PD Research Report for the 2016 year

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Research Theme: Applications of rigidity and algorithm protein function
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Dee understanding of protein function requires knowledge about its motions and dynamics, which is critical in medicine and drug design. Advancements in the rigidity theory have led to fast computational predictions of flexibility/rigidity and protein motions. I have made a number of key contributions to this field by developing various algorithms and methods for studying a functionally critical protein motions. The methods provide novel and computationally efficient insights related to protein functions and their motions. This includes, but is not limited to, protein allosteric interactions, predictions of hydrogen-deuterium exchange, the role of intrinsically flexible proteins and others. We have obtained a number of new results over the past year in allostery, redundant rigidity, and are continuing to work on applications of rigidity to mechanical engineering.

Allosteric regulation of the protein function occurs when a binding event at one site of the protein leads to changes in the conformation, dynamics, and shape of a distant functional site. Allostery is a long-standing unsolved biological problems with direct implications in medicine and drug design. In spite of its importance, the molecular mechanisms that give rise to allostery remain poorly understood. We have previously developed a novel computationally fast rigidity-based allostery detection algorithm. Our method not only provides an entirely new mechanistic view of allostery but it can quantify the strength of allosteric signalling and detect the regions in the protein that are crucial for the allosteric communication. This should eventually allow us to tackle the more difficult signalling events in the cell. Recently a key component of our research has been to link our predictions to experimental data and at the same time seek novel insights on allosteric communication in various proteins, such as enzymes, GPCRs and other allosteric proteins

We have recently been collaborating with a couple of biochemistry groups in University of Toronto, who have gathered various invaluable experimental data on enzyme dehalogenase fluoroacetate. We have performed computational allostery predictions on several structures of this enzyme and the findings indicate that rigidity changes in the substrate binding pocket propagate across to the regions in the other monomer, which is in line with experimental data. This demonstrates the presence of rigidity-based allostery and its role in the function of this enzyme. Moreover, we have recently performed the identification of allosteric pathway between the two monomers and our predicting are in high coloration with experimental evidence. Our findings may have wide encompassing consequences on understanding the role

of allostery in enzyme activation. We are continuing to explore the role of rigidity-based allostery and collaborate with biochemists and understand how our predictions provide better understanding of allostery.

We have also focused our attention on the G-protein coupled receptors (GPCRs). GPCRs are the cell surface proteins which detect and govern enormous number of signaling processes associated with vision, inflammation, neurotransmitters and hormones such as adrenaline, dopamine and caffeine. Pharmacologically these drugs are the most common drug targets, with some estimates suggesting that more than 50% of the current drugs on the market are designed to target GPCRs. How these receptors transmit the allosteric signal across the membrane is still not well understood. To shed some light on the allosteric mechanism in GPCRs, we have recently presented our work on rigidity-based alloseric signalling at two leading international conferences on GPCRs in Hawaii and Keystone. Our findings on a type of GPCR called adenosine A2A receptor, which is a drug target for treatments of inflammation, cancer, diabetes, infectious diseases and neuronal defect disorders, suggest that transmissions of rigidity upon binding of adenosine A2A agonists (natural activating ligands that bind to GPCRs) are important for structural and conformational changes at the distant site on GPCR responsible for binding a partner G protein. Moreover, the antagonist ligands (inactivating ligands) were found to contribute little or no rigidity-based allosteric transmission. We are also currently examining the role of rigidity-based allostery in A2A receptor and how to identify the allosteric hotspot regions, where binding a ligand at a hotspot region causes rigidity and conformational changes at the important functional G-protein binding regions. The results we presented at GPCR conferences have resulted in a few key collaborations, in particular with the Prof. Scott Prosser in University of Toronto and members of the Biozentrum group of Prof. Stephan Grzesiek at the University of Basel. This group collects experimental evidence using NMR and mutation studies and should provide rich data for corroborating the rigidity allosteric predictions. Moreover, we hope to be able to map the allosteric pathway in the protein network responsible for transmitting the allosteric signals.

As we are proposing a general mechanism for allosteric communication in proteins and since most proteins are believed to function through allostery, the number of possible applications and research directions is quite rich. As such, one directions we started to explore is of engineering allosteric control of proteins (detection and design of new allosteric sites that alter active site conformations and rigidity) by predicting regions in the protein that are in rigidity-based allosteric communication with the active sites. In collaboration with Andrew Wooley at University of Toronto who uses light-switchable proteins to control protein function, our initial results show that our predictions on the key translation initiation factor protein 4E (a common cancer target protein) are in direct agreement with previously predicted allosteric drug binding regions. Such collaboration is currently ongoing.

Papers 2016:

[12] Zhu S., Shala A., Bezginov A., Sljoka A., Audette G. and Wilson D., Hyperphosphorylation of Intrinsically Disordered Tau Protein Induces an Amyloidogenic Shift in Its Conformational Ensemble, PLoS ONE, 10(3), 2015.

Yuki Kobayashi, Yuya Higashikawa, Naoki Katoh, Adnan Sljoka: Characterizing redundant rigidity and redundant global rigidity of body-hinge graphs. Inf. Process. Lett. 116(2): 175-178 (2016) DOI: 10.1016/j.ipl.2015.08.011

Taehun Kim, Pedram Mehrabi, Adnan Sljoka, Cris Ing, Alexandr Bezginov, Regis Pomes, Emil Pai, Scott Prosser, Dimer Asymmetry and Subunit Dynamics, Key Factors in Enzyme Catalysis, 2016, submitted.

Adnan Sljoka, Nobuyuki TSUCHIMURA, additional authors to be determined, Rigidity-based allostery as a tool for detection of allosteric control of Translation Initiation Factor 4E, in planning.

Libin Ye, Chris Neil, Adnan Sljoka, Nobuyuki Tsuchimura, Scott Prosser, additional authors to be determined, Bidirectional Regulation of the A2A Adenosine G Protein Coupled Receptor by Physiological Cations, 2016, draft in preparation.

Conference presentations:

Adnan Sljoka, Probing GPCR allosteric communication via transmissions of rigidity, GPCR Workshop, Hawaii, 2015

Adnan Sljoka, Transmission of rigidity at a distance in GPCR alllostery, G Protein-Coupled Receptors: Structure, Signaling and Drug Discovery, Keystone, 2016

Adnan Sljoka, Probing protein flexibility and function via rigidity theory, ANMA, Kathmandu, Nepal