[PHOT-OS] Lensless digital holographic microscopy with optical sectioning and chemical specificity for imaging thick, highly scattering samples

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We will develop a new type of microscope that combines the simplicity and high throughput (very large FOV approx. size of the sensor) of lensless holography with the ability to peer deep into tissue and discriminate its chemical composition - without stains/labels and without complex optics. In PHOT-OS, a team at the Warsaw University of Technology will build an LDHM (lensless digital holographic microscopy) platform that, for the first time in this modality, unites two capabilities long considered out of reach: optical sectioning (multi-layer imaging of 3D samples) and chemical specificity (molecular contrast) based on mid-infrared (MIR) molecular-selective photothermal excitation. This will enable three-dimensional “maps” of large tissue areas that reveal both structure and chemical makeup, such as the distribution of lipids or proteins. It would be a breakthrough for high-throughput in-vitro biomedical imaging, disease diagnostics, and histopathology.

The key is to combine smart acquisition and reconstruction of multiple coded holograms (structured illumination patterns) with gentle MIR absorption that is highly selective to given chemical bonds. This heating induces local drop in refractive index (the photothermal effect), which our system records precisely using holography in the visible range. As a result, we obtain volumetric imaging with a very large field of view - comparable to whole-slide scans - without laborious sample preparation (labeling). In addition, our reconstruction algorithm will handle multiple light scattering in thick tissue sections, which has so far severely limited the achievable imaging depth in lensless imaging (previously restricted to weakly scattering thin samples, e.g., single cell layers).

If successful, PHOT-OS will push the boundaries of label-free imaging: enabling digital histopathology without staining, precise studies of neurodegenerative processes in large brain sections, and rapid, low-cost analyses of organoids and cell cultures in collaboration with expert partners in Poland and abroad. A large field of view, depth information, and chemical selectivity - captured on a easy-to-prepare specimen in one system - could translate into better diagnostics (e.g. fatty liver disease) and more accessible research tools for laboratories worldwide.

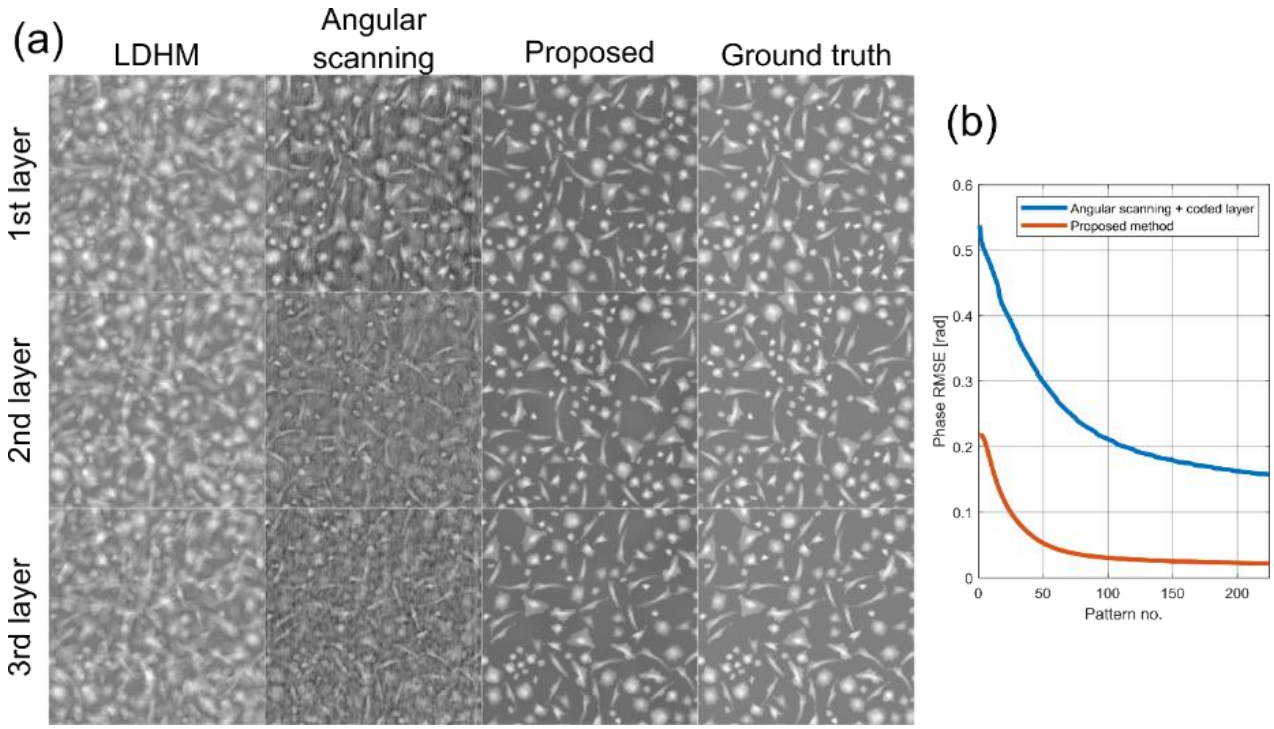

Fig. 1. (a) Exemplifying simulated reconstruction of a synthetic sample consisting of three cellular layers. Conventional LDHM fails to distinguish the individual layers; an illumination-angle scanning approach (Angular scanning) performs only marginally better, whereas the preliminary proposed method (Proposed) closely approaches the ideal result (Ground truth). (b) Convergence curves for the existing algorithm versus the preliminary proposed method, demonstrating its quantitative advantage.