AI-enhanced Low-dose Cryo-ptychographic Tomography for Organic-Inorganic Hybrid Nanostructure

The paramount interests in organic–inorganic hybrid nanomaterials were stimulated by numerous applications in biology, chemistry, medical imaging, and optoelectronics. Hybrid nanomaterials typically consist two distinct classes of materials: inorganic components (metal or oxide particles, etc.) and organic components (ligands, biomolecules, pharmaceutical substances, etc.). Three-dimensional (3D) nanoarchitectures can offer synergistic enhancement of their functional properties, for example, large surface areas that enhance structures’ interactions with environments for sensing applications. Recently, DNA origami nanotechnology that uses DNA, as a means of programming interactions between nanocomponents can create large-scale 3D nanoparticle superlattices in a control manner (Fig. 1 a)) [1]. The physical properties of these are fundamentally determined by the relationship between the inorganic and biological components in the nano hybrid constructs, which requires high-resolution 3D imaging of both the biological and non-biological components simultaneously, for characterisation.

However, due to the poorer contrast of biological molecules (low atomic number) than that of nanoparticles (high atomic number) shown in conventional transmission electron microscopy (TEM) (Fig. 1 b)), it has been tremendously challenging for 3D computer tomography (CT, Fig. 1 d)) to simultaneously resolve both the biological- and non-biological components in the 3D constructs. As a result, the level of attainable positional accuracy of their correlation for the nanostructures is very poor, and the understanding of their properties and functionality is hindered at the most fundamental level. Recently, in physical sciences, high resolution holographic imaging technique, so called ptychography [2,3] is emerging as an important new phase contrast imaging tool in Synchrotron, where a sample is scanned by a probe in an array and a series of 2D diffraction patterns are recorded by state-of-the-art ultrafast detectors as a function of probe position, eventually forming a vast quantity of four-dimensional dataset. Due to its high phase-sensitivity (Fig. 1 c)), robustness to low electron dose data and the recovery of the sample wavefunction, electron ptychography represents a potentially disruptive change in the rapidly growing field of cryo-EM structural biology. This advantage has recently been demonstrated for organic matter (such as unstrained virus particles) at a dose of 27 e/Å² in their native state at a cryogenic temperature, demonstrated by the PI[4], as shown in Fig. 1 e).

Here building on our previous work in 2D cryogenic electron ptychography, we propose to develop high-contrast and high-resolution 3D phase imaging technique to visualize unstained organic-Inorganic hybrid nanostructure (i.e. DNA origami with gold nanoparticles) by combining electron ptychography and computer tomography (Cryogenic Ptycho-CT). In this project, we will use high-contrast 2D phase data reconstructed using ptychographic methods recorded at different sample orientations as an input to a tomographic reconstruction with high resolution. We will quantitatively evaluate the contrast enhanced by ptychography in comparison to conventional TEM under various electron dose conditions and accelerating voltages. To balance the requirement for high-quality, resolution imaging with tight dose budgets and the need to reduce radiation exposure risk for their organic parts, we will further implement Artificial Intelligence (AI) technologies, especially deep learning to enhance the image quality by denoising images [5]. Furthermore, we will develop a comprehensive and standardized protocol for this new 3D tomographic technique based upon cryogenic ptychography (Ptycho-Tomo), which would act as a guideline for other researchers. This work opens up a new frontier in developing a new high resolution 3D CT based on ptychography to address the challenging, but increasingly important topic of studying organic-inorganic hybrid nanostructures or interfaces. In addition, the realization of this new Cryogenic Ptycho-CT has also profound implications due to their wide applications to hybrid materials used in drug-delivery, solar cells and all-solid-state batteries.

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