SORS: Enhanced molecular dynamics to understand the structural and energetics determinants of MEK1 pathological mutations

Speaker: Chiara Pallara, BSC

Abstract: Protein kinases are key regulators of eukaryotic living cells, since they are involved in crucial biochemical functions and signalling networks. These enzymes share a common fold and can switch between distinctive inactive and active states in response to specific cellular signals. One relevant example is the MAPK/ERK cascade, which is involved in important cell processes like gene expression, cell proliferation, differentiation and apoptosis.

Dysregulation of MEK1/2, a key component of MAPK/ERK cascade, is known to cause several important pathologies. At least 15 activating mutations of MEK1/2 are associated with the CFC syndrome, while at least other 10 have been identified in several cancer types (*melanoma, lung and ovarian cancer*).

Understanding the effects of these mutations at molecular level could help to use MEK1 as potential target to develop personalized therapies for cancer and CFC-syndrome. Unfortunately, although both active and inactive MEK1 structures are already known, the detailed mechanism of MEK1 activation and the functional impact of CFC-syndrome related mutations are not yet clear.

During my talk I will summarize our recent findings on the intrinsic propensity for inactive-to-active transition in MEK1 WT and two CFC syndrome-related mutants (Y130C and Q56P), using state-of-the-art enhanced sampling methods such as Parallel Tempering metadynamics in Well-Tempered Ensemble (PT-metaD-WTE.

Biography: Chiara Pallara received her degree in Pharmaceutical Chemistry, at the University of Bologna in 2009.

In 2010, she joined the Protein Interactions and Docking Group, led by Juan Fernandez-Recio, as phD student. During her thesis she gained experience in theoretical chemistry and structural biology, especially in the fields of protein-protein docking and molecular dynamics methods.

Her main research line is currently focused on the development and optimization of computational protocols to integrate conformational flexibility into docking simulations for the characterization of protein-protein interactions. In addition she contributed to several multidisciplinary research projects involving the application of standard molecular dynamics simulations on different protein systems to understand the mechanistic effects of specific mutations, ligands binding or proteins association.

During the last three months, she performed a short-stay in the Biomolecular Modeling group led by Prof. Gervasio in the Department of Chemistry of UCL where she gained experience in enhanced molecular dynamics methods to sample rare events in bio-molecular systems.