Internship project Master M2

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Title: Development of a new cryo-electron tomography (cryo-ET) image analysis approach to conformational variability of biomolecular complexes

Goals: Development of a methodology for analyzing continuous conformational changes of biomolecular complexes by analyzing cryo-ET volumes

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. This progress has made cryo-EM competitive with X-ray crystallography that used to be the primary structural biology technique. To study structures by X-ray crystallography, good quality crystals are required, which is often difficult to obtain for large and flexible complexes. Contrary to X-ray crystallography, cryo-EM does not require the crystallization of complexes. In SPA, a sample containing many isolated copies of the same complex at random and unknown orientations in vitreous ice is imaged untilted in the electron microscope and the orientations and centers of each complex (3 unknown Euler angles and 2 unknown shifts per complex) must be determined computationally in order to reconstruct the 3D structure from images. In ET, a sample that can be a part of the cell or a mixture of isolated multiple copies of a complex is imaged tilted, by covering a range of known tilt angles (2 Euler angles known per image), leading to a reduced number of parameters to determine computationally with respect to SPA and a more straightforward 3D reconstruction from images. In 2015, cryo-EM was recognized "Method of the Year" by the Nature Methods journal and, in 2017, cryo-EM development was honored by a Nobel Prize to three cryo-EM scientists.

Although cryo-EM is now a standard structural biology technique, challenges still exist. One of them is the problem of interpreting cryo-EM data in terms of continuous conformational changes of complexes (conformational changes with an uncountable number of intermediate conformational states) contrary to the traditional description of the conformational variability in terms of discrete conformational changes (conformational changes with a countable number of intermediate states). The conformational changes are linked to biological functions of complexes (e.g., protein synthesis, cellular transport, etc.). To achieve these functions, the complexes undergo large conformational transitions. Different conformations can coexist and their characterization is crucial to understand the functional mechanisms and to develop new drugs.

While a few methods have already been developed to interpret SPA data in terms of continuous conformational variability of complexes, no method is currently available to describe this type of conformational variability from cryo-ET data.

The internship project will be done in the cryo-EM group that pioneered the development of SPA approaches to continuous conformational variability. Their Hybrid Electron Microscopy Normal Mode Analysis (HEMNMA) methodology interprets the conformation in each cryo-EM single particle image by comparing it with 2D projections of a 3D reference model deformed using Normal Mode Analysis (a method for molecular mechanics simulation) and it has been used with complexes of various sizes

and architectures [3, 4]. It has first been incorporated in Xmipp (http://xmipp.cnb.csic.es) and it is currently also available in Scipion (http://scipion.i2pc.es), two open-source software platforms developed and maintained by the EU Instruct I2PC center (Madrid, Spain) and used extensively in 3D cryo-EM field.

A long-term goal of the group is to develop a HEMNMA-like methodology for analyzing subvolumes of 3D cryo-ET reconstructions (each subvolume containing a complex) in terms of continuous conformational variability of complexes. This M2 internship project will be focused on establishing the basis for extending HEMNMA to cryo-ET data. The methods developed during this project will be validated using synthetic and experimental data. This research can be continued in the framework of a PhD thesis in which image analysis strategies based on molecular mechanics simulations could be compared with other possible strategies such as those based on the 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) could be used to accelerate data processing.

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