Allosteric Transitions

Macromolecular communication is both the foundation that builds the life of nucleating molecules and the cause of many catastrophic concerns and pathological aberrations. To this end, studies of the fundamental properties of allosteric proteins are being actively pursued for their potential applications in medicine. In general, these studies can be divided into two classes: (1) those that search for an energy minimum and (2) those that attempt to find a more favorable product. The former may be described as `reaction' and the latter as `synthesis'.

Two Paradigms of Allostery

Amino acid, NMA model of allosteric enzymes. Concentration TR equilibrium potentiates signal to multiple monomers. Right — Signal transduction pathway: A series of conformational and transition information from membrane to nucleus.

Biomolecular Modeling Of Antibody-Antigen binding

Our objective is to develop techniques to predict the structure of therapeutic antibody-antigen (Ab-Ag) complexes. This provides insight into the mechanism of drug action and enables rational manipulation of the Ab structure for better antigen binding.

The Antigen Binding Surface of the Ab is Highly Aromatic

Antigen binding surface formed by 6 Complementarity Determining Regions (CDR's) 33% of Ab interfacial residues are aromatic: 25% of the Ab interfacial residues are Tyrosine

Proteins at Interfaces

As our understanding of protein technology becomes local so does the realization that proteins will change life. We build self-replicating and functional megastructures, and the design of their interfaces. The fundamental property of proteins is that they self-assemble into complexes. These complexes are highly organized and contain proteins that are reversibly linked to one another. The protein-protein interface is a nanoscale complex created by the cooperative properties of the proteins involved. This interface is highly organized and contains a number of different types of interactions, including noncovalent interactions such as hydrogen bonds, salt bridges, and van der Waals interactions.

Allosteric Proteins are Information Transfer Networks

Input Signal • small molecule • protein-protein interaction • phosphorylation
Signal Transducer • conformational switch • long-distance pathways
Amplifier • oligomer interface • cooperative response in other monomers
Output Signal • nhb / 3+ catalytic activity • nhb / 3+ protein-protein interaction

Allosteric Networks are Built from Motions

Sidechain Motions

Conformational Switches

Quaternary Motions

create or destroy functional elements, including binding surfaces
signaling across oligomer interface, produce cooperative responses

Goal 1: Elucidate Structural Mechanisms of Allostery

• Create a benchmark of allosteric proteins with known inactive and active crystal structures
• 12 allosteric enzymes
• 16 GTPase switches
• 15 phosphorylation targets
• Describe signaling mechanisms
• Information transfer pathways
• Structural and energetic pathways of motion

Prediction of Anti-Cancer MAb 806-EGFR Complex Structure

Ligand binding removes intra-molecular interactions of the EGFR Dimers. Interaction with antibody (Ab) converts EGFR to a conformational change to an Active form.

Inter-molecular interactions between the Da’s of two Active EGFR molecules leads to EGFR Dimmerization and intra-cellular Tyrosine Kinase phosphorylation.

MAb 806 inhibits EGFR dimerization by binding to an experimentally identified Peptide epitope.

To which EGFR conformation does 806 bind?

Why Gold?

An allosteric protein (AFP) is typically associated with a specific function, such as the ability to freeze or to inhibit the growth of a particular tumor. The active form of the protein is usually defined as having a specific function, while the inactive form has a different function. The protein is described as being in the active conformation when it is capable of performing its function, and in the inactive conformation when it is not. The active conformation is typically associated with a specific set of interactions, including a specific set of contacts with other molecules. The inactive conformation is typically associated with a different set of interactions, including a different set of contacts with other molecules.

Systems for Exploration in the Near Future

Antifreeze Protein and Ice

A Gold-Binding Protein

Building a Crystal in a Computer

The program can currently generate all of the simple, body-centered, face centered, and hexagonal lattice types.

Current Protocol for Protein Design

Dock moves the native protein about the crystal surface in a global fashion as it searches for an energy minimum.

Fine Search

Design involves inverse folding, i.e. the structure is held constant while the sequence is varied such that a decay undergoes further optimization.

Dock moves a newly designed protein about the crystal surface in a local fashion in an attempt to find a more favorable protein.