**PhD PROPOSAL FOR THE**

**PASTEUR - PARIS UNIVERSITY INTERNATIONAL DOCTORAL PROGRAM**

Time for applicants to contact host laboratories: September 13 – November 2, 2017

Deadline for full application: November 13, 2017

Interviews: January 30, February 2, 2018

Start of the Ph.D.: October 1, 2018

**Title of the PhD project:** Structural Dynamics of Macromolecular Complexes

**Keywords:** Mass Spectrometry, Electron Microscopy, Computer Modeling, Macromolecular Complexes.

**Department:** Department of Structural Biology and Chemistry

**Name of the lab:** Structural Bioinformatics Unit

**Head of the lab:** Prof. Michael Nilges

**PhD advisors:** Dr. Riccardo Pellarin,Prof. Michael Nilges.

**Email address:** michael.nilges@pasteur.fr, riccardo.pellarin@pasteur.fr

**Web site address of the lab:** https://research.pasteur.fr/en/team/structural-bioinformatics/

***Doctoral school affiliation and University*:** Complexité du vivant, Université Paris-6

Presentation of the laboratory and its research topics:

The Structural Bioinformatics Unit at Institut Pasteur is involved in a large variety of projects, including (i) approaches for determination of protein structures and protein assemblies from experimental data, (ii) exploration of protein conformational space using molecular mechanics, molecular dynamics and enhanced sampling approaches, (iii) search of compounds inhibiting functions of bacterial enzymes or ligand-gated receptors, (iv) software development for molecular modeling.

Description of the project:

Macromolecular assemblies are nano-machines that carry out essential cellular processes. A thorough understanding of the structure and the dynamics of these biological systems has vast implications on our health. Yet, macromolecular assemblies are difficult to characterize. Structural and compositional heterogeneity, as well as the transiency of interactions, can hinder characterization using traditional structural biology methods. Integrative methods that employs chemical cross-linking coupled with mass spectrometry (XL-MS) and Electron Microscopy (EM) have been successfully adopted to study the static architecture macromolecular assemblies. Presently, there is a lack of a general methodology which rigorously include static and dynamic information. In this project, the PhD candidate will jointly use XL-MS data and low-resolution EM data acquired on intermediates to infer structural changes. The method, developed within the open source Integrative Modeling Platform (https://integrativemodeling.org), will be applied to model the biogenesis of the eukaryotic Ribosome, as well as the assembly pathway of the bacterial Type 6 Secretion System.

References:

[1] A. B. Ward, A. Sali, and I. A. Wilson, “Integrative Structural Biology,” *Science*, vol. 339, pp. 913–915, 2013.

[2] F. Alber, et al. “Determining the architectures of macromolecular assemblies,” *Nature*, vol. 450, pp. 683–694, 2007.

[3] D. Russel, et al. “Putting the Pieces Together: Integrative Modeling Platform Software for Structure Determination of Macromolecular Assemblies,” *PLoS Biol*, vol. 10, p. e1001244, 2012.

[4] W. Rieping, M. Habeck, and M. Nilges, “Inferential structure determination.,” *Science*, vol. 309, pp. 303–306, 2005.

[5] J. P. Erzberger, et al. “Molecular Architecture of the 40S⋅eIF1⋅eIF3 Translation Initiation Complex.,” *Cell*, vol. 158, pp. 1123–1135, 2014.

[6] Y. Shi, et al. “Structural characterization by cross-linking reveals the detailed architecture of a coatomer-related heptameric module from the nuclear pore complex.,” *Molecular & Cellular Proteomics*, vol. 13, pp. 2927–2943, 2014.

[7] K. S. Molnar, et al. “Cys-Scanning Disulfide Crosslinking and Bayesian Modeling Probe the Transmembrane Signaling Mechanism of the Histidine Kinase, PhoQ.,” *Structure*, vol. 22, pp. 1239–1251, 2014.

[8] S. Hanot et al., "Multi-scale Bayesian modeling of cryo-electron microscopy density maps" http://www.biorxiv.org/content/early/2017/03/04/113951

Expected profile of the candidate:

Programming skills (for instance, C, C++, python, CUDA), usage of Linux-based operating system. Knowledge of statistics, Bayesian probability, statistical mechanics and dynamical models is desirable. Good level of spoken and written English, ability to work in team. Willing to work in an experimental lab is a plus.

Contact:

Michael Nilges

Institut Pasteur, and CNRS UMR 3528, Unité de Bioinformatique Structurale,

25 rue du Dr Roux, 75015 Paris, France

E-mail address: michael.nilges@pasteur.fr

Riccardo Pellarin

Institut Pasteur, and CNRS UMR 3528, Unité de Bioinformatique Structurale,

25 rue du Dr Roux, 75015 Paris, France

E-mail address: riccardo.pellarin@pasteur.fr