Ciclo di incontri – Tavolo di discussione

Enhanced MD Simulations in Computational Drug Discovery

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Bringing a new drug to market is a resource-intensive and time-consuming activity characterized by a high rate of failure. Computational methods can assist the entire process in many ways, and they are nowadays considered an integral part of any modern drug discovery and development program [1]. Thanks to recent progress in hardware performances, Molecular Dynamics (MD) simulations and related methods have gained mainstream status in the field of computational medicinal chemistry, as in principle they allow predicting drug-target binding modes, binding free energies, and kinetic rate constants [1,2]. Unfortunately, the computational cost of MD simulations remains prohibitive, and several workarounds (usually referred to as "enhanced sampling") have been devised to make this kind of computations affordable and therefore appealing from a drug discovery standpoint [2]. One class of such methods is based on the notion of Collective Variables (CV), or reaction coordinates, by which the process of interest can be described and investigated through the introduction of external biases [3]. As a result, rare events can be sampled at a greatly reduced computational cost compared to conventional MD. An adding value of these methods is that the Free Energy Surface (FES) along the chosen CVs is also an outcome of the simulation, providing a mechanistic interpretation of the process under investigation [3]. In this seminar, an introduction to enhanced sampling methods making use of CVs for reconstructing the FES will be addressed. Specifically, the method of metadynamics [4] and its application to pharmaceutically relevant case studies will be discussed. A special emphasis will be given to the importance of choosing suitable CVs for the reliability of the FES, and how trajectories produced by conventional MD simulations can be harnessed to devise optimal CVs in a data-driven fashion [4, 5].

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[5] Bernetti M. et al., Pharmaceuticals 2020, 13, 253.

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