Interactions of Intrinsically Disordered proteins: A Physics-based Approach

Funding Agency	Department of Biotechnology
Sanctioned Amount	Rs. 88 Lakhs
Project Duration	5 years
Project Status	Continuing since 2014

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Brief Description of the Project:

This project intends to focus on the structural and dynamical aspects of intrinsically disordered proteins (IDPs) highly relevant forunderstanding their diverse biological functions. The main thrust of my project would be the study of the structural basis and the mechanistic pathway of the interdependency between phosphorylation and acetylation of intrinsically disordered N- and C-terminals of p53 using molecular modelling and molecular dynamics simulations.

Keywords: Intrinsically Disordered Proteins, p53, post translational modification, acetylation, phosphorylation, molecular dynamics simulations, molecular modeling, force field

Methodologies/Approaches Adopted

The project needs high performance computing. 'Molecular modeling and molecular dynamics simulation' is the main tool of the project. I am using the specialized computational techniques to model the post translational modifications of the tumor suppressor protein p53; two terminal domains of which are intrinsically disordered. Also several mutations are adapted to compare the structural changes of the free protein in solution.

Project Highlights

Due to high abundance of IDPs in lethal diseases e.g. cancer, Alzheimer's, Parkinson etc., and their diverse biological role it is of immense importance to conduct research on interaction and regulation of IDPs for future drug designing and medicinal chemistry. Currently in India few experimental groups are focusing towards IDP research. Computer simulations can strongly complement the experiments and thus we could build our own collaborative research within the country.

The substantial challenge in detailed experimental characterization of IDPs presents a unique and exciting opportunity for molecular modeling to make critical contributions. In particular, atomistic simulations using physics-based molecular mechanical force fields provide information necessary for understanding disordered protein states and their crucial biological functions. There are two main outcomes of the project.

The insight of the interdependency of phosphorylation and acetylation of two disordered terminals of p53 would be revealed at the atomistic detail. This is very important for understanding the structure-function relation of the tumor suppressor p53.We would also be able to extend our knowledge to investigate the interaction of other IDPs.

Successful completion of the project would show that implicit solvent-basedmodeling, various techniques of MD simulations including coarse grain protein model, and necessary development of the parameters might be useful for providing meaningful information about structure, function and dynamics of IDPs.

Facilities Developed

Equipment: High Performance Computing Lab with Dell – Server with both GPU and CPU facility,

Software: CHARMM software, NAMD software

Plan of Future Project Proposal based on the Current Project

Intrinsically disordered C-terminal domain of p53 can adopt different structures upon binding to different proteins. The post transitional modifications of the C-terminal p53 might play a role upon these binding interactions. To study this interaction computer simulation is an essential tool. The result from my running project may helpful to propose my next project based on the study of binding interactions between these types of proteins.