WP1.3. Protein-protein interactions targeted by computational fragment-based design (Hobza)

Research aims

- To assess the conformational flexibility of the insulin receptor-insulin complex based on the crystallographic structures and MD-based flexible fitting.
- To explore dynamics of CTSK and GlpG in complex with known inhibitors.
- To evaluate at the SQM level the binding energy contributions of insulin residues and identify hotspots for peptidomimetic compound design.
- To include novel PPI motifs based on the studied systems into a new database of noncovalent interactions and calculate reference energies.
- To use these energies as benchmarks for the validation and correction of the SQM and MM methods.
- Running virtual screening of fragment libraries for binding to hotspots (followed by experimental verification).
- Iterative designing of new protein ligands by joining or growing fragment-based approach (followed by experimental verification)

Research plan and methodology

Our challenging goal is to explore pharmaceutically relevant PPIs and their individual components, such as insulin receptor-insulin, CTSK-inhibitors and intramembrane protease GlpG-peptide complexes using computational methods. We will investigate the dynamics of the biomolecular structures and the energy contributions to the binding. This knowledge will enable us to search virtual fragment libraries in the quest for the seeds of new potent ligands with a pharmaceutical potential.

We can only address these questions with a proper computational arsenal in hands. We will thus need to build new databases of noncovalent motifs present in PPIs. These will have to be calculated at the precise CCSD(T)/CBS level to serve as benchmarks for parametrization of SQM and MM approaches. Multiple structures around equilibrium geometries, both in terms of distance and angle, will be treated in order to mimic the dynamics of the interaction motifs. The project will extensively exploit the capacities of the computer cluster for molecular modelling and the results will serve also for collaborating experimental groups.

In the first step, we need to understand the dynamical nature of the studied PPIs. For this, we will use our extended expertise on classical molecular dynamics (MD)[1-4] in the case of Site 1 IR-insulin crystal structure our experience with MD-based flexible fitting.[5] The ensembles of binding conformations will be monitored for interaction motifs. We will use them to build a database which we will calculate using highly accurate QM methods including CCSD(T)/CBS.[6] These data will serve for validation and further development of more approximate methods applicable to larger systems, such as the semiempirical QM methods (SQM). The solvation phenomena will be treated using the implicit COSMO model (the powerful SQM/COSMO approach[7]) and also incorporating the thermodynamics of explicit waters at the protein-protein binding interface.[8]

With the computational methodology in hand, we will dock nonpeptidic peptidomimetic fragments to the multiple conformers of the binding interfaces of the insulin receptor (Site 1 was crystallographically described only), CTSK and GlpG (in the latter case, we will search only in the primed side because the unprimed side of the substrates is known crystallographically[3]). Using our accurate and efficient SQM/COSMO scoring function,[7,8] we will select the binding hotspots and follow the fragment-based drug design strategy using either growing or joining (in case of multiple hotspots) strategy.

The project will be realized in a close collaboration with Jiráček, Majer, Mareš, Vondrášek and Stříšovský groups. The synthetic/biological and bioinformatics expertise in these groups will be instrumental in delivering the designed compounds and testing their interactions with the targets. In this step, the Jiráček (for IR-insulin) or Majer (for CTSK and GlpG) groups will synthesize the designed compounds and the biological tests will ensue. Through iterative optimization, compounds with pharmaceutical relevance should be obtained.

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Research schedule

2017-2018

- Running molecular dynamics (MD) of insulin receptor, CTSK and GlpG in complex with known ligands.
- Calculate at the SQM level the binding energy contributions, identify hotspots for the design.
- Identifying noncovalent interaction motifs and add the missing ones in the databases.

2019-2020

- Developing a database of important interaction motifs present at the protein-protein interfaces.
- Validation of SQM and MM methods.
- Deriving corrections for non-covalent interactions in SQM and MM methods.

2019-2022

- Running virtual screening of fragment libraries for binding to hotspots and verify hits experimentally.
- Design and prediction of new protein ligands for insulin receptor, CTSK and GlpG by joining or growing fragment-based approach.
- Iterative optimization of the design of new protein ligands after validation by syntheses and testing of the compounds.

Publications and patents

Publications (Jimp)

	Jimp
2017	1
2018	5
2019	8
2020	8
2021	9
2022	9
Total	40

J. Chem. Theory Comput.
J. Comput. Chem.
J. Phys Chem. B
J. Biol. Chem.
J. Mol. Biol.
J. Virol.

Cooperation with foreign institutions

- Dr. Carsten Baldauf from Fritz-Haber-Institut der Max-Planck-Gesellschaft in Berlin,

- Prof. S. Grimme, University of Munster, Germany,
- Prof. Gregory J. O. Beran, University of California, U.S.A., Prof. M. Becucci, University of Firenze, Italy
- Prof. Klaus Mueller-Dethlefs, University of Manchester, U.K.