Physics-Informed Automatic Differentiation for Single-Shot Nanoscale 3D Imaging in *In Situ* Transmission Electron Microscopy

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1. Introduction

Transmission electron microscopy (TEM) is a powerful tool used to characterize material structures at the nanometer scale. In recent decades, advancements in *in situ* TEM have provided valuable insights into the dynamic processes involved in nanomaterial synthesis, electrochemical reactions, battery systems, and biological structures by capturing critical transient states [1,2]. However, despite these advancements, the structural dynamics of intermediate states are largely limited to two dimensions (2D). Currently, there is no widely accessible imaging technique that can simultaneously provide high-resolution three-dimensional (3D) structural information along with millisecond temporal resolution [3].

In our previous work on single-shot pop-out 3D metrology, we demonstrated that the coherence of electron waves in TEM encodes depth information within micrographs [4]. By computationally retrieving this information, we can extract 3D relief from a single 2D TEM micrograph. Although pop-out metrology can reconstruct the 3D volume of a single-layered homogeneous specimen, extending this principle to geometrically complex structures is not straightforward. Moreover, a decreased signal-to-noise ratio, as we pursue faster native structural dynamics, limits the 3D resolution of these reconstructions.

Here, we present a physics-informed automatic differentiation framework for single-shot 3D TEM imaging that utilizes physics and material priors. The automatic differentiation capabilities of deep learning packages can be utilized directly to minimize a loss between a physics forward model output and measured data [5]. However, the full-field imaging inverse problem requires additional priors [6]. In this work, we employ a physics-based multi-slice forward model, utilize pop-out output volume as an initial guess, and incorporate material-based regularizations.

2. Methodology

Multi-slice wave propagation is one of the most computationally efficient forward models for accounting for heterogeneous densities and dynamic scattering. In the multi-slice formalism, a specimen is divided into multiple thin scattering slices along the optical axis, through which an incoming wave sequentially scatters and propagates. This formalism allows the 3D reconstruction problem to be formulated as an L2 loss minimization between the predicted and measured TEM images [6], with automatic differentiation employed to solve the optimization.

Although reconstructing 3D information from a single 2D projection is inherently ill-posed, as established earlier, the coherent, strong scattering in TEM produces interferograms that encode some of the sample's 3D information within them. Simply put, these interferograms are not mere 2D projections of the 3D structure. Consequently, by incorporating coherent scattering physics within the forward model, we enhance the retrieval of these depth-dependent cues, thereby helping to partially constrain the otherwise ill-posed 3D reconstruction problem.

Nevertheless, due to the fundamental under-determinacy, reliable convergence toward a physically plausible 3D solution still requires a good initial estimate, ideally one that captures the coarse structural features of the true volume (ground truth). We demonstrate that the crude pop-out 3D metrology reconstruction can serve as such an approximate initialization. Thereafter, the L1-norm total variation (TV) regularization further constrains the solution space while also stabilizing the optimization process.

3. Results and Discussion

As a proof of concept, we simulated High-Resolution TEM (HRTEM) frames (Fig. 1A) of a calcium dendrite structure (Fig. 1C). First, we estimated the loss (L2-norm) by varying the volume in the forward model through scaling and sliding along the optical axis to emulate uncertainties in depth. In a noise-free environment, we established that the true solution lies within a narrow valley leading to a vanishing gradient problem (Fig. 1B). Moreover, noise and experimental uncertainties introduce irregularities in the search space, making it 'bumpy' and further worsening the vanishing gradient problem.

The pop-out 3D reconstruction volume in Fig. 1E shows that the complex geometry of the dendrite structures induces depth spillover artifacts, particularly along the boundaries between layers at different depths. Nevertheless, despite these artifacts, the 3D volume serves as an effective initialization for automatic differentiation-based 3D reconstruction (Fig. 1F). Absent appropriate initialization (i.e., using popout metrology or some other technique), the reconstruction remains underconstrained, leading to an incorrect 3D structure (Fig. 1D).

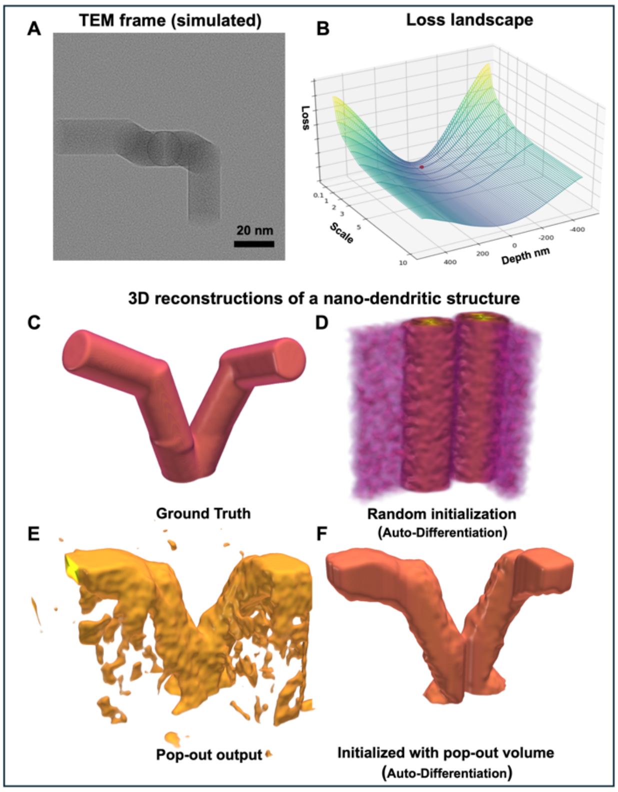

Fig. 1: Pop-out 3D metrology provides the initial guess to address the vanishing gradient problem in the automatic differentiation-based 3D reconstruction. (A) Simulated TEM frame of a nano-dendritic growth. (B) Loss function landscape for sliding (depth) and scaling of the reconstructed 3D volume. The red dot represents the true solution. (C-F) 3D renderings of the ground truth (C) and reconstructions (D-F). Without proper initialization, automatic differentiation-based reconstruction fails due to ill-conditioned optimization (D). The pop-out reconstruction (E), though affected by artifacts, provides a crucial initialization for a stable reconstruction (F).

4. Conclusion

In this work, we introduced a physics-informed automatic differentiation framework for single-shot 3D reconstruction in *in situ* TEM. Our framework employs a preliminary 3D metrology reconstruction as an initial guess for solving the multi-slice wave propagation model-based minimization. Our results show that this approach, combined with material priors and L1-norm total variation regularization, refines the initial crude pop-out reconstruction. This method facilitates high-resolution 3D imaging, providing valuable insights into dynamic nanoscale processes. Future research will focus on refining the constraints and improving robustness under high-noise conditions found in experimental *in situ* TEM frames.

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