Enhanced samping techniques and their application to the study of small substrate translocation

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In the last years, computational methods have acquired a great importance in the study of biological processes, allowing to study the differences caused by point-charge mutations and interactions between single pairs of molecules. One the major problems of molecular dynamics simulations is that the time scales that are currently accessible through this technique are restricted to the order of microseconds. Enhanced sampling techniques allow to speed up specific processes by biasing the evolution over time of the systems of interest, either by forcing the change of variables that are thought of characterizing the processes under study, or by periodically changing the temperature of the system, thus enabling increased transition rates between processes with low probabilities. In this work, we discuss the most known enhancing sampling techniques, with particular emphasis on metadynamics, see Bonomi et al. [1]. We then apply this technique to the study of the permeability of the outer membrane of gram negative bacteria, a problem that is directly correlated to the multidrug resistance that many re-emerging pathogens are showing in the last decade. We show that metadynamics offers a novel way of studying processes that are characterized by steep free energy barriers, allowing not only to speed up the exploration of the system, but also to determine the relative probabilities of different paths in the exploration of the free energy of the process.

[1] M. Bonomi, D. Branduardi, G. Bussim C. Camilloni, D. Provasi, P. Raiteri, D. Donadio, F. Marinelli, F. Pietrucci, R.A. Broglia, M. Parrinello, Comp. Phys. Comm., **2009**, 180, 1961-1972