

Development of a Structure Prediction Method for G-Protein Coupled Receptors

Thesis by

Spencer E. Hall

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Abstract

G-Protein Coupled Receptors (GPCRs) form a major target class of membrane proteins for therapeutic drug design, and the challenge is to design subtype specific drugs. Hence the knowledge of three-dimensional structure is critical to drug design for GPCRs. Since GPCRs are membrane bound proteins, there is only one crystal structure for a GPCR, namely bovine rhodopsin. The prediction of structure and function of G-protein-coupled receptors will allow for designing drugs with minimal side effects.

The focus of my thesis is the development of computational methods for prediction of structure of GPCRs and application of these methods (MembStruk) for a class of important drug targets such as chemokine receptors. MembStruk method is a hierarchical method ranging from coarse grain optimization of the trans-membrane helices to fine grain optimization of the structure in explicit lipid bilayer. The first two chapters of the thesis details the computational steps involved in MembStruk and its application to validating the method for bovine rhodopsin. The first chapter presents the method development in the most current version of the MembStruk method, version 4.30, and its application to bovine rhodopsin. The final predicted structure for bovine rhodopsin deviates from the crystal structure trans-membrane main chain atoms by 2.66 Å coordinate root mean square deviation (CRMSD), and the residues in the binding site of 11cis-retinal is only 1.37 Å CRMSD from the crystal structure for the main chain atoms. The second chapter of this thesis details the computational methods for optimization of the rotation and translation of the trans-membrane regions. These methods of rotation and translation of transmembrane helices has been further extended to the comparison of structures of two membrane proteins, and applied to the comparison

of crystal structures of bovine rhodopsin and bacteriorhodopsin. The third chapter details the graphical user interface that has been developed to automate the various steps of the MembStruk method.

Olfactory receptors are GPCRs and the molecular analysis for the recognition of odorants is very important in understanding the mechanism of olfaction. In a blind study prior to experiments, in collaboration with Dr. Bozza of Rockefeller University, I applied the MembStruk method to understanding the binding of odorants to rat and mouse olfactory receptor I7. Chapter 4 describes the application of the MembStruk method to rat and mouse I7 olfactory receptor and the binding of 65 odorants to this receptor. The last chapter describes the use of MembStruk method in predicting the structure and function of important drug targets, namely chemokine receptors CCR5 and CXCR4.

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