Modeling, inverse problems and machine learning in cryogenic microscopy using three-dimensional tomography

PhD proposal, CREATIS, Lyon, France

The CREATIS laboratory announces the opening of a 36-month, fully funded PhD position starting in September 2025.

Keywords Image Reconstruction, Cryogenic Electron Tomography, Modeling, Deep Learning, Computational Imaging, Optimization.

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Description

Motivation: Cryo-electron tomography (cryo-ET) is an imaging technique that visualizes biological molecules and intracellular structures in their original 3D environment at nanometer resolution. Unlike other methods for determining protein structure, which require molecules to be isolated or crystallized, cryo-ET captures the entire intracellular context that is crucial for understanding biological function. It bridges the gap between molecular imaging and whole-cell analysis, offering a view into cellular organization and dynamics [1].

Reconstruction problem: In practice, biological samples are vitrified (rapidly frozen) and exposed to an electron beam to obtain measurements at a given sequence of tilt angles, see Figure 1. The acquisition model is relatively well understood from a mathematical point of view, and can be modeled by observing $N_\theta \in [40, 60]$ images v of size $n \times n$:

$$v = \mathcal{P}(A(u)) \tag{1}$$

where A is the tomography operator describing the microscope, $u \in \mathbb{R}^{n\times n\times n}$ is the volume density to be reconstructed and $\mathcal{P}$ is a perturbation term (e.g. additive Gaussian noise, Poisson noise, deformation operator). Recovering the volume u from observations described by the equation (1) faces a number of problems:

1. Noise: the sample deteriorates with each exposure, limiting the electron dose and resulting in a very poor signal-to-noise ratio, see Figure 2a.
2. The missing angles: the sample can only be rotated between -60° and +60° in the best of cases. The A acquisition operator then has a kernel that is precisely characterized in the Fourier domain by a wedge of unobserved frequencies of the three-dimensional volume.

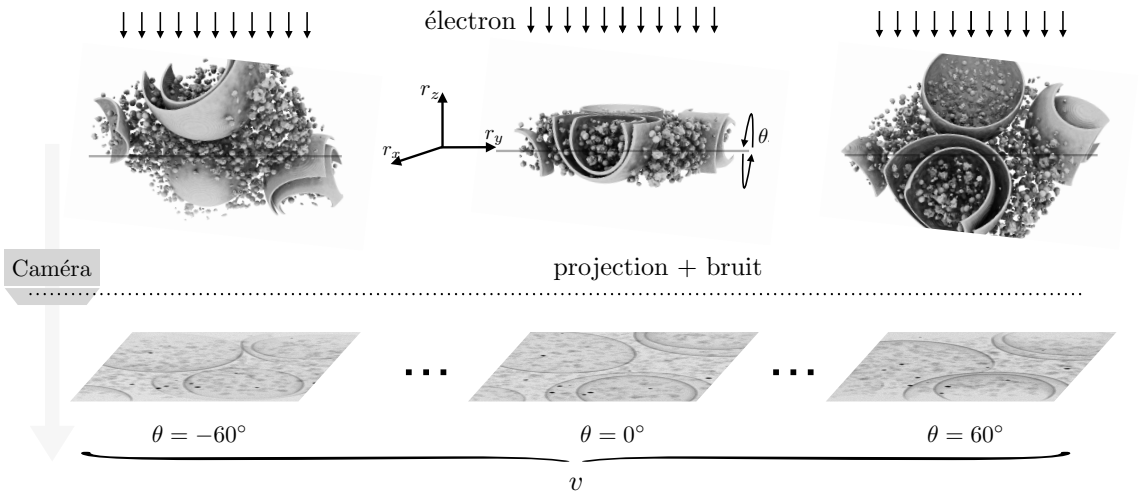
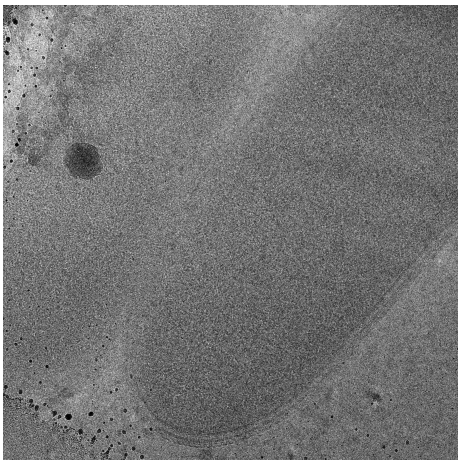
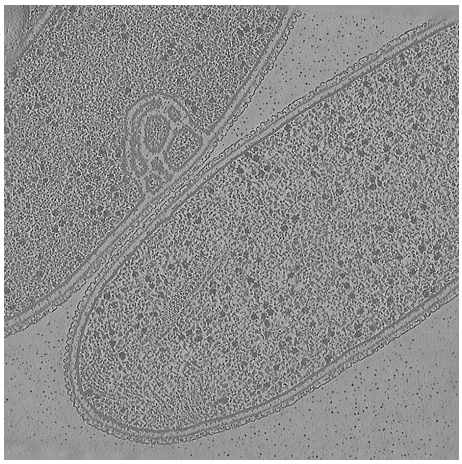


Figure 1: Illustration of the cryo-ET acquisition process.



(a) Observed projection at tilt -40°.



(b) Central plane of the state-of-the-art reconstruction (>5h for an expert).

3. Data size: the measurements obtained typically consist of 40 to 60 images of size 4096×4096 pixels. The volume to be reconstructed can be represented by a grid of $4096 \times 4096 \times 2048$ pixels. Most of the advanced algorithms developed for 2-dimensional tomography are not applicable due to computational cost or memory requirements.

4. Modeling the forward operator A: to a first approximation, the acquisition operator can be considered as an integral along a line. However, to achieve the resolutions promised by new microscopes, it is necessary to take into account the influence of microscope voltage, sample thickness, precise noise terms, etc. These effects can be modeled mathematically. These effects can be modeled mathematically, but require the development of suitable reconstruction algorithms.

Cryo-tomography is a fast-growing technique whose reconstruction and analysis tools can still be perfected. The continuous improvement of these tools is aimed at refining the resolution of observed structures and automating particularly time-consuming analysis tasks. While deep learning has revolutionized many areas of image processing, its use in cryo-tomography remains limited.

Thesis project: In this thesis, we will develop reconstruction algorithms to improve the resolution of cryoET volumes. To achieve this, we will first focus on modeling the acquisition operator as finely as possible. This includes the diffraction induced by the sample [2] or the immense source of information available thanks to the new cameras [3].

These finer models will be incorporated into state-of-the-art reconstruction algorithms, using either standard algorithms or machine learning approaches. We will study the merits of the proposed methods first on simulations, then on real data.

Particular attention will be paid to the numerical efficiency of the algorithms, to enable the processing of large three-dimensional volumes without the need for excessive computational resources. Wherever possible, we will be sensitive to the mathematical motivation of the proposed methods.

Expected skills: To successfully complete this project, skills in mathematics, signal processing, machine learning and computer science are required. An understanding of the physics of the acquisition system and of the biological issues addressed by cryo-tomography will also be essential. No previous knowledge in physics or biology is required, but an interest in these topics will be highly appreciated.

The work carried out in this thesis will be supported by the expertise of the TOMORADIO host team, whose members are interested in other tomographic imaging modalities, particularly in medical imaging.

Environment: The thesis will be carried out at the CREATIS laboratory, at INSA Lyon, on the La Doua campus in Villeurbanne. CREATIS is a recognized multidisciplinary laboratory with extensive expertise in medical imaging, playing a key role in healthcare technologies. The diversity of skills present in the laboratory (physics, mathematics, computer science, etc.) makes it an ideal environment for an interdisciplinary thesis, where the tools developed can find applications in different imaging modalities.

Regular interaction with experimentalists will be essential to understand the phenomena that limit the quality of reconstructions in practice. These exchanges will involve teams in Lyon (INSA, ENS), Grenoble (EPN, IBS, CEA) and Basel, Switzerland (Biozentrum).

This thesis will build on preliminary work [4, 5] in the field. Access to real experimental data and to experts with the latest generation microscopes will be major assets.

The skills developed over the course of this thesis, in artificial intelligence and image processing applied to multidisciplinary issues (microscopy, medicine), will be easily exploited in both academic and industrial fields.

How to apply? Please send a curriculum, a motivation letter, and your academic records before **May 12th** to valentin.debarnot@creatis.insa-lyon.fr and voichita.maxim@creatis.insa-lyon.fr.

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