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Structure-based prediction of protein allostery

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Allostery is the functional change at one site on a protein caused by a change at a distant site. In order for the benefits of allostery to be taken advantage of, both for basic understanding of proteins and to develop new classes of drugs, the structure-based prediction of allosteric binding sites, modulators and communication pathways is necessary. Here we review the recently emerging field of allosteric prediction, focusing mainly on computational methods. We also describe the search for cryptic binding pockets and attempts to design allostery into proteins. The development and adoption of such methods is essential or the long-preached potential of allostery will remain elusive.

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Introduction

Allostery in its broadest sense is the functional change at one site on a protein caused by a change at a distant site. The perturbation at the allosteric site can be non-covalent binding of a molecule (e.g. small molecule, ions, RNA, DNA), covalent binding (e.g. phosphorylation) or light absorption [1]. Changes in structure or dynamics lead to effects such as a reduction or increase in catalytic activity, changes in disordered regions or changes in oligomerisation state.

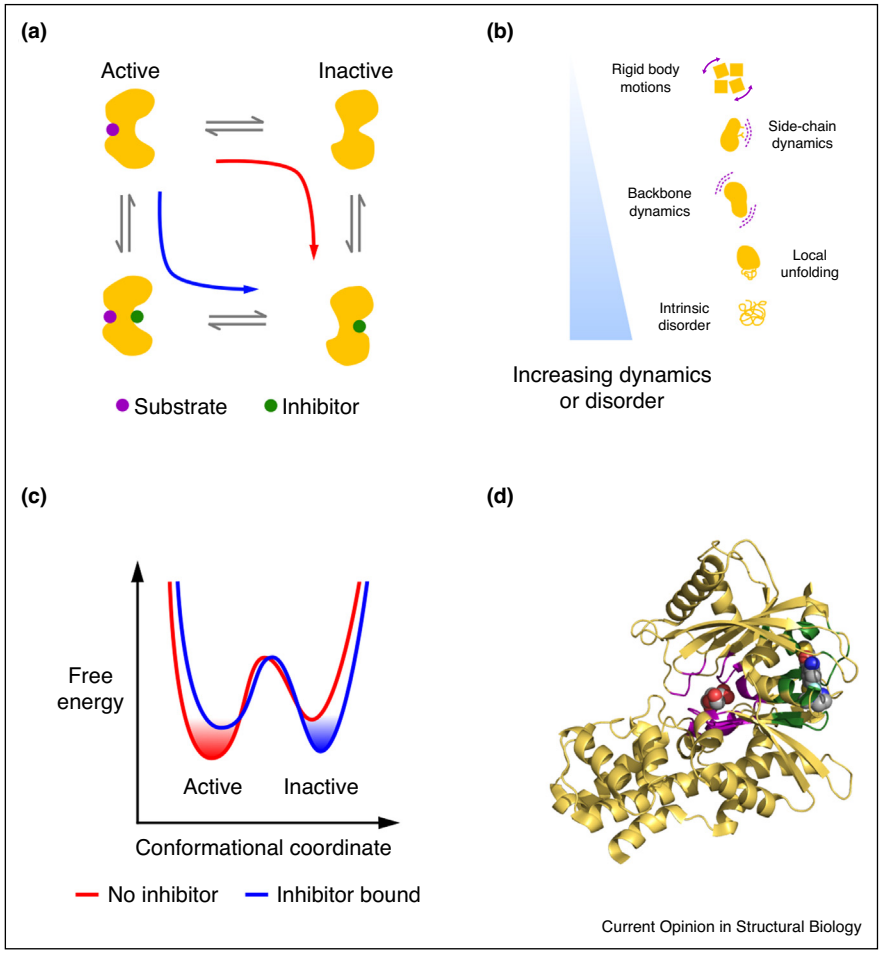
Since the first discovery of allosteric systems more than 50 years ago there have been various models put forward to describe the phenomenon. The dominant proposals for many years were the Monod-Wyman-Changeux (MWC) model, which posited that pre-existing states are subject to an equilibrium shift on modulator binding, and the Koshland–Némethy–Filmer (KNF) model, which advanced the idea that there was an induced fit of a binding site on interaction with a modulator [2••]. The structural view of allostery, which aimed to elucidate the allosteric mechanism by finding structural changes on effector binding, began to fill the gaps left by the phenomenological MWC and KNF descriptions. The discovery that entropic contributions to allostery can be significant predicted the phenomenon of allostery without conformational change, where the allosteric effect is communicated by a change in protein dynamics rather than protein structure [2••].

More recently these views on allostery have been revisited and reconciled in approaches that focus on the ensemble of conformational states that proteins exist in [2••,3]. Figure 1 outlines the current understanding of allostery. A perturbation at any site in the structure leads to a shift in the occupancy of states by the population, so allostery is a property of the conformational ensemble. The effect at the allosteric site is linked to the active site by small conformational changes that transmit the allosteric effect in a wave-like manner along pathways of amino acids in the protein [4]. These pathways may be conserved by evolution. It is also important to consider the effect of allostery on cellular networks and reaction pathways [1], with allosteric effects propagating via protein-protein interactions.

Allosteric drugs have hardly been explored and hold many potential benefits over orthosteric (non-allosteric) drugs: they are highly specific as they do not bind to active sites that are often conserved in protein families; they can activate as well as inhibit a protein; and they can have a ceiling to their effect [5]. Allosteric modulators have been elucidated for targets as diverse as G protein-coupled receptors (GPCRs), protein kinases, the GABA receptor, hepatitis C virus polymerase and RNA. Numerous other allosteric modulators are in various stages of human clinical trails. However, discovery of allosteric drugs presents challenges beyond those encountered in orthosteric drug discovery — see Box 1.

In order to understand and utilise allostery it is necessary to be able to predict allosteric sites, allosteric modulators and residues involved in propagating the allosteric signal. This review outlines advances from the last few years in the structure-based prediction of protein allostery, largely focusing on computational approaches. Previous reviews have covered similar topics [6–9]. The emerging fields of cryptic allosteric site discovery and allosteric site design are described. Challenges faced in the structure-based prediction of allostery and recommended steps for exploring allostery on a protein are also outlined — see Box 1 and Box 2 respectively.

Figure 1



The current conception of allostery. **(a)** A two-state model of allostery where a protein has an active and an inactive conformation. In the presence of the allosteric inhibitor the inactive state is favoured either by the inhibitor binding to the protein when it is in the inactive state (red arrow — conformational selection) or by the inhibitor binding to the active state and causing inactivation (blue arrow — induced fit). **(b)** The variety of motions that can lead to allostery. Larger motions or more disorder are shown further down the vertical axis. Figure based on Figure 2 from [2••]. **(c)** A simplified representation of the change in the energy landscape on binding of an allosteric inhibitor. The shaded regions show the main occupied conformation in each case. On inhibitor binding the relative energies of the active and inactive states are altered. For example, disruption of a hydrogen bond could destabilise the active state and stabilise the inactive state. **(d)** Glucokinase, a well-studied example of allostery [10], is shown as a yellow cartoon. The glucose substrate and the allosteric modulator are shown as spheres coloured by element. The active site and allosteric site are coloured purple and green respectively.

Computational methods

The last few years have seen the emergence of the first general methods that predict allostery based on protein structure. Table 1 summarises these methods, many of which are available as web servers.

Normal mode analysis methods

In normal mode analysis (NMA) the structural fluctuations of a protein around an equilibrium conformation are decomposed into harmonic orthogonal modes. The long-range nature of allosteric communication is often well-described by low-frequency modes that involve the motion of many atoms. The binding leverage approach [21•] predicts how ligand binding couples to the intrinsic motions of a protein. Sites with high binding leverage are predicted to be allosteric. Binding leverage was developed into the web server SPACER [20], and into the general predictor STRESS [22] by a different group. The PARS method [19•,18] calculates normal modes in the presence and absence of a simulated allosteric modulator. If the motions are significantly different the site is predicted as allosteric. The AlloPred method [11] calculates the normal modes of a protein, then holds the springs in the region of a potential allosteric site rigid and measures the effect of this perturbation at the active site. The DynOmics ENM server [15] finds hinge residues that control the two slowest normal modes of a protein, and hence are able to influence its dynamics. NMA is suitable