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Super-Resolved Label-Free Plasmon-Enhanced Array Tomography

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Biological function is closely linked to cell morphology and subcellular structure, making 3D imaging techniques an essential tool for understanding complex biological processes. Typically, 3D imaging involves staining and labelling, which can be time-consuming, error-prone, and reliant on toxic reagents. Imaging based on the intrinsic biophysical properties of cells and tissues, such as refractive index (RI), offers a promising alternative. This approach avoids these challenges, offering the potential to complement or even surpass chemical sensitivity, acting as a non-invasive marker for disease (Wang et al., J. Biomed. Opt., 16(11), p. 116017, 2011). Recently, plasmonic metamaterials, designed to the same dimensions and specifications as traditional microscope slides, have emerged as a means to visualise RI by converting variations in this property into striking colour contrast, offering sensitive, label-free biological imaging (Balaur et al., Nature, 598(7879), pp. 65–71, 2021). These metamaterials exploit the sensitivity of surface plasmon resonance (SPR) at metal-dielectric interfaces, allowing detection of refractive index changes in the near-surface region through a colorimetric response (Balaur et al., Sci. Rep., 6(1), p. 28062, 2016).

In this study, we demonstrate the integration of plasmonic metamaterials with array tomography imaging protocols to reconstruct 3D volumes from resin-embedded tissue sections, each 70-100 nm thick. We present high-resolution reconstructions of malaria-infected red blood cells and optic nerve tissue exhibiting multiple sclerosis-like disease features. In the malaria samples, by-products of cell parasitisation are clearly visible, while the optic nerve sections reveal various inflammatory cell types associated with disease. The tomograms generated through brightfield optical imaging achieve an experimentally determined resolution of 100 nm in the sectioning axis direction, demonstrating super-resolution capabilities. This approach holds significant potential for 3D histology at the subcellular level, paving the way for improved biological imaging and disease monitoring (Caracciolo et al., arXiv:2507.12786).

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