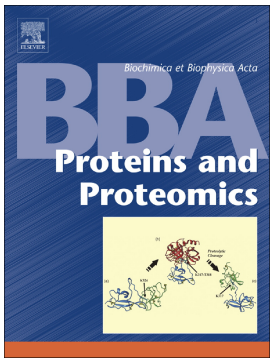

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Computational Membrane Biophysics: From Ion Channels Interactions with Drugs to Cellular Function

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Abstract: The rapid development of experimental and computational techniques has changed fundamentally our understanding of cellular-membrane transport. The advent of powerful computers and refined force-fields for proteins, ions, and lipids has expanded the applicability of Molecular Dynamics (MD) simulations. A myriad of cellular responses is modulated through the binding of endogenous and exogenous ligands (e.g. neurotransmitters and drugs, respectively) to ion channels. Deciphering the thermodynamics and kinetics of the ligand binding processes to these membrane proteins is at the heart of modern drug development. The ever-increasing computational power has already provided insightful data on the thermodynamics and kinetics of drug-target interactions, free energies of solvation, and partitioning into lipid bilayers for drugs. This review aims to provide a brief summary about modeling approaches to map out crucial binding pathways with intermediate conformations and free-energy surfaces for drug-ion channel binding mechanisms that are responsible for multiple effects on cellular functions. We will discuss post-processing analysis of simulation-generated data, which are then transformed to kinetic models to better understand the molecular underpinning of the experimental observables under the influence of drugs or mutations in ion channels. This review highlights crucial mathematical frameworks and perspectives on bridging different well-established computational techniques to connect the dynamics and timescales from all-atom MD and free energy simulations of ion channels to the physiology of action potentials in cellular models.

Keywords: Integral Membrane Proteins, Molecular Dynamics Simulations, Protein-Ligand Interactions, Markov State Models, Kinetic Cell Models

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