Interaction fingerprints patterns. Binding mode analysis of mGlu2 receptor model based on docking studies

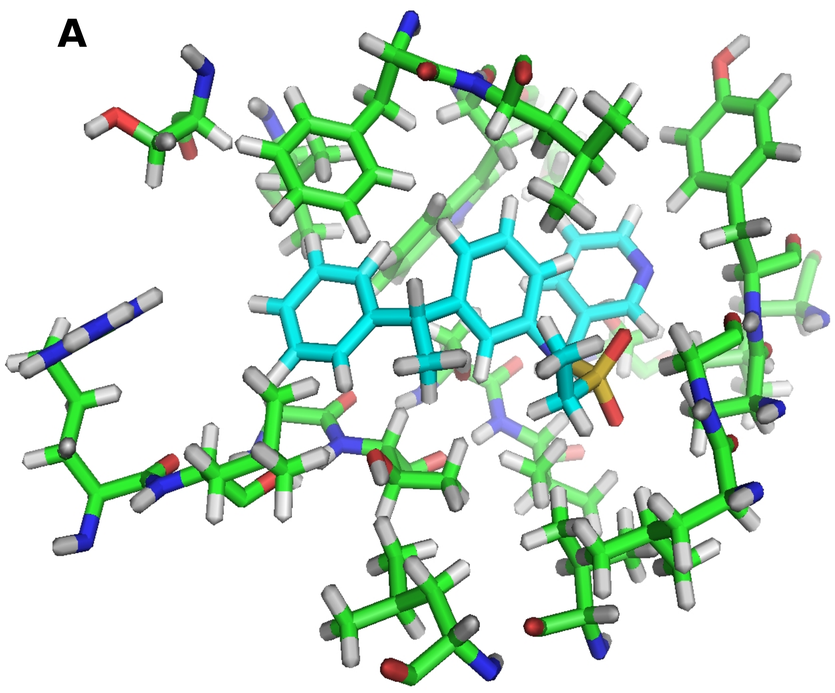
Stefan Mordalski[1] , **Tomasz Kościółek**[1] , **Mateusz Nowak**[1] , **Aina Westrheim Ravna**[2] , **Piotr Brański**[1] , **Ingebrigt Sylte**[2] , **Andrzej J. Bojarski**[1]

(1) Institute of Pharmacology,Polish Academy of Sciences, Krakow, Poland; stefanm@if-pan.krakow.pl
(2) Medicinal Pharmacology and Toxicology, Department of Medicinal Biology, Faculty of Health Science, University of Tromsø, N-9037 Tromsø, Norway

Introduction

One of the most troublesome stages of Computer Aided Drug Design (CADD) process is analyzing huge amount of data provided by docking studies. Simple scoring functions alone can provide only shallow information about ligand-receptor interactions, since they do not distinguish neither residues nor single atoms. Very often a visual inspection is the only way to determine binding mode. In this study we would like to introduce an implementation of interaction profiles[1] based on Structural Interaction Fingerprints (SIFt)[2] to analyze known ligands docking poses within mGluR2 model. The use of interaction patterns allows precise and rapid binding site description.

The mGluR family consists of eight proteins divided into three groups corresponding to sequence similarities, pharmacology and physiological role. These groups are: I (mGluR1, -5), II (mGluR2, -3) and III (mGluR4, -6, -7, -8). Group II lies in field of our interest due to its potential as therapeutic target for antidepressant and anxiolytic drugs. Research was performed on population of 100 mGluR2 models created on Rhodopsin crystal structure template. Building that many virtual receptors provided us with semi conformational search on residues assembling incriminated receptor. Library of 179 known allosteric modulators of group II mGluR was used for docking studies and thus forging the binding mode.



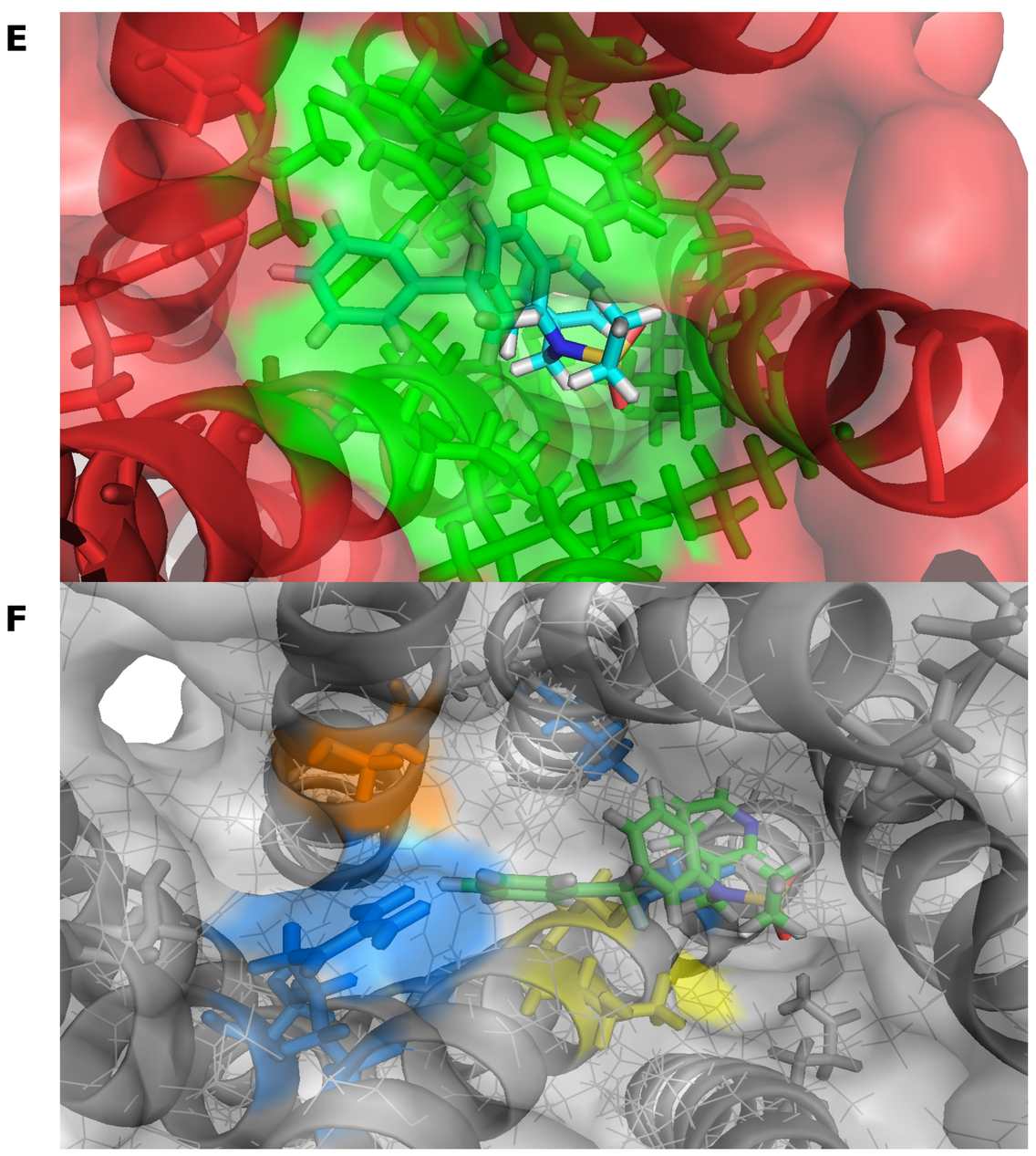
Workflow presenting implementation of SIFts to mGlu2 receptor: processed ligand–receptor complexes returned by Glide (**A**). Receptor structures are indexed with red-black hash table (**B**). Ligand-receptor contacts are classified by interaction type (**C**), and common interactions are evaluated (**D**).

A visualisation of residues most frequently contacting with docked compounds (any contacts on figure (**E**), aromatic interactions (blue), hydrogen bond acceptors (orange) and donors (yellow) on figure (**F**)).

Fingerprint preparation

SIFt is a bit string representing interactions between ligand and receptor. It can be divided into chunks expressing contacts for individual amino acids. In this research nine bits were used to describe those associations: **any contact, backbone, side chain, polar, aromatic, hydrophobic interaction and hydrogen bond donor/acceptor**. Basic algorithm is to find amino acids around bound ligand and from distance and residue types determine class of interaction. This approach was successfully applied in "interaction_fingerprints" module of Schrodinger Suite[3] . In our approach Schrodinger python libraries are used to handle 3D structures of ligand–receptor complexes and to determine hydrogen bonds occurrence, the algorithm itself was tweaked to enhance computations speed and to simplify batch SIFt generation and analysis.

To reduce computation time each atom of receptor structure was indexed using red–black tree hash table. Distance from (0,0,0) was a search key. Analogous orbit calculated for complexed ligand atoms were then queried and for each fragment returned as a result, atom–atom distance was measured to reject false positives. For every approved amino acid fragment, interaction type was determined and appropriate fingerprint bits were switched on. So, generated SIFts were then analyzed to determine amino acids contributing to ligand binding.



Results and conclusions

Applying SIFts to docking poses of known ligands allowed us to select residues forming binding pocket. Also, due to broad spectrum of interaction types used specific contacts can be pointed out in order to support pharmacophore features placement within binding site.

Structural Interaction Fingerprints introduced in this research are simple, fast and clear way to determine binding mode based on extensive ligand docking. It can be used to filter out unwanted poses and so aid visual inspection of docking results.

Literature
(1) Chuaqui C, Deng Z, Singh J *„Interaction Profiles of Protein Kinase-Inhibitor Complexes and Their Application to Virtual Screening"*, J. Med. Chem. 2005, 48, 121-133
(2) Deng Z, Chuaqui C, Singh J *„Structural Interaction Fingerprint (SIFt): A Novel Method for Analyzing Three-Dimensional Protein-Ligand Binding Interactions",* J. Med. Chem. 2004, 47, 337 -344
(3) http://www.icm.edu.pl/kdm/Schroedinger

Acknowledgments
The study was partly supported by a grant PNRF-103-AI-1/07 from Norway through the Norwegian Financial Mechanism, and by the Polish Ministry of Science and Higher Education (MNiSW), Grant No. N N405 184635.