PROPOSITION DE SUJET DE THESE
Campagne 2018/2019

Cible : étudiants Chinois à des thèses à l'ENS de Lyon
Diffusion : en Chine, via la plateforme du CSC

ECOLE DOCTORALE CHIMIE

TITRE DU SUJET DE RECHERCHE : Tracking allosteric signals with network analysis

Research team/Equipe de recherche : Theoretical Chemistry
http://www.ens-lyon.fr/CHIMIE/recherche/Teams/Chimie_Theorique

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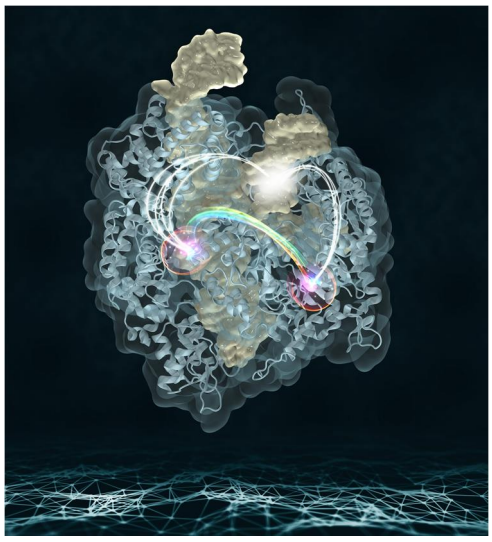
Lab Language/ Langue de travail: ENGLISH

Abstract/Présentation du sujet :
Allostery is a physico-chemical phenomenon that regulates protein structure, flexibility and functions by signal transmission across nanometer distances within (or between) proteins or DNA/RNA-protein complexes. Allosteric signal transduction is ubiquitous in biological systems and regulates essential biochemical pathways. Understanding allosterism at the atomistic level is crucial for controlling protein functions, providing roadmaps for the new developments in drug discovery and enzyme engineering.

Our team has performed several computational investigations in synergy with experimental biophysical studies, providing important insights into allosteric mechanisms of relevant biological systems, including a V-type allosteric enzyme [1-4], and a DNA-nuclear receptor complex. [5] In particular, community analysis of dynamical protein networks, based on mutual information of correlated protein motions obtained by classical molecular dynamics simulations [1], have been succesfully implemented to track allosteric signal transduction. The community network analysis method has allowed to identify allosteric drugs and protein mutants inhibiting the catalytic activity of an allosteric enzyme [4] and to reproduce (and propose new) mutagenesis experiments targeting fundamental transcriptional activities [5]. More recently, this methodology has been applied to the CRISPR-Cas9 system (a DNA/RNA-proteins complex), with the aim of obtaining insights on the allosteric mechanism of this genome editing machinery with leading-edge impact in life sciences.[6]



Schematic representation of allostery in a genome editing machinery as elucidated from information network analysis

In this project, network analysis techniques alternative to community partitioning based on betweenness centrality measure will be explored in order to develop apposite centrality measures to access straightforward recognition of allosteric spots (amino acid residues or secondary structure elements) and predict allosteric modulation by point mutagenesis and allosteric drug binding. The network analysis will be based on extensive classical molecular dynamics simulations using standard and accellerated MD techniques. For benchmark purposes, the first biological targets will be those for which an allosteric mechanism has been already revealed (i.e. the V-type allosteric enzyme and the DNA-nuclear receptor complex).[1-5] Then, the proejct will focus on the unknown aspects of CRISPR-Cas9 allostery, with the aim of understanding the allosteric mechanisms of protein mutants, driven by the imperative need of rational Cas9 engineering, which is currently based on randomized mutagenesis [7].

We seek for highly motivated students interested in this multidiscplinary project, mainly grounded on computational chemistry but with strong overlap with biology/biophysics, physical-chemistry and applied mathematics. Excellent command of both written and spoken English is required as well as aptitude for teamwork and for collaborations with international theoretical and experimental research groups.

References:

[1] I. Rivalta, M. M. Sultan, N.-S. Lee, G. A. Manley, J. P. Loria, V. S. Batista, *Proc. Natl. Acad. Sci. USA* 109 (**2012**) 1428.
[2] G. A. Manley, I. Rivalta, J. P. Loria, *J. Phys. Chem. B*. 117 (**2013**) 3063.
[3] G. P. Lisi, G. A. Manley, H. Hendrickson, I. Rivalta, V. S. Batista, J. P. Loria, *Structure* 24 (**2016**) 1155.
[4] I. Rivalta, G. P. Lisi, N.-S. Snoeberger, G. A. Manley, J. P. Loria, V. S. Batista, *Biochemistry* 55 (**2016**) 6484
[5] C. G. Ricci, R. L. Silveira, I. Rivalta, V. S. Batista, M. S. Skaf, *Sci Rep.* 6 (**2016**) 19940.
[6] G. Palermo, C. G. Ricci, A. Fernando, R. Basak, M. Jinek, I. Rivalta, V. S. Batista, J. A. McCammon *J. Am. Chem. Soc.* 139 (**2017**) 16028
[6] B. L. Oakes et al. *Nat Biotechnol*. 34 (**2016**) 646

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