1. PHD PROJECT DESCRIPTION

Project title: **Optically Regulated Proteins – Computer Modeling (ORP)**

Project goals

- To understand structural effects related to mechanical stability in a virus protein-receptor protein interface (COVID related)
- To model dynamics of optically modulated Pr/Prf protein from bacterial phytochrome from *Deinococcus radiodurans*
- To model dynamics of ADAM10 metalloproteinase coupled to photo-activated drug
- To propose light controlled pre- and postsynaptic protein connection related to a memory function

1.1. Outline

Protein-protein interactions govern a metabolism and health of all living systems. Computational modelling of these important phenomena is very challenging [1-6]. The problem is related to high complexity of the interfaces and high specificity used in the metabolism related signalling. Often quite subtle physical effects, such as amino acids point mutations lead, to serious physiological effects and shift a border between health and disease [2]. There are numerous drugs that affect protein-protein interactions, for example, reducing blood pressure or the progress of cancerous tumours. The electromagnetic radiation (EM) from optical range may affect a protein structure. Photoactive proteins are ubiquitous in nature and are critical, for example, for the primary vision process, phototropism, growth of plants. Artificial light-sensitive ion channels in nervous systems are basic elements of optogenetics – a method gaining nowadays high popularity in neurobiology. Photoexcitation in these proteins leads to a conformational transition. Optically modulated part of the protein changes structure upon irradiation and may change its function. How is goes at atomistic resolution level is often a mystery.

In this PhD project the main goal will be to understand in all atomistic details dynamics of proteins in which the light regulates functions. We hypothesize that modern computer modelling methods, when properly tuned, are effective tools to gain new insights into protein biophysics. We expect that the project will facilitate biotechnological construction new proteins or photoactive compounds with rationally designed functions.

The computational studies of protein-protein interfaces are numerous, but the problem of checking how these interfaces are modulate by the EM is relatively new in biophysics and knowledge in this area is very limited [3]. In the project we will monitor 100 ns or longer dynamics of a series of protein-protein interfaces with increasing complexity. At the first stage an interface between spike S protein from SARS_Cov_2 virus and human ACE2 receptor protein will be studied. This will be a part of ongoing ANTICO project funded

by IDUB (WN is PI). Then we will model cross-sections of free energy hypersurface related to light activated bacterial phytochrome from *Deinococcus radiodurans* (drBphP). We will try go beyond ongoing simulations of D ring rotations in BV chromophore (collaboration with prof. K. Kuczera, Univ. of Kansas, USA). In human brain there are numerous sheddases and a metallo-protein called ADAM10 cuts–off extracellular parts of some proteins and is probably involved in tumor (glioma) progression [7]. We will model dynamics of ADAM10, but in the presence of light-activated inhibitors. Activation will happen after photo-cleavage of a covalent bond by blue light. Finally, MD modeling methods, tested on these prototype systems, will be applied to an exploratory study of protein-protein contacts present in neuronal synapses (#MEMOBIT team). We plan to select a pair of proteins that participate in formation of long term memory, and for the first time will check how adding an artificial photoactive part to such a protein can turn such a connection into biological, light-controlled storage device. After finishing this PhD project we expect to add a new tool and expertise to explorations of proteins, going beyond the classical ground electronic state MD [2,3].

1.2. Work plan

- Mastering molecular dynamics. Literature studies on light sensitive protein interfaces.
- Extensive studies of mechanical stability of spike S-ACE2 complex
- MD and metadynamics studies of (drBphP) complex. Excited states included.
- Search for light activated ADAM10 selective inhibitor. Literature and computational studies.
- Testing new approaches on a pre- and post-synaptic neuronal proteins pair. Search for optical control of biological memory.

1.3. Literature

1. Nowak, W., Handbook of Computational Chemistry, Springer, 2017
2. Rydzewski, J. & Nowak, W. J. Chem. Phys. (2018) 148 (11), 115101
3. Rydzewski, J., & Nowak, W., Handbook of Computational Chemistry, Springer, 2016
4. Rydzewski, J., Jakubowski, R., Nowak, W., & Grubmüller, H. (2018) J. Chem. Theory Comput., 14, 2843
5. Rydzewski, J., & Nowak, W. (2017a) Sci. Rep., 7, 7736
6. Rydzewski, J., & Nowak, W. (2017b) Phys. Life Rev. 22, 58
7. Venkatesh, H. S., et al., (2017) Nature 549 (7673), 533–537.

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1.4. Required initial knowledge and skills of the PhD candidate

- High motivation
- Eager to analyze big data
- Some programming skills, Linux
- Curiosity
- Very good knowledge on proteins
- Understanding of physics, chemistry will be a plus

1.5. Expected development of the PhD candidate's knowledge and skills

- Better understanding of advanced modelling methods
- Practical knowledge of protein interfaces
- Advanced programming skills (Unix, Python, C++)
- "Fluency" in work in international scientific settings