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Predicting the Quaternary Structures of Homo-Oligomeric Transmembrane Proteins (HoTPs)

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Abstract

Transmembrane proteins play important roles in the mechanism of diseases such that >50% of small molecule drugs target transmembrane proteins. In order to study the functions of these proteins, we require the 3D structures of these proteins at the atomic level. Unfortunately, it is difficult to experimentally solve the 3D structure of transmembrane proteins using X-ray crystallography or with Nuclear Magnetic Resonance. However, with homology modeling, we can predict the 3D structure of a protein with high confidence if it has high protein sequence identity (>30%) with a protein that has been previously solved. But predicting the protein's quaternary structure remains a challenging problem.

Many of the target proteins are homo-oligomeric transmembrane proteins (HoTPs) and ~97% of them are cyclic (C_n) symmetric. Here, we exploit this observation and rigid-body molecular docking method to build a docking protocol called DR-SIP for predicting HoTPs. The protocol is able to predict HoTPs without any prior knowledge of its size (dimer, trimer and etc.).

DR-SIP is able to recover 52.6% and 76.3% of HoTPs within the top-20 poses when given or not-given the complexes' native size, respectively. Predictions can be further improved by making use of experimentally derived distance data such as those from single-molecule FRET (smFRET).