

On the use of Normal Mode Analysis in computer assisted drug design: applications to Enzymes and Receptors.

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The past few years, the interest in computer assisted drug design has considerably increased. Because of degrees of freedom, Ligand-Protein (and in a more extended manner Protein-Protein) docking studies can usually consider a fully flexible ligand but a quasi-completely rigid target; this feature limits the results of predictions in terms of binding sites, modes, or affinities.

One solution is to preliminary study the internal flexibility of the unbound target at the atomic level; molecular dynamics simulations (Mds) may appear as a method of choice but identifies only low amplitude motions; because ligand binding and the subsequent effects on target conformation are thought to also involve high amplitude motions, Normal mode analysis (Nma [1]) is another alternative.

Nevertheless, standard Nma is intrinsically limited by a quadratic approximation of the potential energy function which prevents to obtain realistic models of the studied protein along the computed normal modes. Recently, we described a protocol of energy minimizations under normal mode coordinates restraints [2] which overcomes this difficulty.

Presently, we will describe the wide range of applications of our approach through several examples:

- I. Ligand-protein docking in Matrix Metalloproteinases (MMP-s) [2]
- II. Protein-Protein docking between Thrombospondin and its receptor (TSP-1:CD-47)
- III. Conformational effects of ligand binding in Glucosamine-6P Synthase (Glms)

Discussion will open on the future developments and applications of such approaches, especially applied to G-Proteins Coupled Receptors (GPCRs).

- [1] Perahia, D. and Mouawad, L. (1995). Computation of low-frequency normal modes in macromolecules: improvements to the method of diagonalization in a mixed basis and application to hemoglobin. *Comput. Chem.* 19, 241-246.
- [2] Floquet, N., Marechal, J.D., Badet-Denisot, M.A., Robert, C.H., Dauchez, M. and Perahia, D. (2006). Normal mode analysis as a prerequisite for drug design: application to matrix metalloproteinases inhibitors. *FEBS Lett* 580, 5130-6.