M2 Internship
Supported by the Société Française des Microscopies

Responsible for internship

Name: Slavica JONIC

Location : IMPMC - 4 place Jussieu, 75005 Paris – Tower 22/23, Office 5.0.5

Group: Bioinformatique et Biophysique (BiBiP)

E-mail: slavica.jonic@upmc.fr

Telephone : +33 (0)1 44 27 72 05

Website: http://www.impmc.upmc.fr/~jonic

Internship topic: Development of a new cryo-electron tomography image analysis approach to conformational variability of biomolecular complexes

Recent progress in instrumental and software developments for cryo-electron microscopy (cryo-EM) has allowed near-atomic structural resolution of various biomolecular complexes from single particle analysis (SPA) [1] and electron tomography (ET) [2] images. One of the main current cryo-EM challenges is the data interpretation in terms of continuous conformational changes of complexes (an uncountable number of intermediate conformational states) contrary to the traditional description of the conformational variability in terms of discrete conformational changes (a countable number of conformational states) [3]. Different conformations can coexist and their individual characterization is crucial to understand the functional mechanisms of complexes and develop new drugs. While a few methods have already been developed to interpret SPA data in terms of continuous conformational variability, no method is currently available to describe this type of variability from cryo-ET data. The goal of this internship is to establish the basis of a methodology for analyzing continuous conformational changes of complexes by analyzing cryo-ET volumetric data. The internship will be done in the group that pioneered the development of SPA cryo-EM approaches to continuous conformational variability [4, 5]. Our HEMNMA methodology interprets the conformation in each cryo-EM single particle image by comparing this image with 2D projections of a 3D reference model deformed using Normal Mode Analysis (a molecular mechanics simulation method) and it has been used with complexes of various sizes and architectures [4].

The M2 student will work on establishing the basis for extending HEMNMA [4] to cryo-ET data, to allow analyzing subvolumes of 3D cryo-ET reconstructions (each subvolume containing a complex) in terms of continuous conformational variability of complexes. This new approach will be partly based on tools that we developed to analyze conformational variability from a set of EM density maps [5]. As these previous methods, the new methods will be integrated in Scipion (http://scipion.i2pc.es), open-source software platform developed and maintained by the EU Instruct I2PC center (Madrid, Spain) and used extensively in 3D cryo-EM field. The new methods will be tested with synthetic and experimental data. Regarding the experimental test data, we have a possibility to collect cryo-ET data of a solution with Tomato Bushy Stunt Virus particles for which a continuum of conformations can be obtained by a change in pH or by removing Ca2+ ions from the interface between the domains of the capsid, as we showed in [4]. Also, we have a possibility to use already available cryo-ET data, collected by collaborators. For instance, through this project, we will establish collaboration with Dr Amélie Leforestier (Laboratoire de Physique des Solides, UMR 8502, Orsay) and Dr Mikhail Eltsov (Buchmann Institute for Molecular Life Sciences, Frankfurt am Main, Germany) regarding conformational variability of the nucleosome, following their recent cryo-ET studies of the nucleosome

conformational variability *in vitro* and *in situ* [6].

This internship could be followed by a PhD thesis on *in situ* cryo-ET data processing in which image analysis strategies based on molecular mechanics simulations will be compared with deformation modeling approaches originally developed for computer vision and medical imaging (e.g., optical flow approaches) as well as in which machine learning approaches (e.g., deep learning neural networks) will be used to accelerate data processing.

References:

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2. Schur, F.K., Obr, M., Hagen, W.J., Wan, W., Jakobi, A.J., Kirkpatrick, J.M., Sachse, C., Krausslich, H.G., and Briggs, J.A. (2016). An atomic model of HIV-1 capsid-SP1 reveals structures regulating assembly and maturation. Science *353*, 506-508.
3. Jonic, S. (2017). Computational methods for analyzing conformational variability of macromolecular complexes from cryo-electron microscopy images. Curr Opin Struct Biol *43*, 114-121.
4. Jin, Q., Sorzano, C.O., de la Rosa-Trevin, J.M., Bilbao-Castro, J.R., Nunez-Ramirez, R., Llorca, O., Tama, F., and Jonic, S. (2014). Iterative elastic 3D-to-2D alignment method using normal modes for studying structural dynamics of large macromolecular complexes. Structure *22*, 496-506.
5. Sanchez Sorzano, C.O., Alvarez-Cabrera, A.L., Kazemi, M., Carazo, J.M., and Jonic, S. (2016). StructMap: Elastic Distance Analysis of Electron Microscopy Maps for Studying Conformational Changes. Biophys J *110*, 1753-1765.
6. Eltsov, M., Grewe, D., Lemercier, N., Frangakis, A., Livolant, F., and Leforestier, A. (2018). Nucleosome conformational variability in solution and in interphase nuclei evidenced by cryo-electron microscopy of vitreous sections. Nucleic Acids Res *46*, 9189-9200.

Techniques involved: Image analysis methods development, molecular mechanics simulation, statistical analysis, cryo-electron tomography

Paid internship: Yes

Can this internship be continued for a PhD? Yes

If yes, type of PhD funding envisaged is: TBD

Unité mixte de recherche 7590
Campus Pierre et Marie Curie – Tours 22 et 23 – BC 115
4 place Jussieu – 75252 Paris Cedex 5 – France
Tél. : +33 (0)1 44 27 52 17 – hwww.impmc.upmc.fr