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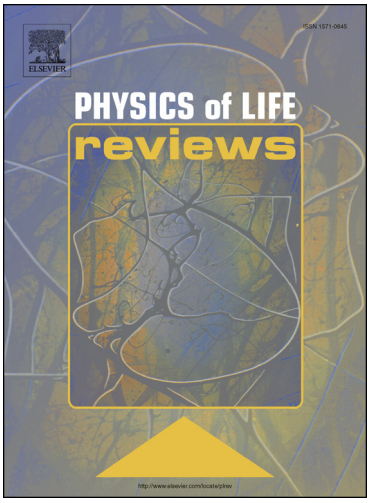

Ligand migration and steered molecular dynamics in drug discovery

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Ligand migration and steered molecular dynamics in drug discovery: Comment on Ligand diffusion in proteins via enhanced sampling in molecular dynamics by Jakub Rydzewski and Wieslaw Nowak

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The problem of ligand diffusion inside proteins is important in many domains of science, especially, in drug design. In the context of drugs this process is very challenging to study experimentally because current methodologies often do not provide direct information about their specificity and life time [1, 2]. The complexity of ligand migration through protein cavities and tunnels makes it difficult to describe theoretically. Due to limited computation time the direct application of conventional all-atom molecular dynamics (MD) simulation techniques to the problem of ligand migration is impractical. This has motivated computational researchers to develop and use different tools to enhance sampling.

In the present review, Rydzewski and Nowak [3] provide a summary of existing computational methods for sampling ligand migration pathways between bound and unbound states, including steered molecular dynamics (SMD), random acceleration MD (RAMD), and locally enhanced sampling (LES) with a special emphasis on the memetic algorithm (MA) recently developed by these authors [4]. MA is based on the rational assumption that a ligand moves along pathways which minimize the ligand-protein interaction on-the-fly during the MD simulation. This interesting method was successful in revealing pathways in M2 muscarinic G-protein-coupled receptor, enzyme nitrile hydratase, and heme-protein cytochrome P450cam complex [4, 5].

Considering the process of ligand migration in proteins is a complex rare event, the authors have presented a concise discussion of various collective variables (CV) that can reduce the complexity of describing this phenomenon. The simplest CV is the distance between the centers of mass of two molecules, which is used to study the binding/unbinding in SMD. The potential energy and work performed during ligand migration are also useful CVs. Complex-path CVs have been introduced to construct diffusion pathways between two metastable states separated by a free energy bottleneck [6]. Assuming that relevant information can be obtained in low dimensional CV space embedded in a high dimensional space several techniques for dimension reduction are discussed in detail, including the sketch-map method and the machine learning technique called T-distributed stochastic neighbor embedding. The reader can also find useful information on the application of popular methods including the Jarzynski equality, metadynamics and umbrella sampling for studying binding, unbinding and migration of small molecules in different systems.

Despite a wealth of information within a relatively short review all relevant topics cannot be covered. Therefore, in the next part of this comment we present complementary material on recent developments of the application of SMD to drug design.

SMD: Pulling along a single direction

SMD was first implemented by Grubmuller *et al* [7] in 1996 to probe binding affinity of streptavidin to biotin. In this method a time-dependent external force is applied to facilitate

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ligand unbinding from the receptor. Namely, the ligand is attached to a spring with a given force constant, and the harmonic constraint is moved with a constant velocity along the direction allowing a smooth exit from the binding site. Using SMD one can calculate the exerted force and the work performed on the system. Because the process is not at equilibrium the results should depend on the pulling direction which may be obtained by different softwares such CAVER [8] and MOLE [9]. However, none of them takes into account geometry of ligand assuming it as a sphere with a given radius, and this may lead to artifacts. To overcome this drawback we have proposed a new approach for navigating pathways for ligand egress from the binding pocket, where the scoring function is defined as the total weighted hindrances exerted by the receptor on each atom of the ligand during its movement in the pulling direction [10]. The optimal route should correspond to the minimal steric hindrance (MSH) condition. The MSH and CAVER methods provide nearly the same pathways for a ligand that has spherical geometry. In general, pulling along the direction predicted by MSH yields better agreement with experimentally measured binding affinities than CAVER [10].

Typical force-displacement profiles are shown in Fig. 1, where F_{max} is called rupture force. In the context of SMD-based drug design it is important to notice that in 2010 Colizzi *et al.* [11] and Mai *et al* [12] reported that the rupture force is correlated with experimental IC50 in such a way that the larger is the rupture force the smaller IC50 or higher binding affinity. In addition it has been shown [10] that the non-equilibrium work, defined as $W_{pull} = \int \vec{F}.\, d\vec{r}$, has a better correlation with experiment than the rupture force because W_{pull} is a function of the entire process while F_{max} is computed only in a single state. Thus, the rupture force and non-equilibrium work may be used as a scoring function for discerning inactive from active inhibitors. Because SMD provides results as accurate as the standard (MM-PBSA) but computationally much faster [13], it has proven to be a valuable tool in the virtual screening of drug candidates from big databases [14].

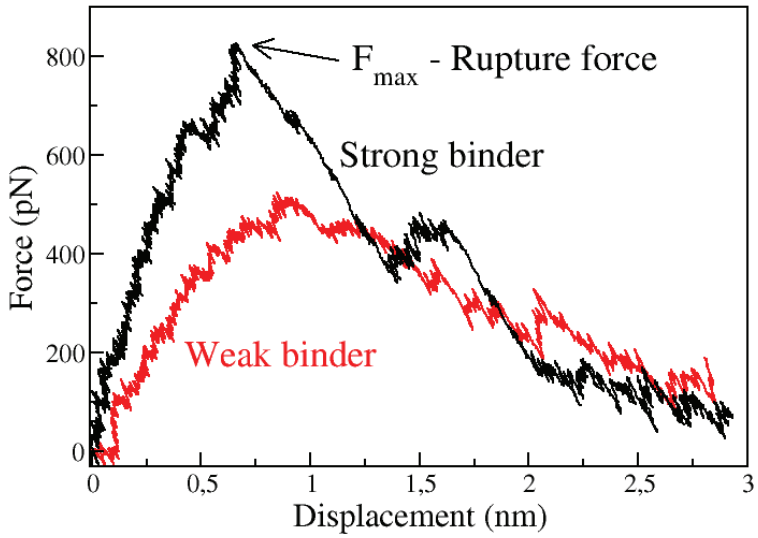

FIG. 1: Typical force-displacement profiles for strong (black) and weak (red) binders with high and low rupture force, respectively.

SMD: Multi-directional pulling

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Although conventional SMD with a single pulling direction provides reasonable results for binding affinity [10-12, 15] it remains unclear whether the ligand can move along the most favorable pathway if the external force is applied in one direction. Motivated by this possible inconsistency Yang *et al.* [16] and Gu *et al.* [17] have proposed a SMD method with adaptive direction adjustments where an optimum path of ligand dissociation is navigated by minimizing the pulling force automatically during the simulation. For the cytochrome P450 3A4-metyrapone complex the multidirectional pulling provided the pathway with lower energy barrier or smaller rupture force than that predicted by the standard SMD [16]. The self-adaptive SMD also yielded a good correlation between the rupture force and binding affinity for two sets of protein-ligand complexes [17] but what method, conventional or non-conventional SMD, is better remains to be elucidated.

Recently, applying the free energy perturbation (FEP) method and OPLS force field to a wide range of ligands and protein targets Jorgensen *et al.* [18] have obtained astonishing agreement with experimental data on binding free energies. Since this work is expected to have a significant impact on industrial pharmaceutical research, the important question emerges whether SMD can compete with the highly robust and accurate FEP methodology in drug discovery. Different algorithms, described in the review of Rydzewski and Nowak for navigating ligand diffusion paths in protein, may be useful in solving this problem.

Finally, the methods and concepts discussed in this well written Review are general and applicable not only to ligand migration but also to other phenomena in living matter. The Review covers a vast literature making it an essential reference for those who wish to expand the knowledge on the subject.

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