Free Energy Perturbation Calculations as a Predictive Tool in Structure-Based Drug Design

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Abstract

Structure-based drug discovery is central to the efficient development of therapeutic agents and to the understanding of metabolic processes. In recent years, advances in computer simulations have facilitated the calculation of changes in free energies of binding and the description of detailed underlying molecular and atomic interactions involved in ligand-protein interactions, which help guide molecular design. State of the art structure-based drug design methods include virtual screening and *de novo* drug design; these serve as an efficient, alternative approach to experimental high-throughput screening. However, these methods have inherent limitations such as the absence of solvent and protein flexibility as well as the limited accuracy of scoring functions implemented in them [1]. Thus, these methods are rarely used for the ranking of congeneric series or for the optimization of lead compounds. In contrast, free energy perturbation calculations are currently considered state of the art method to estimate relative free energies of binding, ΔΔG, between similar ligands [2].

In this talk are presented a series of docking and free energy perturbation calculations coupled with Molecular Dynamics or Monte Carlo calculations targeting the M2 ion channel of the influenza A virus and the Arp2/3 complex [3]. Low correlation between docking scores and the experimentally measured binding affinities of congeneric compound sets was obtained for both proteins. Our analysis suggests that the weak correlation between the binding affinities predicted from docking calculations and the measured inhibition constants is at least partly due to the fact that protein and water molecules are kept rigid in the docking process. FEP calculations in contrast, allow the system to evolve dynamically and to provide a more realistic representation of protein-ligand interactions. A high correlation (>0.65) between the FEP-calculated and experimental results was found. In several instances, when comparing the FEP calculations of the parent compound with respect to the analogs, we noted changes in the positions of water molecules, side chains and even backbone. These movements appeared to be critical contributors to the ΔΔG of binding. It is also demonstrated in which cases one can perform FEP calculations keeping a rigid backbone and when the protein should be left fully flexible. The correlation between the FEP calculations and the measured inhibition constants, demonstrate the value of the FEP calculations in predicting the difference in binding affinity of close analogs without the immediate need for synthesis. Moreover, they allow us to construct structure-activity relationships and streamline the development of improved inhibitors of the M2TM ion channel and the Arp2/3 complex.

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[2] Jorgensen, W. L. (2009) Efficient Drug Lead Discovery and Optimization. *Acc Chem Res.* 42:724-733
[3] Baggett, A.W.*; Cournia, Z*; Patargias, G.; Glass, A. C.; Liu, S.-Y.; Nolen, B. J. (2012) Computer-aided Optimization of a Small Molecule Inhibitor of Arp2/3 Complex, a Key Regulator of the Actin Cytoskeleton. *Submitted.*