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Applications Note

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Alloscore: a method for predicting allosteric ligand–protein interactions

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Abstract

Summary: Allosteric ligands have increasingly gained attention as potential therapeutic agents due to their higher target selectivity and lower toxicity compared with classic orthosteric ligands. Despite the great interest in the development of allosteric drugs as a new tactic in drug discovery, the understanding of the ligand–protein interactions underlying allosteric binding represents a key challenge. Herein, we introduce Alloscore, a web server that predicts the binding affinities of allosteric ligand–protein interactions. This method exhibits prominent performance in describing allosteric binding and could be useful in allosteric virtual screening and the structural optimization of allosteric agonists/antagonists.
Availability and implementation: The Alloscore server and tutorials are freely available at http://mdl.shsmu.edu.cn/alloscore
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Supplementary information: Supplementary data are available at *Bioinformatics* online.

1 Introduction

Allostery, as a major regulatory mechanism, is of fundamental importance in a wide variety of biological phenomena, including signal transduction, catalysis and metabolism (Nussinov *et al.*, 2011). The functionality of allosteric proteins consists of their ability to orchestrate the activity of orthosteric sites in response to a signal, which is quintessentially fomented by effectors binding at distinct, often distant, functional sites, which are also referred to as allosteric sites (Huang *et al.*, 2013). Compared with orthosteric ligands, which target highly conserved orthosteric sites, allosteric ligands can bind to any evident suitable pockets on protein surfaces. Thus, allosteric ligands are capable of discriminating between closely related proteins (e.g. receptors, protein kinases). This specific mode of action endows allosteric ligands with unparalleled advantages compared with orthosteric ligands, including higher specificity, fewer side effects and lower toxicity (Nussinov and Tsai, 2013). Current drug discovery efforts under pharmaceutical regimes are increasingly investing in allosteric ligands, and structure-based drug design depends mainly on protein-ligand interactions. In this regard, characterizing allosteric ligand–protein interactions contributes to allosteric drug discovery (Huang *et al.*, 2015; Lu *et al.*, 2014; Panjkovich and Daura, 2014).

Despite the distinctive advantages shared by allosteric ligands, the development of allosteric drugs remains daunting, due to the special binding modes of allosteric ligand–protein interactions compared with orthosteric ligand–protein interactions. Recent studies have pinpointed conspicuous differences between the physicochemical properties of allosteric and orthosteric ligands (Wang *et al.*, 2012; Nussinov and Tsai, 2014). Allosteric ligands are generally more lipophilic and more rigid compounds than orthosteric ligands, which suggests that current universal computational algorithms are incapable of effectively portraying the associations of allosteric ligands with proteins. Thus, there is a pressing need for the development of a novel method to assess the binding affinities of unique allosteric ligand–protein interactions.

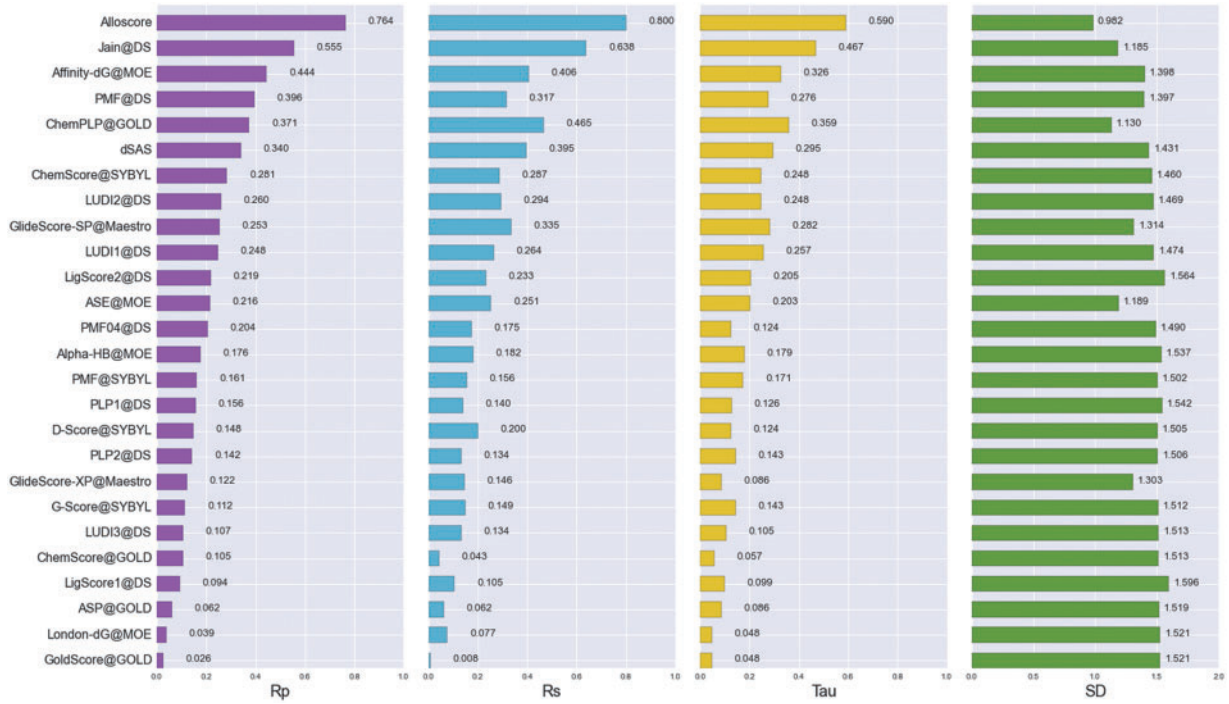

Fig. 1. Performance of Alloscore and other 25 methods in the prediction of binding affinities of allosteric ligand–protein interactions in external test set. Rp is Pearson's correlation coefficient; Rs is Spearman's correlation coefficient; Tau is Kendall's tau; SD is standard deviations in linear correlation (in logKd units). Detailed information is described in the Supplemental Tables S1 and S4

In this study, we introduce Alloscore, a web server that predicts the binding affinities of allosteric ligand–protein interactions, for the first time. This method elaborately selects a subset of energy terms that are best suited to delineate the characteristics of allosteric binding. Alloscore exhibits good performance in dissecting allosteric binding and could be useful in allosteric virtual screening and structural optimization of allosteric agonists/antagonists.

2 Methods

The most recent version of ASD (v3.0, July 2015), (Shen *et al.*, 2016) containing experimentally determined allosteric complexes with binding affinity, was utilized to develop the method for the affinity prediction of allosteric ligand–protein interactions. Based on knowledge from our previous analyses (Li *et al.*, 2013; Wang *et al.*, 2012), a subset of energy terms that is best suited to delineate the characteristics of allosteric binding affinities was selected. Then, the predicted model of allosteric binding affinity was trained and tested, and a final model was deployed on the Alloscore web server. Detailed information about the process of model construction is provided in the Supplementary Information.

3 Results

Using six selected energy terms (van de Waals, hydrogen bond and hydrophobic interactions between allosteric ligands and proteins, rotatable bonds in allosteric ligands and the buried volume and polar surfaces of ligands when binding to allosteric sites) and the experimental pK_i values of the training set complexes, Alloscore was trained as an empirical linear regression model for evaluating allosteric protein-ligand binding affinities. The regression resulted in a value of 0.647 for Pearson's correlation coefficient, R (Rp) (Supplementary Table S1 and Fig. S1), which is superior to available popular binding prediction methods for the training set (Supplementary Fig. S2). The interpretation of the Alloscore model is straightforward based on coefficient signs and weights (Supplementary Table S2). Hydrophobicity (45.16%), the buried ligand volume (18.70%) and rotatable bonds (15.83%) represent the three most important energy term contributions for allosteric interactions in the model (Supplementary Table S2), which is in good agreement with previous analyses of allosteric ligands and sites (Li *et al.*, 2013; Wang *et al.*, 2012). To provide a more realistic estimate of the actual model performance, Alloscore was evaluated with an external test set in comparison with other methods. The result show that Alloscore clearly outperforms other methods in the prediction of allosteric protein–ligand binding affinities (Fig. 1), resulting in values of 0.764 and 0.800 for Rp and Spearman's R (Rs), respectively (Supplementary Table S1). Therefore, the specific model of Alloscore is expected to improve allosteric drug design and optimization in real-world scenario applications.

3.1 Usage and output

For each job, the user can specify allosteric complexes of interest by uploading a protein in a PDB file and multiple ligands in an Mol2 file under 'Base Structure'. After defining the query protein and ligands, a 'Job Name' must be set before submission, which will allow the users to locate their queries in the 'Job Queue'. Once the run is submitted, a unique Job ID appears on the submission page. The users can apply this Job ID or Job Name to track the job's status or to access results on the Alloscore 'Job Queue' page. Upon completion of a job, a button labeled 'Finished' emerges in the 'Job Queue'. A representative run of an Allosite job takes 15–30 s, depending on both the number of input ligands and the complexity of the input protein.

Clicking the 'Finished' button links to the result, which includes the predicted energy terms, binding affinity and interactive 3D representation of each allosteric ligand–protein complex (Supplementary

Fig. S3), which can also be downloaded for offline analysis under the 'Download Results' panel. The Alloscore website includes a step-by-step tutorial on the 'Help' page. The server requires Javascript to be enabled and has been tested on all major web browsers.

4 Conclusion

The Alloscore web server conveniently provides a user-friendly interface to predict the binding affinities of allosteric ligand–protein interactions. Furthermore, critical energy contributions that contribute to allosteric binding are offered. To the best of our knowledge, this web server is the first of its kind and will be of considerable value to scientists interested in allosteric drug design and screening.

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Conflict of Interest: none declared.

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