Exploring Anti-cancer Drugs Membrane Permeation: A Molecular Dynamics Study Using Umbrella Sampling

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Abstract

This study investigates the permeation of various anti-cancer drugs through lipid bilayers using molecular dynamics (MD) simulations enhanced by umbrella sampling techniques. The focus is on understanding how different lipid compositions affect the membrane interaction and transport properties of these therapeutics, which is crucial for optimizing drug delivery systems. In our approach, we systematically analyse multiple anti-cancer agents, including both hydrophilic and hydrophobic compounds, to elucidate their permeation mechanisms across lipid membranes with varying compositions, such as phosphatidylcholine, sphingomyelin, and cholesterol. The umbrella sampling method is employed to calculate the potential of mean force (PMF) associated with drug insertion into the lipid bilayer, providing insights into the free energy landscape governing drug-membrane interactions. By defining a reaction coordinate based on the distance between the drug molecule and the center of mass of the lipid bilayer, we create multiple overlapping windows to enhance sampling efficiency. This allows us to capture critical conformational changes and energy barriers during the permeation process. Our findings reveal that lipid composition significantly influences drug permeability, with certain lipid environments facilitating or hindering drug translocation, and our simulations revealed distinct variations in the free energy landscape based on the physicochemical properties of the drugs, including lipophilicity and molecular size. Notably, smaller and more hydrophobic drugs exhibited lower energy barriers, facilitating their permeation compared to larger, more polar compounds. The results underscore the importance of employing umbrella sampling in molecular dynamics studies to accurately characterize the complex interactions between anti-cancer drugs and lipid membranes. This research contributes to a deeper understanding of drug delivery mechanisms and may inform the design of more effective anti-cancer therapies by optimizing their membrane permeation properties.

Keywords: Molecular Dynamics, Lipid Bilayers, Anti-cancer Drugs, Umbrella Sampling, Permeation, Drug Delivery