Modelling ligand binding and allostery in kinases and GPCRs with enhanced-sampling algorithms

Francesco L. Gervasio

Institute of Structural and Molecular Biology

University College London, UK

Allosteric regulation plays a fundamental role in biology. In signalling proteins such as protein kinases and G protein-coupled receptors (GPCRs), ligand binding to allosteric sites are able to up- or down-regulate the catalytic activity and activate downstream signalling cascades. Understanding the molecular mechanisms underlying the observed allosteric effects is of great importance for the rational design of novel biologically active allosteric regulators. One major challenge and opportunity in computational chemistry is the accurate description of the conformational landscape prior to and upon the binding of the allosteric regulator. To this aim we have developed, tested and successfully applied various enhanced sampling algorithms (based on Metadynamics and/or Hamiltonian replica exchange) together with atomistic simulations. Here we show how these methods were successfully used to compute complex conformational landscapes associated with kinase and GPCR activation and predict how they change in response to ligand binding and post-translational modifications.[1-8] We also show how atomistic simulations were used to reveal a previously unknown catalytic activity of glutamine synthetase.[9]

[1] L. Sutto & F L Gervasio* Effects of oncogenic mutations on the conformational free energy landscape of EGFR kinase *Proc Natl Acad Sci USA* **2013**, *110*, 10616-10621.

[2] A. Cavalli, A. Spitaleri, G. Saladino & F.L. Gervasio *Acc. Chem. Res.* **2015**, *48*, 277-285.

[3] T. D. Bunney, S. Wan, N. Thiyagarajan, L. Sutto, S. V. Williams, P. Ashford, H. Koss, M. A. Knowles, F. L. Gervasio, P. V. Coveney, M. Katan *EBioMedicine* **2015**, *2*, 194-204.

[4] E. Papaleo et al. *Chem. Rev.* **2016**, *116*, 6391-6423.

[5] V. Oleinikovas, G. Saladino, B. P. Cossins & F.L. Gervasio* *J. Am. Chem. Soc.* **2016**, *138*, 14257-14263.

[6] A. Kuzmanic, L. Sutto, G. Saladino, F.L. Gervasio*, A. Nebreda, M. Orozco Molecular mechanism of canonical activation of p38α MAP kinase *e-Life* **2017**, 6:e22175.

[7] N. Saleh, G. Saladino, F. L. Gervasio* & T. Clark* Investigating allosteric effects on the functional dynamics of β2-adrenergic ternary complexes with enhanced-sampling simulations *Chem. Sci.* **2017**, *8*, 4019-4026.

[8] L. C. Zanetti-Domingues et al. The architecture of EGFR's basal complexes reveals autoinhibition mechanisms in dimers and oligomers *Nat. Comm.* **2018**, *9*, 4325.
Page.

[9] G. Eelen et al. Glutamine Synthetase Regulates Vessel Sprouting by Modulating RHOJ *Nature* **2018**, *561*, 63-69.