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DOCTORAL THESIS

Implications of loop reconstruction model on protein functionality

Analiza skutków wyboru modelu zrekonstruowanej pętli na funkcjonalność białka

Supervisor: dr hab. Artur Góra

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SUMMARY OF DOCTORAL THESIS

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Results presented in this thesis are related to homology modelling of protein structures. The protein secondary structure consists of organised and less flexible α-helices and β-sheets, and also less organised and flexible loops. Loops are linkers between the organised elements, they participate in protein folding and stabilize its structure. Most of all, loops can be involved in substrate and products transportation to and from the active site, interactions with small molecules, DNA, RNA or other proteins. Based on their flexibility and their ability to change their conformation, loops can be divided into two groups: static and flexible. Static loops stabilize the protein structure, while flexible loops, due to conformational changes, interact with substrates and/or products or participate in signal transduction.

The aim of the work was to achieve two goals: i) to provide a loop model selection method based on their geometrical parameters which improves the classification of a particular loop as a static or flexible without a need to run multiple molecular dynamics simulations, and ii) to provide a method of protein interior functionality analysis.

The loop model selection method was used in other projects ran by Tunneling Group, to which the student belongs, such as research focused on rare diseases conducted in collaboration with the National Research Institute of Oncology in Gliwice.

The protein functionality analysis method is based on tracking of small molecules (such as water molecules, cosolvents, ligands etc.) within the protein interior during the course of molecular dynamics simulations and was implemented into AQUA-DUCT software. The first paper on that software was published in 2017, and two years later new functionalities were added into AQUA-DUCT, such as identification of potentially attractive regions (so-called hot-spots) for analysed molecules. Due to their chemical properties. This functionality was used during inhibitors design for the SARS-CoV-2 main protease. Water tracking approach was used during analysis of several other proteins, such as:

- human and porcine D-amino acid oxidase (DAAO) and *Pyrococcus furiosus* phosphoglucose isomerase, ran in collaboration with a Netherlands research group; in both studies AQUA-DUCT was used to explain the reasons of changes in mutant variants activity;
- potato (*Solanum tuberosum*) epoxide hydrolase, in which the hot-spots analysis was used to predict amino acids which could contribute to enzyme's activity and/or selectivity changes, and
- SARS-CoV-2 main protease (Mpro), which was ran in collaboration with research groups from abroad. First results were published in April and the work on inhibitors design is still ongoing.