Master 2 Internship

Exploring Heterogeneous Reconstruction in Cryo-EM with deep learning approaches: A Study on Fmoc-FFY Tripeptide Nanofibers

In the past decade, cryo-electron microscopy (cryo-EM) has emerged as a pivotal technique for obtaining atomic-scale molecular models. This method involves capturing multiple 2D projections of a 3D sample from various angles, which are then amalgamated to reconstruct its 3D structure (Fig. 1). Deep learning approaches can be used for this task (see [1] for a review). While homogeneous reconstruction [5, 2] assumes a single conformation, heterogeneous reconstruction [4, 3] considers conformational variations, offering a more comprehensive and adaptable perspective. While cryo-EM is mainly used in structural biology, our goal is to apply heterogeneous reconstruction to a self-assembled modified tripeptide, Fmoc-FFY (where Fmoc represents fluoromethoxycarbonyl, F stands for phenylalanine, and Y denotes tyrosine), known for forming nanofibers in water. It presents unique challenges due to the distinctive properties of peptides: they are more flexible than proteins (introducing additional noise) and have relatively small helicoidal parameters, limiting available information. The obtained results will impact our comprehension of catalytic pockets that arise from the self-assembly of peptides and may lead to a more suited design of hydrogelators. In the absence of state-of-the-art methods dedicated to our data, our strategy involves adapting techniques used in structural biology, which will unfold in two distinct phases.

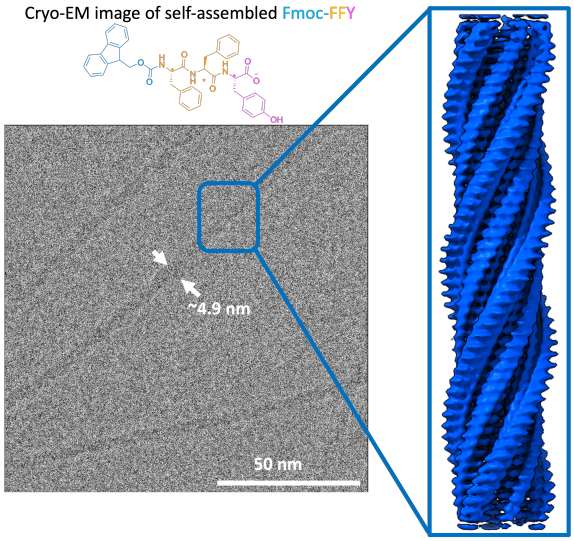

Figure 1: Example of a cryo-EM image (left) and of its 3-D reconstruction obtained with an homogeneous reconstruction [2].

Phase 1: Testing Heterogeneous Reconstruction Methods in Cryo-EM

The primary goal of the first phase of the internship is to test various cryo-EM Heterogeneous reconstruction methods such as cryoSPARC [4] and cryoFIRE [3]. The intern will use our dataset composed of two thousands of images to reconstruct the structure with possibly different conformations. It will evaluate their effectiveness and suitability for this type of data.

Phase 2: Adapting the Most Promising Method to our data

In the second phase of the internship, the intern will focus on the most promising reconstruction method

identified during the first phase. The intern will adapt this method, considering the peculiarities of helical assemblies. A possibility is to introduce this prior in the latent representation of a Variational Auto-encoder. There is a significant interest in exploring how geometrical priors can be integrated into deep neural networks. It will allow us to further enhance the accuracy and efficiency of cryo-EM reconstruction methods. This perspective aligns with the need to improve the robustness of reconstruction techniques, especially for complex structures like helical assemblies.

Working environment

The intern will be a member of the IMAGeS team (`http://images.icube.unistra.fr/`) in the ICube laboratory in Illkirch. The internship will begin between January and May 2024, for a period of 6 months. Supervisors: Alexis Bigo - - Simon (Post-doctoral researcher, `abigosimon@unistra.fr`), Denis Fortun (CNRS researcher, `dfortun@unistra.fr`), Sylvain Faisan (Assistant Professor , `faisan@unistra.fr`).

Profile of the candidate

We are seeking a motivated M2-level student enrolled in a program specializing in computer science, machine learning and deep learning. Proficiency in the programming language Python is required. An interest in biology and microscopy would be advantageous but is not required. The successful candidate will work closely with our team, benefiting from collaboration with chemists and physical chemists.

Application

Send a CV and a short description of your motivation, as well as the transcript of marks for the past 2 years to Alexis Bigo - - Simon (`abigosimon@unistra.fr`), Denis Fortun (`dfortun@unistra.fr`), and Sylvain Faisan (`faisan@unistra.fr`).

References

[1] C. Donnat, A. Levy, F. Poitevin, E. D. Zhong, and N. Miolane. Deep generative modeling for volume reconstruction in cryo-electron microscopy. *Journal of Structural Biology*, 214(4):107920, 2022.

[2] S. He and S. H. Scheres. Helical reconstruction in relion. *Journal of Structural Biology*, 198(3):163–176, 2017.

[3] A. Levy, G. Wetzstein, J. N. P. Martel, F. Poitevin, and E. D. Zhong. Amortized inference for heterogeneous reconstruction in cryo-em. *Advances in neural information processing systems*, 35:13038–13049, 2022.

[4] A. Punjani, J. L. Rubinstein, D. J. Fleet, and M. A. Brubaker. cryosparc: algorithms for rapid unsupervised cryo-em structure determination. *Nature methods*, 14(3):290—296, March 2017.

[5] S. H. Scheres. Relion: Implementation of a bayesian approach to cryo-em structure determination. *Journal of Structural Biology*, 180(3):519–530, 2012.