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Prediction of Binding Free Energy Calculation Using Molecular Mechanics/Poisson-Boltzmann Surface Area (MM-PBSA) Method in Drug Discovery: A Short Review

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Abstract

Structure-based drug design possibly benefit from in silico methods that precisely predict the binding affinity of small molecules to target macromolecules. There are many limitations arise from the difficulty of predicting the binding affinity of a small molecule to a biological target with the current scoring functions. There is thus a strong interest in novel methodologies based on MD simulations that claim predictions of greater accuracy than current scoring functions, helpful for a regular use designed for drug discovery in the pharmaceutical industry. Herein, we report a short review on free energy calculations using MMPBSA method a useful method in structure based drug discovery.

Key words: Structure-based Drug Design, Molecular Dynamics, MMPBSA, Free Energy Calculations

1. Introduction

Structure-based drug design (SBDD) has become an established pattern in modern drug discovery to search for novel drug-like molecules able to bind to biomolecules of important pharmaceutical interest[1]. Because it is highly expensive and highly time consuming to prepare and assay large numbers of small molecules, there is strong interest in computational methods that can accurately predict small molecule binding affinities and hence reduce the time and resources. The low costs and speed at which docking studies can be conducted make the procedure valuable to prioritize compounds to assay in a drug discovery program, or to assist the design of improved ligands. Various computational chemistry techniques are often used to assist the structure based drug design process[2]. A distinctive example is the virtual screening by docking, whereby the contents of databases of drug-like molecules are docked into the binding site of a protein of interest. Probable binding modes of ligand and its interaction with the receptor are generated and the binding affinity of the resulting complex is estimated[1,3,4].

Regrettably, obtaining accurate estimates of binding affinities from docked ligands was found to be more difficult. Despite the fact that binding affinities obtained are routinely estimated by empirical scoring functions, the general view is that they are too inaccurate to reliably rank order small molecules by potency[5]. There are many aspects of drug discovery that could be improved if binding affinities could be predicted more accurately. It was during the middle of 1980's, the idea of using molecular dynamic simulations begin to predict binding affinities using free energies of binding[6,7]. Several approaches such as Free Energy Perturbation (FEP), Thermodynamic Integration (TI), Linear Interaction Energy (LIE) and Molecular Mechanics Poisson–Boltzmann Surface Area (MM-PBSA) methods have been proposed to compute binding free energies of small compounds to macromolecules[8].

The Molecular Mechanics/Poisson-Boltzmann Surface Area (MM-PBSA) method calculates binding free energies using molecular mechanics (force fields) and continuum (implicit) solvation models[9]. This methodology has been successfully applied across a range of targets and is implemented in software programs such

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as Amber[10]. Previously we have reported several short reviews covering different in silico applications such as Pseudoreceptors, development of search algorithm in docking and importance of partial charges.[11-15] Continuing this effort, in this study we report on a short and critical overview of MM- PBSA method and its applications. We then discuss key aspects which improve the accuracy of results, and highlight potential caveats due to the approximations inherent in the methods. We conclude with a review of recent representative application, which illustrate both successes and limitations.

2. Experimental Section

By using MM-PBSA method, relative binding affinities for a set of ligands to a given target can often be reproduced with good accuracy and considerable less computational effort compared to full-scale molecular dynamics FEP/TI simulations. Furthermore, free-energies can be decomposed into insightful interaction and desolvation components. In MMPBSA, the binding free energy (ΔG_{bind}) between a ligand (L) and a receptor (R) to form a complex RL is calculated as

$$\Delta G_{bind} = \Delta H - T\Delta S \approx \Delta E_{MM} + \Delta G_{sol} - T\Delta S \quad (1)$$

$$\Delta E_{MM} = \Delta E_{internal} + \Delta_{E electrostatic} + \Delta E_{vdw} \quad (2)$$

$$\Delta G_{sol} = \Delta G_{PB} + \Delta G_{SA} \quad (3)$$

where ΔE_{MM}, ΔG_{sol} and $-T\Delta S$ are the changes of the gas phase MM energy, the solvation free energy, and the conformational entropy upon binding, respectively. ΔE_{MM} includes $\Delta E_{internal}$ (bond, angle, and dihedral energies), $\Delta E_{electrostatic}$ (electrostatic), and ΔE_{vdw} (van der Waals) energies. ΔG_{solv} is the sum of electrostatic solvation energy (polar contribution), ΔPB, and the non electrostatic solvation component (nonpolar contribution), ΔG_{SA}. The polar contribution is calculated using PB model, while the nonpolar energy is estimated by solvent accessible surface area (SASA). The conformational entropy change $-T\Delta S$ is usually computed by normal-mode analysis on a set of conformational snapshots taken from MD simulations.

A common strategy to reduce noise and cancel errors in simulations is to run molecular dynamics (MD) simulations on the complex only. Snapshots taken from this single trajectory of MD simulation are used to calculate each free energy component in the above equations. In such a single trajectory approach, ΔEinternal is canceled between ligand, receptor, and complex, which can significantly reduce the noise in most cases. One can also use a separate trajectory approach to calculate the energy terms by taking snapshots from three individual MD simulations of the complex, protein, and ligand separately. In principle, this approach is more accurate than the single trajectory approach. Meanwhile, it is also more expensive in terms of computational cost.

3. Results and Discussion

3.1. Limitations of MMPBSA

MM-GBSA methods are widely recognized as valuable tools in CADD applications. However there are some limitations and caveats need to be considered. At first, this method lacks the required accuracy for absolute binding free energy predictions[16,17]. Force-field inconsistencies may also be an issue. PB results depend strongly on adequate atomic charges and van der Waals radii, which are often optimized for MD simulations. The MM-PBSA results may be influenced by system-dependent properties, such as the features of the binding site, the extent of protein and ligand conformational relaxation upon association, and the protein and ligand charge distribution[16,18]. Continuum electrostatics models ignore the molecular structure of the solvent and in some cases this might affect the results, particularly when key receptor-ligand interactions are bridged by water molecules[19]. In a recent MM-PBSA study, researchers suggested that the use of $\varepsilon_{in} = 4$ for a highly charged protein-ligand binding interface, $\varepsilon_{in} = 2$ for a moderately charged binding interface and $\varepsilon_{in} = 1$ for a hydrophobic binding interface may improve ligand ranking[16]. The lack of a consistent optimum dielectric constant for MM-PBSA calculations has been noted by other[20], although generally a value $\varepsilon_{in} = 4$ often gives satisfactory results[20-22]. Finally, MM-PBSA calculations require some degree of user expertise and planning, from the initial set-up and analysis of the MD simulations through to the binding free energy calculations.

3.2. Successful Applications of MMPBSA

There are many successful applications have been reported in the literature. In this review, we will review

the use of MM- PBSA calculations reported by Rastelli and co-workers[23]. They explored the reliability of using a single energy minimized receptor–ligand complex in MM-PBSA and MM-GBSA calculations to estimate ligand binding affinities for a series of structurally diverse inhibitors of *Plasmodium falciparum* DHFR with known binding modes and affinities. They obtained excellent correlations between MM-PBSA or MM-GBSA binding affinities and experimental values, similar to those obtained after averaging over multiple snapshots from periodic boundary MD simulations in explicit water in the traditional sense, but with significant savings on computational time and effort. Different methods were used for generating the structures for the MM-GB(PB)SA calculations from minimizations in implicit and explicit solvent models, to minimization using a distance dependent dielectric function, and finally minimization followed by a short MD simulation and then re-minimization. The approach has been implemented in an automated workflow called BEAR (Binding Estimation After Refinement) which produces both MM-GBSA and MM-PBSA predictions of binding free energies, and is fast enough to be suitable for virtual screening applications[23,24].

4. Conclusion

MM-PBSA free energy calculation is computationally efficient, end-point free energy method that has been widely used to study protein-ligand binding affinities. Even though there are some limitations, this method is proved to be useful. Accurate incorporation of solute entropy and solvent effects in binding affinity calculations is challenging, but future extensions and development of MM-PBSA method will undoubtedly serve to address these limitations.

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References

[1] H. Jhoti and A. R. Leach, “Structure-based drug discovery”, Springer, Dordrecht, Netherlands, 2007.
[2] W. L. Jorgensen, “The many roles of computation in drug discovery”, Science, Vol. 303, pp. 1813-1818, 2004.
[3] G. Klebe, “Virtual ligand screening: strategies, perspectives and limitations”, Drug. Discov. Today, Vol. 11, pp. 580-594, 2006.
[4] C. McInnes, “Virtual screening strategies in drug discovery”, Curr. Opin. Chem. Biol., Vol. 11, pp. 494-502, 2007.
[5] G. L. Warren, C. W. Andrews, A. M. Capelli, B. Clarke, J. La-Londe, M. H. Lambert, M. Lindvall, N. Nevins, S. F. Semus, S. Senger, G. Tedesco, I. D. Wall, J. M. Woolven, C. E. Peishoff, and M.S. Head, “A critical assessment of docking programs and scoring functions”, J. Med. Chem., Vol. 49, pp. 5912-5931, 2006.
[6] W. L. Jorgensen and C. Ravimohan, “Monte carlo simulation of differences in free energies of hydration”, J. Chem. Phys., Vol. 83, pp. 3050-3054, 1985.
[7] C. F. Wong and J. A. McCammon, “Dynamics and design of enzymes and inhibitors”, J. Am. Chem. Soc., Vol. 108, pp. 3830-3832, 1986.
[8] N. Foloppe and R. Hubbard, “Towards predictive ligand design with free-energy based computational methods?”, Curr. Med. Chem., Vol. 13, pp. 3583-3608, 2006.
[9] P. Kollman, “Free energy calculations: Applications to chemical and biochemical phenomena”, Chem. Rev., Vol. 93, pp. 2395-2417, 1993.
[10] D. A. Case, T. E. Cheathham III, T. Darden, H. Gohlke, R. Luo, K. M. Merz, Jr, A. Onufriev, C. Simmerling, B. Wang, and R. Woods, “The amber biomolecular simulation programs”, J. Comput. Chem., Vol. 26, pp. 1668-1688, 2005.
[11] G. Kothandan, T. Madhavan, C. G. Gadhe, and S. J. Cho, “Pseudoreceptor: concept and an overview”, J. Chosun Natural Sci., Vol. 3, pp. 162-167, 2010.
[12] S. J. Cho, “Recent development of search algorithm on small molecule docking”, J. Chosun Natural Sci., Vol. 2, pp. 55-58, 2009.
[13] S. J. Cho, “Search space reduction techniques in small molecular docking”, J. Chosun Natural Sci., Vol. 3, pp. 143-147, 2010.
[14] S. J. Cho, “Calculation and application of partial charges”, J. Chosun Natural Sci., Vol. 3, pp. 226-230, 2010.
[15] S. J. Cho, “Meaning and definition of partial charges”, J. Chosun Natural Sci., Vol. 3, pp. 231-236, 2010.
[16] T. Hou, J. Wang, Y. Li, and W. Wang, “Assessing

the performance of the MM/PBSA and MM/GBSA methods. 1. The accuracy of binding free energy calculations based on molecular dynamics simulations", J. Chem. Inf. Model., Vol. 51, pp. 69-82, 2011.

[17] N. Singh and A. Warshel, "Absolute binding free energy calculations: On the accuracy of computational scoring of protein-ligand interactions", Proteins, Vol. 78, pp. 1705-1723, 2010.

[18] B. Kuhn, P. Gerber, T. Schulz-Gasch, and M. Stahl, "Validation and use of the MMPBSA approach for drug discovery', J. Med. Chem., Vol. 48, pp. 4040-4048, 2005.

[19] J. M. Hayes, V. T. Skamnaki, G. Archontis, C. Lamprakis, J. Sarrou, N. Bischler, A. L. Skaltsounis, S. E. Zographos and N. G. Oikonomakos, "Kinetics, in silico docking, molecular dynamics, and MM-GBSA binding studies on prototype indirubins, KT5720, and staurosporine as phosphorylase kinase ATP-binding site inhibitors: The role of water molecules examined", Proteins, Vol. 79, pp. 703-719, 2011.

[20] A. Aleksandrov, D. Thompson, and T. Simonson, "Alchemical free energy simulations for biological complexes: powerful but temperamental", J. Mol. Recogn., Vol. 23, pp. 117-127, 2010.

[21] G. Archontis, T. Simonson, and M. Karplus, "Binding free energies and free energy components from molecular dynamics and Poisson-Boltzmann calculations. Application to amino acid recognition by aspartyl-tRNA synthetase", J. Mol. Biol., Vol. 306, pp. 307-327, 2001.

[22] D. Thompson, P. Plateau, and T. Simonson, "Free-energy simulations and experiments reveal long-range electrostatic interactions and substrate-assisted specificity in an aminoacyl-tRNAsynthetase', ChemBioChem., Vol. 7, pp. 337-344, 2006.

[23] G. Rastelli, G. Degliesposti, A. Del Rio, and M. Sgobba, "Binding estimation after refinement, a new automated procedure for the refinement and scoring of docked ligands in virtual screening", Chem. Biol. Drug. Des., Vol. 73, pp. 283-286, 2009.

[24] G. Degliesposti, C. Portioli, M. D. Parenti, and G. Rastelli, "BEAR, a novel virtual screening methodology for drug discovery", J. Biomol. Screen., Vol. 16, pp. 129-133, 2011.