Interferometric time-stretch microscopy for ultrafast quantitative cellular imaging at 1 µm

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Abstract: We demonstrate the first interferometric time-stretch microscopy in the 1 µm wavelength regime, for high-speed (sub-MHz) single-shot quantitative phase cellular imaging – a step forward for realizing high-throughput and high-content imaging-based screening.

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The ever-increasing demand on retrieving a wealth of quantitative information from a large population of biological cells using optical microscopy has been accelerating the advancement in disease diagnostics. However, effective high-content measurements of numerous cells inevitably require high-throughput imaging capability, which is hindered by the trade-off between the sensitivity and speed that appeared in all conventional image sensors. To this end, an entirely new optical imaging modality called, optical time-stretch microscopy, has recently emerged to offer an unprecedented imaging frame rate (> MHz) and sensitivity for high-throughput screening applications [1-3]. In this paper, we further develop this technology by demonstrating, to the best of our knowledge, the first interferometric time-stretch (ITS) microscopy in the short near-infrared (NIR) window, i.e. ~1 µm. In contrast to the prior works, which operated in the telecommunication band (1550 nm), our ITS microscope works in the short NIR range, making it more favorable for a wide range of biomedical diagnostic applications. Incorporated with the interferometric configuration, ITS is capable of not only enhancing the image contrast of the transparent biological cells, but also accessing their quantitative information (e.g. cell volume, mass, refractive index, stiffness) at nanometer scale based on the phase-shift measured by interferometry [4]. ITS thus represents an attractive tool for realizing imaging-based high-throughput and high-content screening, e.g. imaging flow cytometry.

In the present setup, the one-dimensional spatial coordinates of the sample are first encoded in the wavelength spectrum of a supercontinuum (SC) pulse (centered at 1064 nm) by a diffraction grating. The pulse is then interfered with another reference pulse, and is time-stretched by group velocity dispersion (GVD) in a dispersive fiber (GVD ~0.3 ns/nm). Consequently, the image-encoded temporal interferogram is finally captured by a high-speed photodetector and a real-time oscilloscope (16GHz, 80GS/s). The entire two-dimensional quantitative phase image is captured by scanning the specimen in the orthogonal direction and is then reconstructed by a series of digital signal processing steps, including Hilbert transform for phase extraction, and Goldstein's algorithm for phase unwrapping. The single-shot line-scan rate is as high as 0.2 MHz, which is merely governed by the repetition rate of the SC pulses. For comparison, the same sample of unstained nasopharyngeal epithelial cells was imaged by conventional phase-contrast microscopy, time-stretch imaging and ITS imaging (Fig. 1(a-c)). Compared with the time-stretch image, ITS image not only exhibits higher image contrast, but also reveals quantitative cellular structures with ultrafast single-shot line scans (Fig. 1(c)-(d)), each of which was captured in ~5 ns. Moreover, the high-speed operation does not seriously compromise the image quality. This can be evident by comparing it with the phase-contrast image (Fig. 1(a)).

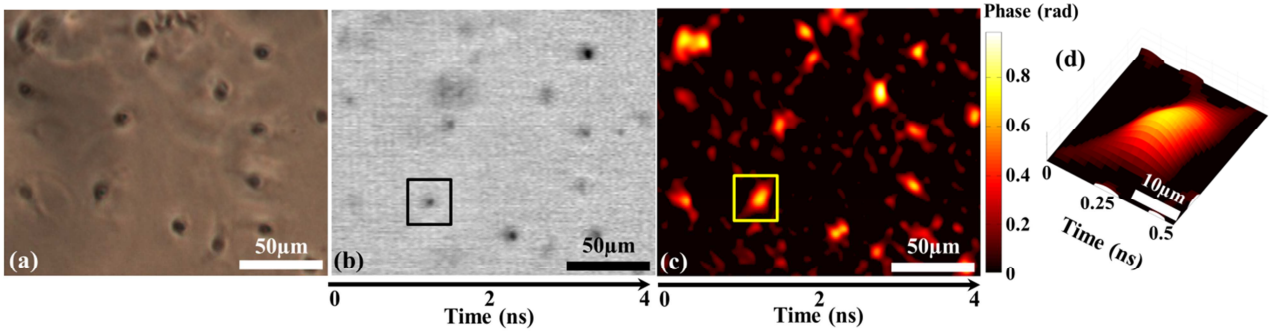

Fig. 1. Nasopharyngeal epithelial cells captured by (a) phase contrast microscopy, (b) time-stretch microscopy, and (c) interferometric time-stretch microscopy. (d) A close-up view of the quantitative phase map of the highlighted cell in (b,c).

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