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Protein Structural Dynamics Revealed by Time-Resolved X-ray Solution Scattering

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Abstract

Proteins fold in very specific three-dimensional structures within a few seconds. Highly complex and organized, their three-dimensional structure is closely related and often essential for their function. They perform a vast array of vital functions within organisms. Myoglobin, for example, stores dioxygen within muscles, while photoreceptors, such as phototropins or cryptochromes, respond to their light-environment to regulate growth, metabolism or the circadian clock. Protein aggregation, misfolding and unfolding have been associated with many pandemic pathologies. Therefore, a crucial need for biophysical techniques investigating protein structure and dynamics in real-time, has emerged over the past decades. Time-resolved X-ray scattering in solution has the advantage of being directly sensitive to structural changes happening on broad time scales from the atomic level to the general shape of a protein.

In this thesis, time resolved X-ray solution scattering has been applied together with molecular dynamics simulations to address various biochemical questions. These techniques were used to bring new insights in the folding process of small globular proteins at the atomic level. By following the conformational transitions of apomyoglobin unfolding, we showed that globular proteins fold in defined pathways starting with the hydrophobic collapse of non-conserved residues. Time-resolved X-ray scattering has also been applied to establish a comprehensive mechanism of signal transduction in the light-oxygen-voltage domain of two blue-light photoreceptors: Ytva and phototropin. The data showed that the mechanism of signal transduction is conserved in photosensory domains. On a greater length-scale, time-resolved solution scattering gave a detailed picture of the signal relay in cryptochromes. The results provided a structural link between the conformational changes in cryptochrome, and the interaction and regulation with its downstream partners.

This work demonstrated the potential and various applications of time-resolved X-ray solution scattering. This technique allows the investigation of protein structure and dynamics on different length-scales, with high-temporal resolution.

Keywords: Time-resolved X-ray solution scattering, MD simulations, protein structural dynamics, folding, blue-light photoreceptors.