PD Research Report for the 2015 year

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Research Theme: Applications of rigidity and algorithm protein function
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In the field of protein science, understanding 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 in diseases such as Alzheimers 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. Many drugs are designed to directly alter the function of the protein through allosteric inhibition or activation and diseases such as cancer are routinely turned off or on through allosteric switches. 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 report on a few of the recent developments on these projects.

Since the Summer of 2015 we began to collaborate with a couple of biochemistry groups in University of Toronto, who have gathered 5 years' worth of 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. Our findings may have wide encompassing consequences on understanding the role of allostery in enzyme activation. This collaboration is currently ongoing.

Another key class of proteins that we have focused our attention on are 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 The results we presented at GPCR conferences have resulted in a few key collaborations, in particular with the 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.

We are building on this work to further understand how signals by small molecules or drugs are propagated across the protein structures and lead to conformational changes and ultimate functional control of proteins. 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 very recent 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 2015-2016:

[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, in preparation.

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.

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