A novel technique to determine allosteric interaction networks from molecular dynamics simulations of proteins

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***Short Abstract* — G protein coupled receptors (GPCRs) are trans-membrane proteins that bind extracellular ligands and then activate intracellular G protein cascades. Evidence suggests the binding of agonists promotes a conformational change that exposes the G protein-binding site. In order to understand this mechanism, we have developed a novel statistical technique to identify interaction networks using Molecular Dynamics simulations. The method determines conformational correlations between residues, and then identifies interaction networks coupling distant sites. Using a microsecond-scale, multi-state simulation of the class A GPCR CB2, we identified correlations between the binding site and ionic lock and network topology differences between states.**

***Keywords* — Allostery, GPCR, Molecular Dynamics, membrane proteins, network models**

I. Introduction

A. Protein Allostery

Protein allostery is the biophysical phenomenon in which the states of two spatially distant functional sites are coupled, and has been proposed to be present in nearly all biomolecules (1). There has yet to be a successful model for protein allostery that has been able to predict essential allosteric residues or pathways.

B. Allostery in GPCRs

The G protein coupled receptors (GPCRs) are involved in many cell-cell interactions (5). GPCRs bind and activate an intracellular G protein in response to binding an extracellular ligand, triggering a G protein signaling cascade. It is believed that conformational change in structural motifs and functional microdomains (SM/FMs) is essential for activation. For class A GPCRs, activation is often characterized by the isomerization of a tryptophan (the toggle switch) in the active site and the breaking of a salt bridge (the ionic lock) in the intracellular domain (6).

C. Cannabinoid Receptor 2

Recently, a microsecond-scale simulation of the cannabinoid receptor 2 (CB2) was published in which the ligand, 2-AG, partitioned out of the membrane and bound to CB2, resulting in the characteristic trans-isomerization of the toggle switch and the opening of the intracellular ionic lock (7). This simulation provides an opportunity to gain insight into the allosteric couplings between the binding site and SM/FMs.

II. Methods

We use k-means clustering to transform the dihedral angle space sampled by a given residue throughout a simulation into a sequence of conformational states. We then calculate the correlation coefficient of each conformational state of each residue with each conformational state of each other residue. In order to identify allosteric pathways between distant residues, we find the shortest path between two nodes through a subset of the reciprocal graph made by correlations formed by residues within a contact distance cut-off.

III. Results

A. Significant correlations exist between functional sites and correlation topology varies by state.

B. Allosteric control changes between the unbound inactivated state and the bound activated state of CB2.

C. A network of correlated residues in TM 3 may couple the toggle switch and ionic lock.

Conclusion

Here we present a novel technique to analyze allosteric interaction networks using Molecular Dynamics simulations. We are able to describe the allostery in the CB2 receptor and predict interaction networks that lead to the allosteric couplings.

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