Allosteric Drug Discovery

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Understanding molecular mechanisms underlying the complexity of allosteric regulation in proteins has attracted considerable attention in drug discovery due to the benefits and versatility of allosteric modulators in providing desirable selectivity against protein targets while minimizing toxicity and other side effects. The proliferation of novel computational approaches for predicting ligand–protein interactions and binding using dynamic and network-centric perspectives has led to new insights into allosteric mechanisms and facilitated computer-based discovery of allosteric drugs. Although no absolute method of experimental and *in silico* allosteric drug/site discovery exists, current methods are still being improved. As such, the critical analysis and integration of established approaches into robust, reproducible, and customizable computational pipelines with experimental feedback could make allosteric drug discovery more efficient and reliable. In this article, we review computational approaches for allosteric drug discovery and discuss how these tools can be utilized to develop consensus workflows for *in silico* identification of allosteric sites and modulators with some applications to pathogen resistance and precision medicine. The emerging realization that allosteric modulators can exploit distinct regulatory mechanisms and can provide access to targeted modulation of protein activities could open opportunities for probing biological processes and *in silico* design of drug combinations with improved therapeutic indices and a broad range of activities.

Keywords: Allostery ; allosteric modulators ; network analysis ; MD-TASK ; drug resistance ; precision medicine

1. Introduction

Allosteric regulation is often a mechanism of choice for proteins and biomolecular assemblies to operate in complex signalling cascades and to modulate their activity levels, adapting to binding partners in the cellular environment during signal transduction, catalysis, and gene regulation [1][2][3][4][5]. The advances in X-ray crystallography, Nuclear Magnetic Resonance (NMR), and biophysical techniques have enabled numerous detailed investigations of large protein systems and conformational dynamic processes at atomic resolution [6][7][8][9][10][11][12][13][14][15][16][17][18][19]. These developments have facilitated the integration of computational and experimental studies of allosteric regulation, eventually leading to new conceptual outlooks and attempts to develop a unified theory of this allosteric phenomenon. The thermodynamics-based conformational selection model of allosteric regulation has been particularly fruitful in explaining a wide range of experiments by assuming that a statistical ensemble of preexisting conformational states and communication pathways is inherent to any protein system and can be modulated through allosteric ligand perturbations [20][21][22][23][24][25][26]. While great leaps have been made in the field of molecular modelling, NMR spectroscopy, and X-ray crystallography, it should be noted that no single method can provide allostery information for all cases due to the complexity and incomplete understanding of allosteric phenomena.

2. Integrated Computational Approaches and Tools for Allosteric Drug Discovery

Understanding molecular mechanisms of allosteric regulation in proteins has attracted considerable attention in both academia and industry owing to the importance of discovering allosteric modulators of therapeutically important targets [27]. These efforts are motivated by fundamental differences in structural and evolutionary diversity between active and allosteric sites even among structurally similar proteins of the same family. While active sites for structurally related proteins and protein families are often highly conserved and present a formidable challenge for design of selective modulators, allosteric binding is typically more dynamic and structurally and evolutionarily diverse, thereby often alleviating conceptual difficulties in the design of target-specific therapies and addressing lingering problems of toxicity and side effects [28]. Another important incentive for the development of allosteric drugs is that, while traditional orthosteric drugs usually inhibit protein activity, allosteric modulators may not only inhibit but also increase protein activity (allosteric activators) [29]. In the last decade, drug discovery has been shifting its focus toward targeting allosteric sites in

order to improve compound selectivity [28][29][30][31][32][33]. Allosteric drugs also feature distinct physicochemical properties, adding further freedom for discovery of novel active compounds, and can often be combined with orthosteric drugs into synergistic drug cocktails to modulate and improve enzyme activities, specificity, and pharmacological profiles.

While orthostery-based therapies have enhanced the quality of life for patients, they have brought forth many daunting challenges for which allostery may provide new solutions. Drug discovery against more diverse protein targets can result in less toxic and more specific therapies. The incorporation of dynamic and network analysis tools has proven their effectiveness in drug discovery studies of several target proteins [32][33][34][35] and offer a promising direction for the analysis of large datasets [36]. With the maturation of open-source projects, the availability of cheaper computation, and large datasets, in silico simulations are a very attractive venture for early-stage drug discovery as they offer cost-effective drug development. The integration of such approaches into robust, reproducible, and customizable workflows should make in silico allosteric drug discovery more efficient and reliable. In this review article, we discuss how the integration of state-of-the-art structural, dynamic, and network-based approaches for simulation of ligand–protein binding can provide a comprehensive methodological framework for advancing computer-aided discovery of allosteric sites and allosteric modulators of protein functions and mechanisms.

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