Internship project Master M2

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

Goals: Improvements of a cryo-EM data analysis methodology for analyzing continuous conformational changes of biomolecular complexes

Recent progress in instrumental and software developments for single-particle cryo-electron microscopy (cryo-EM) has allowed near-atomic structural resolution of various biomolecular complexes [1-3]. This progress has made cryo-EM competitive with X-ray crystallography that used to be the primary high-resolution 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 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.

The internship project will be done in the cryo-EM group that pioneered the development of image analysis 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 (NMA, which is a method for molecular mechanics simulation) and it has been used with complexes of various sizes and architectures [4, 5]. 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 improve HEMNMA methodology, including its acceleration using machine learning approaches (e.g., deep learning neural networks) and combining NMA with other molecular mechanics simulation methods such as Molecular Dynamics (MD) simulation. This M2 internship project will be focused on accelerating HEMNMA using machine learning approaches and its combination with MD simulations. 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 (to be implemented), such as those based on the deformation modeling approaches originally developed for computer vision and medical imaging (e.g., optical flow approaches).

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