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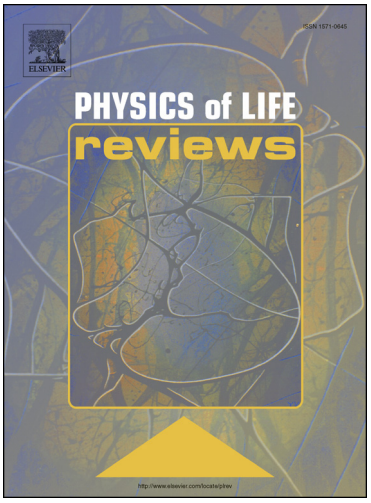

Ligand migration and steered molecular dynamics in drug discovery

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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