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Allosteric modulation: The Hsp70 case study

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Allostery is a long-range macromolecular mechanism of internal regulation in which the binding of a ligand in an allosteric site induces distant conformational changes in a distant portion of the protein, modifying its activity. From the drug design viewpoint, this mechanism can be exploited to achieve therapeutic effects; since allosteric ligands are able to regulate target proteins reducing side effects. Computational tools are a valid support in this sense, since they allow the characterization of allosteric communications within proteins, which are essential to design modulator ligands. We will discuss *in silico* approaches to characterize allosteric modulations, describing the Heat Shock Proteins family Hsp70, which is involved in many cancers, neurodegenerative diseases and plays an important role in pathogens survival under stress conditions. We apply an all-atom MD approach, in order to elucidate the molecular determinants underlying the allosteric inter-domain communication from the NBD to the SBD and back. In detail, a comparative analysis of an allosteric (Hsp70-DnaK) and a non-allosteric structural homolog (Hsp110-Sse1) of the Hsp70 family is carried out, starting from different conformations and ligand-states. Besides, Hsp70 complexes with a different ligand combination bound to the two Hsp70 binding sites, the nucleotide-binding site and the substrate-binding site are simulated to analyze the allostery from the SBD to the NBD. Moreover, we performed a differential analysis of DnaK and human Hsp70 to identify hot spots in the bacterial protein that are not present in the human homolog with the aim of characterizing the key pharmacological features necessary to design selective inhibitors for DnaK.

Biography

Federica Chiappori has received Master's degree in Bioinformatics in 2005 from the University of Milano-Bicocca. She has received her PhD in Environmental Science and Public Health in 2010. Her research activities take place in the field of structural molecular modeling, particularly in the field of drug discovery and interaction analysis, employing docking and molecular dynamics for the study of protein-ligand and protein-protein binding. She is author of a dozen of peer-reviewed publications.

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