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Microscopic simulations of biological systems: An intensive computational drug screening approach

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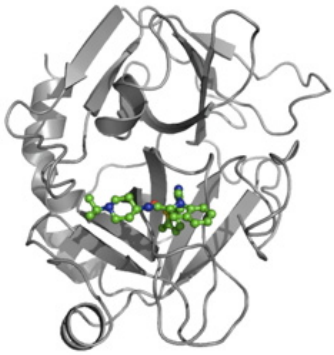
Two main families of theoretical approaches are used to simulate a molecular system at the atomic scale: quantum methods, based on the Schrödinger equation, and molecular modeling techniques, based on a classical formalism. The latter ones are at least 10^3 more efficient compared to the quantum methods. That explains their intensive use to compute in particular difference in free energy, $\Delta\Delta G$, a thermodynamic quantity allowing a direct comparison with experiment. For instance, to theoretically estimate the relative affinity of two ligands (drugs) for a target protein, one may consider the $\Delta\Delta G$ value corresponding to the energy cost for transforming one drug into the other, in an alchemy sense.

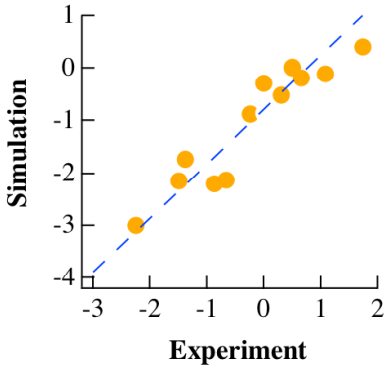
The $\Delta\Delta G$ computation requires the simulation at the atomic scale of several virtual molecular systems, intermediate between the two real systems under investigation. Our team is developing a new generation of atomic polarisable force-fields, which can be coupled with a mesoscopic solvent approach[1]. Such a multi-scale method is well suited to compute $\Delta\Delta G$'s, as it requires reduced computational resources to simulate each single virtual system.

The aim of our "Grand Challenge" is to compute from our multi-scale approach, $\Delta\Delta G$ values corresponding to the interaction of two series of 14 different drugs developed by the pharmaceutical group Aventis-Sanofi with the serine protease factor Xa[2], a key enzyme involved in the activation cascade of the blood coagulation. This protein is thus considered as a target for the therapy of thrombosis-related diseases, a major cause of mortality in western countries.

For each $\Delta\Delta G$, we consider 40 intermediate virtual systems solvated in water. All the 28x40 simulations were performed in less than 32h on the supercomputer TERA100 system, by using only 4480 cores. Particularly encouraging results have been obtained: a true linear relation exists between our theoretical results and experimental $\Delta\Delta G$'s. Moreover, the accuracy of our method in computing $\Delta\Delta G$'s is <0.8 kcal mol^{-1}, a value close to that corresponding to the uncertainty of high level quantum methods.



The protein fXa (shown in gray) interacting with a potent ligand developed by Sanofi-Aventis[2].



Comparison of theoretical and experimental $\Delta\Delta G$'s (expressed in kcal mol^{-1})

This work paved the road towards high throughput dockir techniques, whose aim is to generate "*in silico*" new families of dru by knowing only their *in vivo* biological target (hence, a true *ab ini* approach). Such methods are expected to have a profound inciden in a near future on the way pharmaceutical researches are handle in particular, by exploring new therapeutic approaches, by reduci the cost of development of the future drugs, and by limiting tl testing on animals. Moreover, the intensive testing of drug affinity f protein target variants may also be readily performed using o approach, which will help the development of personaliz therapeutics.

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[1] Michel Masella et al., "Combining a Polarizable force-field and a coarse grained solvent model", J. Comput. Chem., **29** (2008) 1707 ; *ibid* , **32** (2011) 2664

[2] Marc Nazaré et al, "Probing the subpockets of factor Xa reveals two binding modes for inhibitors based on a 2-carboxyindole scaffold", J. Med. Chem., **48** (2005) 451