PHD PROJECT DESCRIPTION
(4000 characters max., including the aims and work plan to be published online)

Project title: Physical Basis of Memory – Computer Modeling of Brain Proteins.

1.1. Project goals

The main goal of this project is to understand the role of dynamics of proteins present at neuronal synapses and involved in memory processes. We plan to develop an efficient computational pipeline to study dynamics and mechanical properties of selected proteins involved in brain functioning and storing information.

1.2. Outline

The brain is the basis of natural intelligence. It contains billions of interconnected neurons. Success of Artificial Neural Networks is based on imitation of this biological organ. Its functioning is still poorly understood and poses numerous great scientific questions. The brain is the most critical structure for learning, so short and long term memory is indispensable for that. During learning new connections between neurons are formed, thus new synapses arise. To keep information for a long time complex proteins are involved. The main goal of this project is to understand the role of dynamics of proteins present at neuronal synapses and involved in memory processes. We plan to develop an efficient computational pipeline to study dynamics and mechanical properties of selected proteins involved in brain functioning and storing information.

Following experimental data presented in the literature we plan to computationally study several major protein players in this process, such as: ROBO1, AMPAR, secretogranin-2, CaMKII and /or metalloproteinases (ADAM10). We will apply modern computational biophysics/bioinformatics methods and software tools. At the same time we will delineate what minimal computational protocols are required to have an effective tool to study possible abnormalities and pathological processes induced by point mutations in systems related to storing information via brain processes.
In our theoretical molecular biophysics group (NCU Inst of Physics) we have extensive experience in using molecular dynamics methods for protein modeling [1-6]. Recently a virtual atomic force microscope set of programs has been developed to study mechanical anisotropy of proteins [7]. That system together with classical (NAMD) and non-classical (metadynamics, GROMACS) MD simulations tools will be used for this PhD project. Mechanical properties of proteins are adapted to their functions, how mechanical stress modifies protein's architecture is a very basic question. This problem can be studied computationally using Steered Molecular Dynamics (SMD) simulations. We plan to get a detailed picture of mechanical anisotropy of ROBO1 – a protein guiding neurons during brain development. It is possible to use SMD to enforce rare conformational changes in proteins. We will adopt this method to mimic large pore formation in P2X7 purinergic receptors; activation of this protein is currently considered as a possible strategy for glioma (brain cancer) treatment. Very recently a gene coding for secretogranin-2 protein has been identified as playing a major role in the learning process and establishing new spine-spine connections (rearranges of F-actin in neurons). As a part of this

project a novel computational model of secretogranin-2 will be created and its dynamics will be studied. A central player in memory formation, namely calcium–calmodulin-dependent protein kinase II will be modelled. Several papers described its properties but based on protein fragments. We will try to prepare a complete model of this system, which might be used to study the phosphorylation process in other steps of storing information at the molecular level. Finally we will try to construct some models of a receptor AMPA, critical in certain psychiatric disorders and long term memory. Here collaboration with Cambridge University (UK) is expected The ultimate part of these efforts will be a collection of effective practices, leading to formation of a semiautomatic route (pipeline) for routine (a gray box) MD simulations of various memory-linked proteins.

1.3. Work plan

Y1
1.3.1 Literature search for molecules involved in long lasting memory formation
1.3.2. MD/modeling training – simulations of L-asparaginase/GO system.
1.3.3. Modeling of ROBO1 – SMD training- neuron guidance protein-nanomechanics.
Y2
1.3.4. Modeling of P2X7 purinergic receptor (closed and open form, SMD applications – exploratory study, link with glioma treatment).
Building of AMPA receptor models
Y3
1.3.5 Modeling dynamics of AMPA receptor models.
1.3.6. Modeling of dynamics and function of secretogranin-2 (Alphafold2 P13521 structure)
1.3.7. Building of calcium–calmodulin-dependent protein kinase II (CaMKII) protein model.
Y4
1.3.9 Modeling of dynamics of CaMKII.
1.3.10 Summary of best modeling practices useful for memory-related proteins. Computational pipeline recommendation.
1.3.11 – Thesis writing

1.4. Literature (max. 7 listed as a suggestion for a PhD candidate preliminary study)

1. Nowak, Handbook of Computational Chemistry, 2016 (Computational methods for protein dynamics).
2. Walczewska-Szewc & Nowak, J. Phys. Chem. B, 2021 (Photo-switchable sulfonylureas & insulin release).
3. Mikulska et al., Chemical Physics Letters, 2012 (Nanomechanical unfolding of α-neurexin).
4. Mikulska-Ruminska et al., Scientific Reports, 2017 (Nanomechanics of neuronal protein contactin).
5. Sun et al., Nature Chemical Biology, 2021 (iPLA2β role in averting ferroptosis).
6. Zhang et al., Bioinformatics, 2021 (ProDy 2.0: protein dynamics modelling in Python).
7. Walczewska-Szewc et al., JCIM, 2025 (multiSMD toolset for Steered Molecular Dynamics).

1.5. Required initial knowledge and skills of the PhD candidate

- Interest and motivation in doing good science. Background in physics and/or computer science, some understanding of biochemistry, chemistry. Some Python programming skills, knowledge of Linux is a plus. Ready to work hard.

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

PhD related to molecular biophysics makes a good starting point for a job in academia or big pharma or a research start-up. You will gain good experience in independent computer modelling. You will improve programming skills and work with modern software. Research experience related to drug design and protein receptors. You will have very well developed computer skills, running large computational project experience. Fluency in PYTHON. Advanced understanding of physics, including quantum methods. Good familiarity with AL/ML based methods.