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How conformational dynamics descriptors may help in remodeling of allosteric regulation in proteins

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Allostery controls nearly all biological processes, and it has been declared by Monod to be "the second secrete of life" after the genome. This universal phenomenon in nature represents a target response on a perturbation (e.g. a ligand binding) leading to a functional change at the target through alteration of the structure or dynamics. Such an event can be described in terms of a large-scale transmission of information between residues. This concept is the cornerstone of our method MONETA that delivers descriptor encoding of the communication network in a protein. Using MONETA, we described the allosteric regulation of several proteins involved in cell signalling. Studying the receptors tyrosine kinases (RTKs), KIT and CSF-1R, and their numerous clinically-relevant mutants, we showed that the allosteric communications between the major regulating fragments in the native proteins were disrupted by the gain-of-function mutations. The diverging impact of equivalent mutations on communication in homologue RTKs permits us to distinguish between the mutation-induced effects that lead to the constitutive activation of KIT and the mutation-induced effects promoted the resistance in CSF-1R. In STAT5s, RTK downstream signalling proteins, we showed the sequence-dependent asymmetry in the STAT5s' communications and their different responses to phosphorylation. Our recent study provided a fascinating illustration of how the binding of agonist ligands controls intrinsic conformational dynamics in human NMDA receptors that stabilize the channel opening. The allosteric binding sites, which were identified by a pocket search at the proteins surface adjacent to the communication pathway, may constitute valid targets for the development of inhibitors able to modulate the function-related communication properties of a protein. Such communication-inspired and communication-targeted modulation may selectively block several activation or post-transduction processes. Our work opens the way to novel and rational strategies for the definition of targets, and the development of efficient target-specific inhibitors.

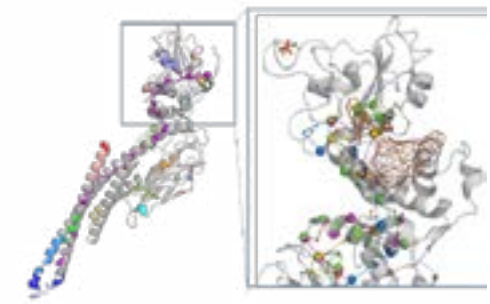

Figure1: *Communication pathway in STAT5 (left) and location of pockets at the protein surface adjacent to the communication pathway (right).*

Biography

Luba Tchertanov is a Research Director at CNRS-France, leader of the Bioinformatics, Molecular Dynamics and Modeling (BiMoDyM) team in Centre Mathématiques et leurs Applications (CMLA-CNRS) at the Ecole Normale Supérieure (ENS) de Cachan. She has multidisciplinary high-level skills, with extensive experience in structural biology, molecular modelling and numerical simulation (more than 100 papers in peer-reviewed journals). She coordinated or contributed as team-leader to different research projects (CEE, ANR, Fondation de France, OSEO, SIDACTION) and industrial contracts (LIPHATECH, the SERVIER Institute, the Pierre FABRE Laboratory, UNILIVER). The research topics are focused on exploration of protein structure–dynamics–function relations. In particular, she is working at the mechanisms of the receptors activation, the mechanisms of resistance to inhibitors, the conformational plasticity and dynamics of inter-molecular interactions and molecular recognition. She is specifically interested in description of allosteric regulation at an atomistic level. Important part of research is dedicated to the development of new methodology and computing tools for description of proteins dynamics.

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