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Sidekick for membrane simulations: Automated ensemble molecular dynamics simulations of transmembrane helices (Article)

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Abstract

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The interactions of transmembrane (TM) α-helices with the phospholipid membrane and with one another are central to understanding the structure and stability of integral membrane proteins. These interactions may be analyzed via coarse grained molecular dynamics (CGMD) simulations. To obtain statistically meaningful analysis of TM helix interactions, large (N ca. 100) ensembles of CGMD simulations are needed. To facilitate the running and analysis of such ensembles of simulations, we have developed Sidekick, an automated pipeline software for performing high throughput CGMD simulations of α-helical peptides in lipid bilayer membranes. Through an end-to-end approach, which takes as input a helix sequence and outputs analytical metrics derived from CGMD simulations, we are able to predict the orientation and likelihood of insertion into a lipid bilayer of a given helix of a family of helix sequences. We illustrate this software via analyses of insertion into a membrane of short hydrophobic TM helices containing a single cationic arginine residue positioned at different positions along the length of the helix. From analyses of these ensembles of simulations, we estimate apparent energy barriers to insertion which are comparable to experimentally determined values. In a second application, we use CGMD simulations to examine the self-assembly of dimers of TM helices from the ErbB1 receptor tyrosine kinase and analyze the numbers of simulation repeats necessary to obtain convergence of simple descriptors of the mode of packing of the two helices within a dimer. Our approach offers a proof-of-principle platform for the further employment of automation in large ensemble CGMD simulations of membrane proteins. © 2014 American Chemical Society.

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