UMG

dubium sapientiæ initium

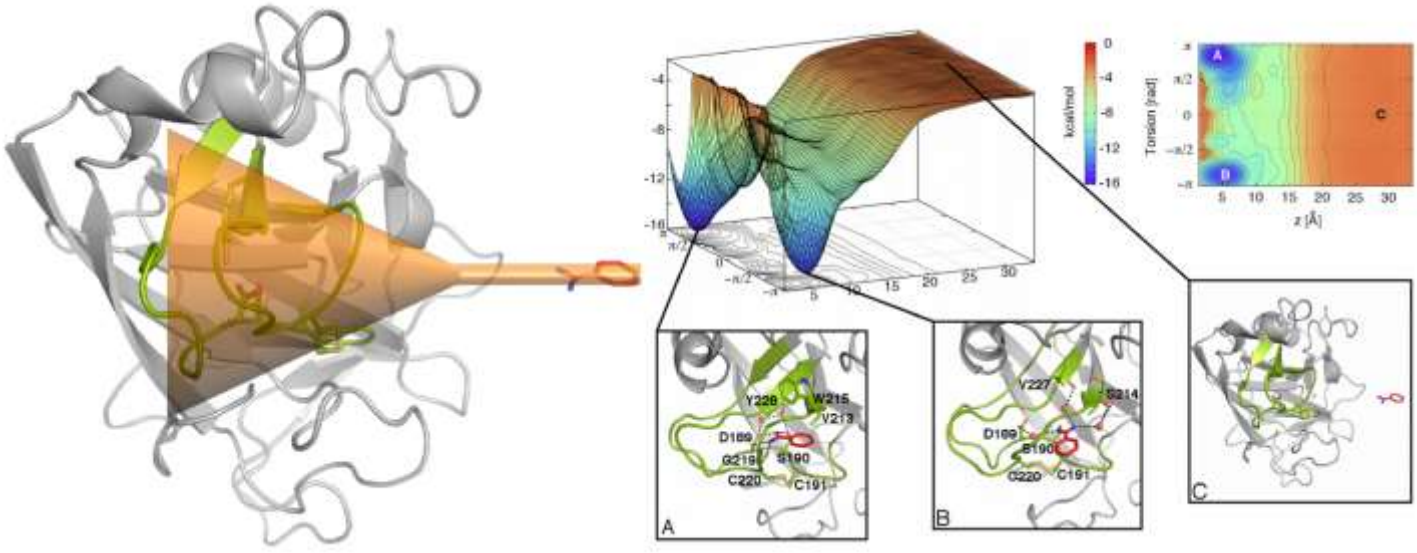
Università degli Studi *Magna Græcia* di Catanzaro
- Dipartimento di Scienze della Salute -
- Dottorato di Ricerca in Scienze della Vita -

SEMINARIO

Dr. Vittorio Limongelli

Dipartimento di Farmacia, Università "Federico II" di Napoli
vittoriolimongelli@gmail.com

"FUNNEL-METADYNAMICS: AN ACCURATE BINDING FREE-ENERGY METHOD"



Giovedì 24 aprile 2014, ore 15.30

University Club
Campus universitario "S.Venuta", Viale Europa, Catanzaro
Host: Stefano Alcaro – Dipartimento di Scienze della Salute - UMG

Abstract

Disclosing the events ruling the binding process of a drug to its target with an accurate estimation of their binding free energy is of great value to shed light on its mechanism of action and develop new medications (1,2,3). Here, I illustrate a new approach, called Funnel-Metadynamics (4), that fulfills both these aspects. Our method enhances the exploration of the ligand bound poses and its solvated states leading to an accurate estimation of the free-energy surface of the docking process and the calculation of the protein-ligand binding free energy. Two docking systems have been studied, benzamidine/trypsin and SC-558/COX-2. The latter one represents a particularly challenging case study characterized by the presence of protein motions, solvent effect and winding ligand pathways during the binding. In both cases, the x-ray conformation was found as the lowest energy pose and the computed binding free energy in good agreement with experiments. Furthermore, our approach allows also to unveil precious details of the docking process, such as the presence of alternative binding modes and the role of the solvent. The promising results achieved at limited computational cost makes this approach a most valuable tool in drug discovery as well as in other research fields, where calculating binding energy is important.

Finally, I will also illustrate our recent results in a complex DNA folding study (5) and our latest advances in combining enhanced sampling and coarse-grain methods to sample long time-scale events in very large systems at a reasonable computational cost.

References

1. Jorgensen WL. *Nature* **2010**, *466*, 42-43.

2. Limongelli V et al. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 5411-5416.

3. Limongelli V et al. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 1467-1472.

4. Limongelli V, Bonomi M, Parrinello M. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, 6358-6363.

5. Limongelli V et al. *Angew. Chem. Int. Ed.* **2013**, *125*, 2325-2329.