

Computational Biophysics *Junior Group*

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Francesco L. Gervasio

Junior Group Leader

Francesco L. Gervasio was trained in physical chemistry and spectroscopy at the Molecular Spectroscopy Laboratory and the European Laboratory for Non-linear Spectroscopy, the *Università di Firenze* (Italy) from where he was awarded his MD in 1997.

Upon completing his civil service duties, he started a PhD in computational chemistry at *Università di Firenze*, studies which he continued at the International School for Advanced Studies in Trieste at the department of Statistical and Biological Physics. He received his PhD in Chemistry in 2002 and that same year he joined the Swiss National Supercomputer Centre as a Junior Scientist.

In 2004 he joined the group of M. Parrinello as a Post-doctoral Fellow at the *Eidgenössische Technische Hochschule* (ETH) in Zurich (Switzerland). In 2006 he was promoted as Assistant Professor in computational chemistry at the ETH. He was appointed as Professor (2006-2009) at the prestigious *Scuola Normale di Pisa* (Italy).

Gervasio joined the CNIO in February 2009 to lead the Computational Biophysics Group. He is an expert in molecular modelling and simulations and has developed effective algorithms to study large-scale protein dynamics and to predict the structure-activity relationship of drug-like molecules. He has authored 45 scientific papers in international journals which have been cited 1090 times thus far. His h-index is 19.

He received a Fellowship Award in Drug Design in 2002, participated in a Royal Society International Joint Project in 2006-2007, and has been collaborating with Sanofi-Aventis SA for three years. He is part of the Open PHACTS (an EU funded Innovative Medicines Initiative under the 7th Framework Programme) consortium on behalf of the CNIO.

Summary

Bio-macromolecules are by no means static and often undergo specific conformational changes to perform basic biological functions such as catalysis, regulation, transport and aggregation. Deregulation of conformational dynamics is linked to numerous diseases including cancer. Our goal is to understand the atomic details of the underlying dynamics linking specific oncogenic mutations to changes in activation mechanism(s) and how small drug-like molecules can counter these effects. To achieve this, we develop and apply advanced computational techniques and validate them using NMR and spectroscopy.

Strategic Goals

- Analyse the activation dynamics of proteins related to cancer
- Understand the role of induced folding and conformational selection in drug binding
- Develop advanced algorithms to increase the time and length scales of simulations





Staff scientist: Marco D'Abramo. **Post-doctoral fellows:** Neva Besker (since March), Jaroslaw Juraszek (until June) and Ludovico Sutto. **Graduate student:** Ilaria Mereu.

Highlights

Epidemiological evidence suggests a connection between inflammation and a predisposition for the development of cancer, i.e. long-term inflammation leads to the development of dysplasia. In the clinic non-steroidal anti-inflammatory drugs are widely used for the treatment of inflammation, pain, and cancer. These drugs inhibit cyclooxygenase enzymes (COXs), however, the non-selective inhibition of the different isoforms, in particular COX-1, causes toxicity and associated side effects (ulcers, prolonged bleeding time, kidney problems). Thus a selective inhibition of COX-2 is desirable and the necessity to better understand the molecular basis of selective inhibition, critical.

Using an advanced computational technique we simulated the full dissociation process of a highly potent and selective COX inhibitor SC-558, in both COX-1 and COX-2 enzymes (Figure). We found an alternative binding mode in COX-2 that is not present in COX-1 that has not been reported to date. Our finding explains the disparity in residence times within the two isoforms and the complex time-dependent inhibition exhibited by this class of inhibitors.

This novel free energy-based approach has allowed us to illuminate the highly dynamical character of the ligand/protein recognition process, explaining a wealth of experimental data and paving the way to an innovative strategy for designing new COX inhibitors with tuned selectivity.

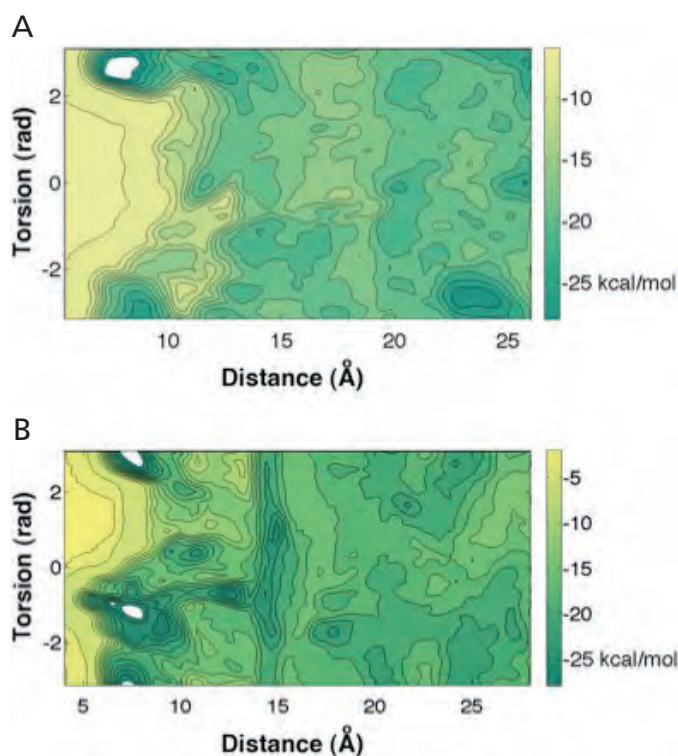


Figure: Free-energy surface (FES) of binding of SC-558 to COX1 and COX2, calculated as a function of the distance from the binding pocket and the angle of approach. The iso-contours are one kcal/mol each. In the FES of Cox1 (A) there is only one main free-energy minimum corresponding to the crystallographic structure, while in Cox2 (B) there are two.

Publications

Limongelli V, Bonomi M, Marinelli L, Gervasio FL, Cavalli A, Novellino E, Parrinello M (2010). Molecular basis of cyclooxygenase enzymes (COXs) selective inhibition. *Proc Natl Acad Sci USA* 12, 5411-5416.

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Fidelak J, Juraszek J, Branduardi D, Bianciotto M, Gervasio FL (2010). Free-energy-based methods for binding profile determination in a congeneric series of CDK2 inhibitors. *J Phys Chem B* 114, 9516-9524.