Keywork: Simulating the Cellular Context in Synthetic Datasets for Cryo-Electron Tomography

Antonio Martinez-Sanchez[1,2][0000−0002−5865−2138]

[1] AIKE, Department of Information and Communications Engineering, Faculty of Computer Sciences, Universidad de Murcia, Campus de Espinardo, Murcia 30100, Spain

[2] Biomembranes and Cell Signalling, Instituto Murciano de Investigación Biosanitaria (IMIB), Campus de Ciencias de la Salud, 30120 Murcia, Spain

anmartinezs@um.es

Abstract. Cryo-electron tomography enables the visualization of cellular structures at near-atomic resolution, but the lack of reliable ground truth limits the application of deep learning methods. The keywork paper [IEEE Trans. Med. Imaging 43(11):3742-54 2025] proposes a comprehensive framework to generate realistic synthetic datasets that simulate cellular environments. The approach models membranes, filaments, and macromolecular clusters using parametric and stochastic methods, producing diverse and biologically relevant volumetric data. These datasets are used to train deep learning models, demonstrating strong generalization to real tomograms and robustness to distortions. This paper provides a concise summary of the methods, results, and contributions of the original work.

Keywords: cryo-electron tomography · synthetic data · deep learning · image processing · scientific computing

1 Introduction

Cryo-electron tomography (cryo-ET) allows the reconstruction of three-dimensional (3D) cellular environments with high resolution. However, its analysis is challenging due to noise, distortions such as the missing wedge effect, and the absence of annotated ground truth data. This limitation hinders the effective use of deep learning methods for segmentation and analysis.

The original paper [1] addresses this problem by introducing a framework capable of generating realistic synthetic datasets that approximate cellular context. These datasets aim to support both deep learning training and quantitative biological analysis.

2 Methods

The proposed framework models the cellular context as a synthetic 3D density map composed of multiple biologically inspired structures. The methodology

combines deterministic geometric modeling with stochastic processes to generate diverse and realistic simulations.

The synthetic tomogram is defined as a density function over a volume of interest (VOI), where each voxel intensity corresponds to the electron density of structural components such as membranes, filaments, or macromolecules. The generation process follows three main steps: (i) Definition of structural models, (ii) stochastic parameter sampling and transformations, and (iii) iterative structure insertion under spatial constraints. This modular design enables flexible generation of complex cellular environments.

Membranes are modeled as parametric surfaces representing lipid bilayers. Each membrane is defined using geometric primitives such as spheres, ellipsoids, and tori. A double Gaussian profile is applied along the surface normal to simulate the bilayer structure observed in cryo-ET. The membrane geometry is controlled through parameters such as radius, thickness, and layer variance, allowing the generation of diverse membrane morphologies.

Filaments are represented as flexible polymers following helical trajectories. The model captures both curvature and torsion through parametric equations governed by the persistence length, which determines filament rigidity. Additionally, branching probability allows the construction of interconnected filament networks, mimicking cytoskeletal organization.

Macromolecules are modeled as discrete volumetric entities that can be either isolated or aggregated into clusters. The clustering process is governed by the self-avoiding worm-like chain (SAWLC) model, which ensures spatial coherence while preventing overlap. Two main configurations are considered: cytosolic macromolecules are randomly distributed within the volume, but membrane-bound macromolecules are constrained to membrane surfaces. The framework supports heterogeneous clusters composed of different macromolecule types, enabling realistic biological variability.

Structural parameters (e.g., radius, curvature, persistence length) are sampled from predefined statistical distributions. This allows the generation of a wide range of valid biological configurations. Each structural instance undergoes random rigid transformations.

The construction of the synthetic tomogram is achieved through iterative insertion of structures using a trial-and-error strategy. At each try, a candidate structure is generated and inserted only if it satisfies: no overlap with previously inserted structures, and full containment within the VOI. If these conditions are not met, the structure is regenerated. To ensure termination, a maximum number of insertion attempts is defined. For filament and cluster structures, insertion is sequential: each new unit depends on the previous one, enforcing continuity and structural coherence.

Although the focus is on structural realism, the framework optionally simulates key artifacts of cryo-ET acquisition and 3D reconstruction. Firstly, noise is modeled using Gaussian distributions to achieve target signal-to-noise ratios. Afterward, misalignment effects are introduced via random offsets in projection

images. Finally, missing wedge distortion is simulated through limited-angle projection and reconstruction.

Finally, the framework produces: synthetic 3D tomograms, ground truth annotations (label maps), and structural metadata (positions, orientations) for every feature. These outputs are suitable for training and evaluating deep learning models, particularly in semantic segmentation tasks.

3 Results

Fig. 1 illustrates how the simulated data reproduces main cellular features and key cryo-ET artifacts, including a high level of noise and the elongation effects and loss of information due to the missing wedge. In addition, the framework can generate highly crowded environments with controlled occupancy levels.

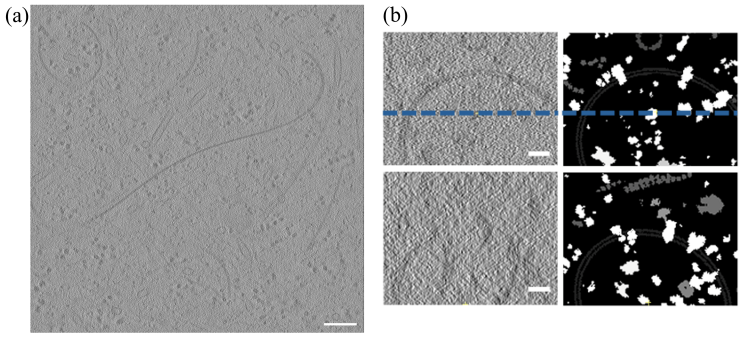


Fig. 1. (a) Reconstructed synthetic tomogram and (b) comparison with its corresponding simulated ground truth (b) (taken from the original paper). Scale bars: (a) 200 nm and (b) 20 nm.

The synthetic datasets are used to train an nnU-Net [2] model for the semantic segmentation of main cellular features at a single nanometer resolution. Fig. 2 demonstrates that the trained model generalizes well to real cryo-ET data, successfully identifying membranes, filaments, and macromolecules despite being trained exclusively on synthetic data.

4 Discussion

This paper summarizes the work of Martinez-Sanchez et al. [1], which introduces a flexible and realistic framework for generating synthetic cryo-ET datasets. The proposed approach successfully models cellular structures and produces data suitable for training deep learning algorithms.

The study shows that a realistic simulation of low-order cellular structures is sufficient to train deep learning models capable of generalizing to real data.

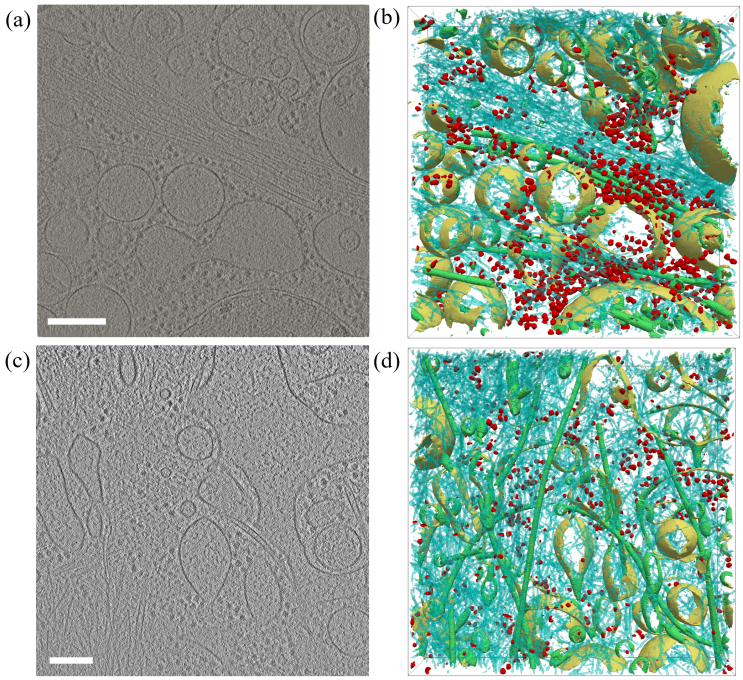


Fig. 2. Segmentation results obtained from real data using a U-Net model trained only on synthetic data (taken from the original paper). (b) is the segmentation of the tomogram (a), and (d) is the segmentation of (c). Scale bars 200 nm.

Notably, the model recovers structures affected by missing wedge distortions, filament representations generalize beyond specific types, and synthetic data enables training without manual annotation. However, the approach does not yet model higher-order structures such as organelles and relies on computationally expensive insertion strategies.

Overall, the results demonstrate that synthetic data can bridge the gap caused by the lack of ground truth, providing a powerful tool for advancing cryo-ET analysis.

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References

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