Predicting binding kinetics and free energy profiles of drug receptor complexes from all-atom simulations

Francesco Luigi Gervasio

Computational Biophysics Group, Spanish National Cancer Research Centre, Madrid

The manipulation of binding kinetics is emerging as a critical parameter to optimize the efficacy and minimize the toxicity of lead compounds in vivo. A computational method able to link the structure of the ligand to the observed binding kinetics would be very valuable. Unfortunately, computing accurate free energy profiles along physical association pathways, let alone the binding kinetics is extremely complex. Long sampling times, significant conformational changes of the target protein and shortcomings with current ligand force-fields concur in frustrating the long ongoing efforts.

Here I report on our efforts in combining approaches based on metadynamics [1,2] together with multiple-replicas [3] and path-sampling [4] can be used to converge the free energy profile along a physical association pathway, to quantify the effect of large-scale conformational changes [5] and to compute binding kinetics with (force-field permitting) reasonable accuracy.

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