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DOCTORAL DISSERTATION ABSTRACT

Scientific discipline: Physics

Title of the doctoral dissertation: Computational Modeling of Structural Changes in Selected Optically Regulated Proteins and Ligands

Doctoral dissertation abstract:

Although electromagnetic radiation is a harmful factor that degrades most organic macromolecules, some proteins can profit from interaction with light. Furthermore, these proteins have essential functions in all living organisms. Direct interaction with light in these proteins is possible because they contain a small light-sensitive molecule called a chromophore. After absorbing a photon, this molecule changes its spatial conformation, triggering a series of structural changes in the protein and influencing its function and the course of metabolic processes in cells.

The dissertation explores the application of molecular modeling methods to examine the mechanisms underlying light-induced conformational changes in two photoactive systems and to investigate the potential for optical regulation of the receptor P2X7, which plays a crucial role in glioma development. In the first photoactive system – bacterial phytochrome – advanced molecular dynamics (MD) methods were used to overcome high-energy barriers and study conformational changes induced by biliverdin photoisomerization. Previously unknown metastable states were revealed, and two signal transduction pathways from the chromophore-binding pocket to the remote protein domains were identified. The second photoactive system – photoactive yellow protein (PYP), which contains the chromophore para-coumaric acid, was studied using a new machine learning technique called spectral map. Data from the MD simulation were used to train neural networks and to construct slow collective variables that describe conformational changes upon light absorption. In the purinergic P2X7 receptor, the binding affinities of light-sensitive ligands to the orthosteric pocket were studied using molecular docking. The results showed that the compounds fit the receptor pocket sufficiently well, demonstrating that using photoactive ligands to regulate chromophore-free proteins is a promising novel drug development approach.

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