数学与系统科学研究院

计算数学所学术报告

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报告题目：

Both Pore Waters and Counterions Play Functional Role in Regulating the Conductance of the Calcium Release-Activated Calcium Channel

邀请人：　　卢本卓　研究员

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报告地点：　　数学院南楼七层

702 会议室

Abstract:

Calcium release-activated calcium (CRAC) channels are integral proteins of the plasma membrane, and play a central role in cellular signaling by generating a sustained influx of calcium following its depletion from the intracellular repositories. The recent published crystal structure of Orai, the pore unit of a CRAC channel, is used as the starting point for molecular dynamics (MD) and free energy calculations designed to probe this channel's conduction properties. In the first part of our work, the potential of mean force (PMF) was calculated for displacing a single Na+ ion along the pore of the CRAC channel. The computed PMF indicates that the central hydrophobic region provides the major hindrance for ion diffusion along the permeation pathway, thereby illustrating the non-conducting nature of the crystal structure conformation. Strikingly, further PMF calculations demonstrate that the mutation V174A decreases the free energy barrier for conduction, rendering the channel effectively open. This seemingly dramatic effect of mutating a nonpolar residue for a smaller nonpolar residue in the pore hydrophobic region suggests an important role for the latter in conduction. We show that even without significant channel gating motions, a subtle change in the number of pore-waters is sufficient to reshape the local electrostatic field and modulate the energetics of conduction; a result that rationalizes recent experimental findings. In the second part of our work, we further study the flux of monovalent ions through the V174A mutant channel. The presence of a hyperpolarized potential facilitates the passage of ions, so the "anion-assisted permeation" was observed in our MD simulations: Na+ can easily pass through the central pore with the help of Cl–, with the major barrier height of ~5 kcal/mol, in the presence of the external field. The functional role of anions we have identified provides a rationale for the presence of the basic region in the cation channel. Our computations thus illustrate how the intrinsic properties of membrane protein design can contribute to channel gating. In summary, both pore waters and counterions, the two basic elements in biological systems, play functional role in regulating the conductance of CRAC channels.

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