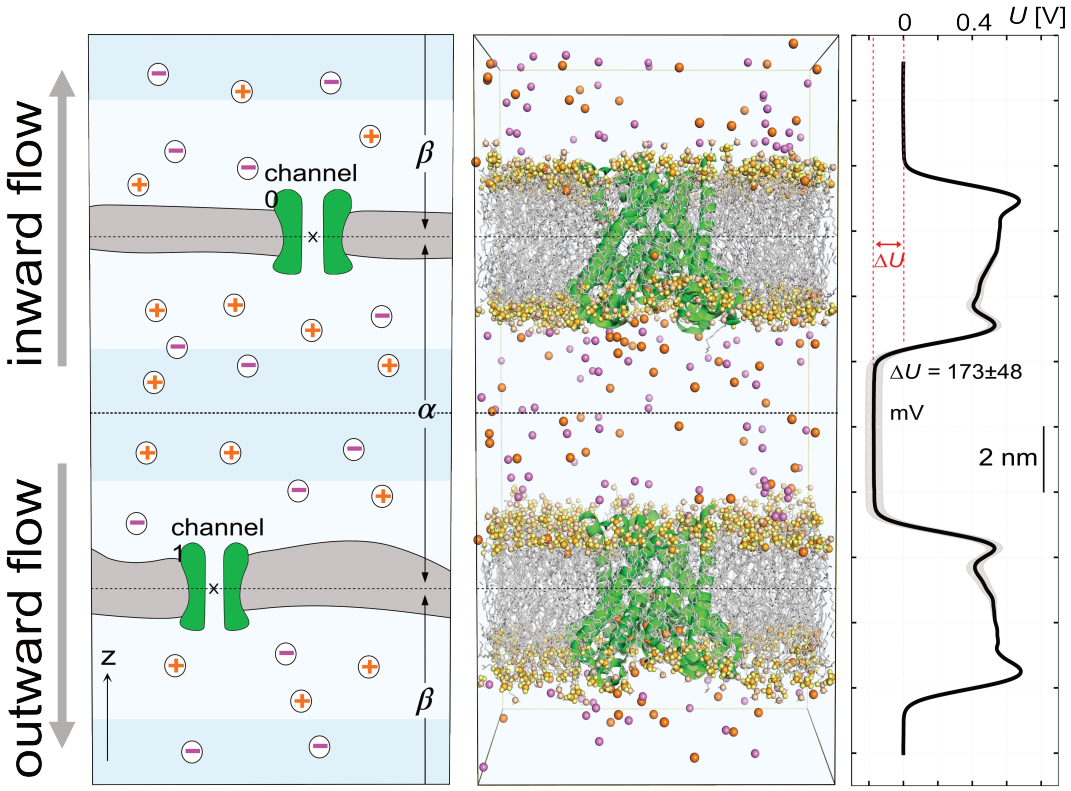

Figure 1: Computational electrophysiology method. *(A)Two compartments are created by double membranes along the z axis. (B) Snapshot of simulation system of CNGA1 channel. (C) Potential difference along the z axis.*

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Project Partners

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