Farewell to Docking: Accelerating ligand binding and unbinding with molecular dynamics simulations

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(Bio)molecular recognition and assembly are key concepts in chemistry, biology and drug design. Chemical and life processes are critically dependent on the association and dissociation of (bio)molecules. Understanding the mechanisms of these relevant processes is of utmost importance. Experimental methods provide information on stable structures, binding affinities, or kinetics but cannot offer a complete description of binding and unbinding pathways at the required atomic detail. Molecular dynamics can provide an atomistic dynamic view of such processes. However, a tremendous amount of conformational sampling is required to obtain accurate pathways and reliable stationary and kinetic properties. Current computational methods to study assembly, binding, and unbinding of (bio)molecules either require access to high-performance computing resources or the definition of a complex reaction coordinates to enhance conformational sampling.

Our goal is to develop a computational protocol to study, at atomic level, the mechanisms of self-assembly, association and dissociation of (bio)molecules at a reasonable computational cost. This protocol relies on the basic ideas of accelerated molecular dynamics (aMD),[1,2] an unconstrained enhanced sampling technique that does not require the a priori definition of any reaction coordinate. The novel strategy consists in redefining aMD by selectively boosting non-bonded interactions (aMD-nB) between interacting molecules. aMD-nB allows to enhance conformational sampling of associative and dissociative processes and to recover stationary and kinetic properties.

Here, we focus on showing the potential of this novel technique as a tool to efficiently explore the free energy landscape of drug binding and unbinding. In particular, we have reconstructed the pathways of inhibitor binding and unbinding to rationalze the origin of inhibitor selectivity and to improve drug design for a set of p38s and CDKs protein kinases involved in liver cancer.

References:

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