Posudek diplomové práce

Matematicko-fyzikální fakulta Univerzity Karlovy

Thesis author	Jakub Kopko
Thesis title	Comparative Markov state analysis of APOE protein dynamics by neural networks
Submitted	2023
Program	Computer Science **Specialization** Artificial Intelligence

Review author	Jiří Sedlář **Role** advisor
Position	CIIRC, Czech Technical University in Prague

Review text:

The objective of this master's thesis was to investigate the molecular dynamics of apolipoprotein E (APOE) by machine learning. The APOE protein is closely associated with the development of Alzheimer's disease and insights into its dynamics are important for understanding the molecular basis of the disease and estimating the effect of potential drug candidates. The project was motivated by ongoing research on APOE and Alzheimer's disease drug treatment and done in collaboration with the Loschmidt Laboratories at Masaryk University in Brno, who kindly provided the molecular dynamics data and advice on the specifics of the APOE protein.

The thesis analyzes the APOE dynamics using neural networks based on the Variational Approach for Markov Processes (VAMP), namely the Comparative Markov State Analysis (CoVAMPnet). While this approach has proven useful in analyzing the dynamics of small proteins, it has not been used for proteins of the size of APOE. The thesis compares the dynamics of two APOE variants (APOE3 and APOE4) within the 4-helix bundle domain of the APOE monomer and evaluates the effect of a small molecule drug candidate on the dynamics of each variant. Based on this analysis, the thesis identifies key structural differences in the main subdomains of the 4-helix bundle across the four molecular systems (free APOE3, free APOE4, APOE3 with the small molecule, and APOE4 with the small molecule). The results not only confirm findings obtained with more basic methods in previous studies but also provide interesting new observations.

The student was motivated, quickly learned about the research area from relevant papers and reports, acquired an understanding of the mathematical background, and comprehensively summarized the mathematical theory. This was not easy considering the interdisciplinary nature of the project. He reviewed state-of-the-art VAMP-based methods for protein dynamics analysis and adapted the CoVAMPnet code to process the molecular dynamics simulations of APOE. Based on these preliminary results and relevant studies on APOE, he identified the 4-helix bundle as

a key domain for the analysis of APOE dynamics. He processed the 4-helix bundle domain of four molecular systems (free APOE3, free APOE4, APOE3 with the small molecule, and APOE4 with the small molecule) using CoVAMPnet and performed a comparative analysis of the resulting Markov state models. He summarized the observations and compared them with the results of existing studies. He also discussed possible limitations of both the available molecular dynamics data and the CoVAMPnet method. The thesis is well structured and clearly describes the performed work and obtained results. The figures in the thesis are illustrative, well-annotated, and adhere to high scientific standards.

Overall, the student fulfilled the objectives of the thesis topic and his work has contributed to the advancement of this interdisciplinary research project. He will present his results at the 4th Joint Workshop of CIIRC CTU and Masaryk University – ICRC on 21-22 September 2023 in Brno. We are planning to submit the results of the thesis to the 3D-BioInfo — ICSB 3D-SIG — ELIXIR Czech Republic Community Meeting in Structural Bioinformatics on 15-17 November 2023 in Prague.

I recommend the thesis for defense.

I suggest to not consider the thesis for the annual award.

28.8.2023

Signature: