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A new protocol to investigate conformational population patterns in the enzymatic activity cycle of proteins using molecular dynamics and normal mode analysis

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Human immunodeficiency virus type-1 protease (HIV-1 PR) is an aspartic protease whose proteolytic activity is essential for cleaving precursor viral polyproteins into individual proteins implied in viral replication. Once HIV enters within a host cell, its RNA is transcribed into DNA through reverse transcriptase, integrated and amplified along with the replication of the host cell's DNA. *Gag* and *gag-pro-pol* genes are transcribed into messenger RNA, translated into *gag* and *gag-pro-pol* precursors proteins in the cytoplasm, and then assembled at the cell surface for budding and formation of the immature viral particles. In this work, we propose a computational protocol to generate and select HIV protease conformations relevant to its function using Normal Mode Analysis (NMA). We have considered structures of the apoenzyme, the protein with its substrate and product and the protein with a drug. This set of structures should reveal large amplitude motions that are critical to the protease activity cycle as: substrate acquisition; substrate cleavage and product release. The apoenzyme presents an increased flap conformational diversity compared to the various complexes, predominantly populated with open flap conformations, that can possibly be related to the substrates acquisition. The enzyme-substrate complexes show more structural diversity than enzyme-product complexes, suggesting a role of these conformational changes in catalytic activity. We present a promising protocol to identify the conformational diversity induced by different types of ligands and that can help the drug design process.

Biography

Luis Paulo B Scott is an Associate Professor in Federal University of UAFBC. He has his expertise in conformational changes and functional movements of macromolecules, specially proteins. Over the last four years, his research group has been financed to investigate molecules related to neurodegeneration and aggregate formation by means of normal mode analysis and molecular dynamics combined. The laboratory coordinated by him has become more and more specialized in the study of macromolecules structural dynamics (functional movements in collaboration with Dr. David Perahia from France.

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