Intrinsic Flexibility and Structural Stability of Proteins

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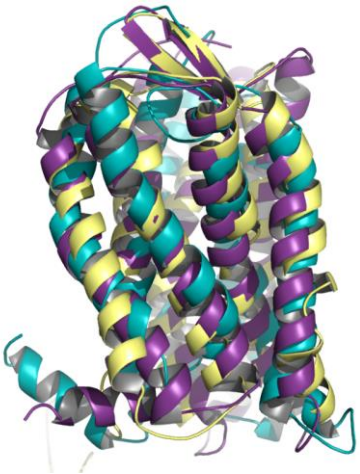
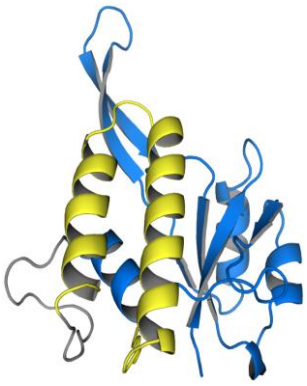
The properties of a protein are based on its fold and thus, based on the sequence of the amino acids. Molecular and structural biology have provided a wealth of information about proteins, however, the underlying dynamical processes are not yet fully understood. I will show you how I used MD (molecular dynamics) simulations to gain atomistic information on the dynamical behavior of biologically relevant proteins.



G-protein coupled receptors (GPCRs) interact with small molecules, peptides, or proteins and transmit a signal over the membrane via structural changes to activate intra-cellular pathways. GPCRs are characterized by a rather low sequence similarity and exhibit structural differences even for functionally closely related GPCRs. I propose a computational approach that relies on the generation of several independent models based on different template structures, which are subsequently refined by MD simulations. The conformational stability and the agreement with GPCR-typical structural features is then used to select a favorable model. This strategy was applied to predict the structure of the herpesviral chemokine receptor US28 by generating three independent models based on the known structures of the chemokine receptors CXCR1, CXCR4, and CCR5. Model refinement and evaluation suggested that the GPCR-typical structural features, such as a conserved water cluster or conserved non-covalent contacts, are present to a larger extent in the model based on CCR5 compared to the other models. A final model validation based on the recently published US28 crystal structure confirms that the CCR5-based model is the most accurate and exhibits 80.8 % correctly modeled residues within the transmembrane helices. [1]



The transcription factor RfaH from Escherichia coli consists of an N-terminal domain (NTD) and a C-terminal domain (yellow alpha-helices, CTD), which tightly interact in the autoinhibited conformation of RfaH. Upon activation, the CTD is released and undergoes a large-scale $\alpha \rightarrow \beta$ structural transition. Investigation of RfaH under different environmental conditions revealed that not only high temperatures, but also a decrease in ionic strength significantly enhances CTD dynamics. None of the conditions investigated caused CTD dissociation suggesting that this process needs to be triggered by the interaction with DNA or other proteins of the transcription machinery. [2]

[1] A. Kahler, H. Sticht, AIMS Biophysics, **2016**, *3*, 211–231.
[2] A. Kahler, A.H.C. Horn & H. Sticht, Curr Biotechnol, **2015**, *4*, 26–38.