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Simulation Methods for Prediction of Membrane Protein Structure

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IMPs are important to cells in functions such as transport, energy transduction and signalling. Three dimensional molecular structures of such proteins at atomic level are needed to understand such processes. Prediction of such structures (and functions) is necessary especially because there are only a small number of membrane protein structures determined in atomic resolution. The existence of the lipid bilayer provides powerful constraints on the methods employed to predict the structure; two dimensional nature of the lipid bilayer provides a constraint on the arrangement of the membrane spanning segments of IMPs: The aim of this study is to develop a systematic method to predict the IMP structure. The prediction method consists of three parts; 1) generation of initial candidate models for subsequent SA/MD simulation; 2) SA/MD simulation using the initial model structures; 3) verification of the predicted structures. In the first stage, the need for a fast algorithm for initial bundle generation is most pressing for those channel and transport proteins, eg, CFTR, which do not appear to possess N-fold rotational symmetry about a pore axis. Each helix is treated as a rigid body represented by a direction vector and the coordinates of its center of mass. Helix packing is optimized according to a simple semi-empirical potential. A Monte Carlo simulated annealing protocol is employed to optimize the helix bundle system, ie, to find low energy structures. Our results suggest that transmembrane helix bundles resembling experimentally observed structures may be predicted by simulations using simple potentials.