Integrated Computational and Experimental Studies on the Structure and Function of Ion Channels

Speaker: Professor Huan-Xiang Zhou

**Departments of Chemistry and Physics,
University of Illinois at Chicago**

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＜場所＞ 理学部 １号館2階　２０１号室

I will start with an overview of my research program, which includes studies on protein association, macromolecular crowding, and peptide self-assembly. The focus will then shift to our studies on ion channels. These membrane proteins, relative to water-soluble proteins, have less intrinsic stability and are more prone to influences of the solubilizing environments. Indeed, our recent assessment of helical membrane protein structures in the Protein Data Bank identified many cases of potential distortions in transmembrane domains, attributable to sample preparations used for X-ray crystallography and solution NMR spectroscopy [1]. To achieve native-like structures, we use solid-state NMR data for refinement through restrained molecular dynamics simulations in native-like environments, i.e., in lipid bilayers. For the Influenza M2 protein (an acid-activated proton-selective channel), our study further targeted its functional center, i.e., a histidine tetrad within the channel pore that acts as both the pH sensor and ion selectivity filter. Based on solid-state NMR data and quantum chemistry calculations, we developed a mechanism for acid activation and proton conductance [2]. We have also remodeled transmembrane domains from crystal structures, both for correcting distortions [3] and for generating structural models in different functional states [4]. Lastly we have used molecular dynamics simulations and structural modeling to develop mechanisms for ionotropic glutamate receptors on channel gating, partial agonism, and disease-associated mutations, and are integrating these results into electrophysiological studies [5, 6].

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