Free Energy methods to study complex biological phenomena

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Protein plasticity represents both a challenge and an opportunity for computational drug design. Exploring the conformational space of a target with sufficient detail is computationally very demanding and often beyond the reach even for state-of-the-art atomistic molecular simulations techniques. If it were possible, however, it could open the avenue to the design of more selective drug candidates. Here we show how methods developed to accelerate rare events can be used to study both large-scale conformational transitions and ligand binding.

Using a new sampling method which is able to find the low free energy channel between an initial and final state [1] we determined the atomistic dynamics of the open-to-closed movement of the cyclin dependent kinase 5 (CDK5). We found that the inactivation movement has a two-step mechanism in which Arg149 plays a key role, allowing a concerted movement of the C-terminal and N-terminal lobes. A complementary method, Metadynamics [2] was used to study the undocking path of a congeneric series of ligands to CDK2 and of selective inhibitors from COX and COX-2 [3]. Also in these cases the large scale dynamics of the target proteins plays a fundamental role.

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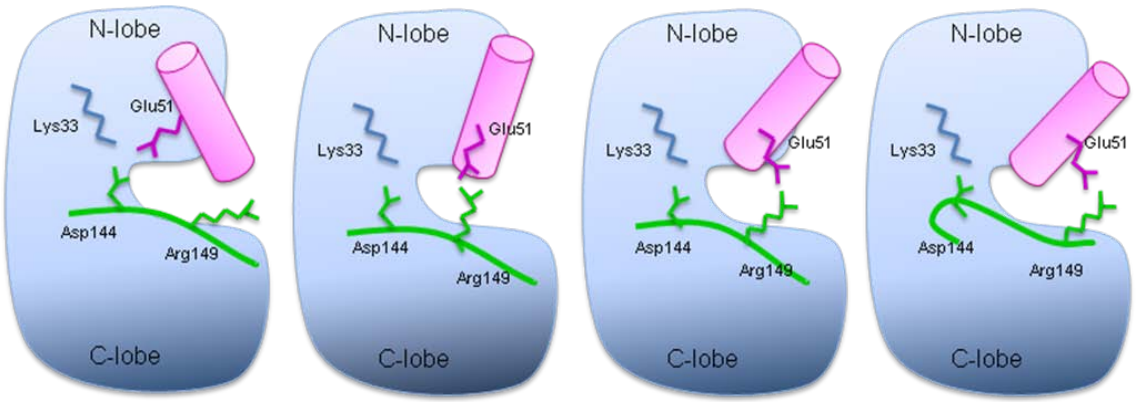
2. A. Laio and F. L. Gervasio* Metadynamics: a method to simulate rare events and reconstruct the free energy in biophysics, chemistry and material science Rep. Prog. Phys. , 2008, 71, 126601 (22p).

3. V. Limongelli, F.L. Gervasio et al. Proc. National Acad. Sci. USA, 2010, in press.



Mechanism of CDK2 deactivation obtained with path collective variables [1].