Learning framework for unsupervised cellular refractive index and thickness measurement

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Abstract:

In this work, we develop a framework to experimentally extract thickness and refractive index maps from biological cells using AI-driven inverse search from RGB photographs.

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Main Text

The refractive index of a cell is an essential biophysical property. Knowledge of the refractive index distribution of a cell enables the study of cell differentiation, cycles, growing mechanisms, and other processes, which can contribute to disease diagnosis [1–3]. It has been shown recently [4] that some parasite borne diseases, such as malaria, lead to significant structural refractive index modifications to the host biological cells.

Presently, optical methods such as quantitative phase microscopy can indirectly measure refractive index maps by obtaining the optical path length (OPL) of a cell [1,5]. The OPL results from the product of the cell's thickness and refractive index point-wise, as such, the thickness map of the cell needs to be reconstructed using auxiliary instruments or by multiple measurements at different angles before the refractive index map can be recovered.

Fig. 1. (a) Photograph of a completed light-trapping surface structure. (b) Visual representation of a 3D thickness map of a human colon cancer cell (HCT112) stretched on top of our light-trapping surface surface (a). (c) Corresponding Scanning Electron Microscope (SEM) image of stretched cell on top of a surface. (d) Corresponding RGB image from a camera. (e) Results of the inverse search for a pre-processed image (e) with recovered thickness (f) and refractive index (g) maps.

This work presents an alternative technique of extracting both refractive index and thickness maps of biological specimens from a single RGB photograph obtained with a typical optical setup. Compared to the state-of-the-art, our method enables single measurement recovery using minimal equipment in the form of a reflected light

microscope and a digital camera. To validate the proposed approach, we analyze a set of human colon cancer cells (HCT116). Our method successfully extracts refractive index and thickness maps consistent with the results available in the literature [3].

Figure 1 summarizes the performed analysis. The key element of this approach is a light-trapping surface produced using a low-cost electroplating process (Fig. 1a). The surface consists of a large number of micro-scale coral reef-like Pd structures with nanoscale modulations. Upon covering the structure with 20 nm of Al₂O₃, through an ALD process, over 90% coupling efficiency of light from 350 nm to 950 nm is achieved at the metal/dielectric interface. In addition to the light-trapping property, this surface can stretch biological cells (Fig. 1b). Namely, a microorganism placed on top of this surface will anchor itself to the structures and stretch as it dehydrates, reaching sub-micron thickness (Fig. 1c). This stretching ability opens a possibility to extract material-specific fingerprints in the visible resulting from a thin-film interference.

Using a conventional color camera (CMOS or CCD), we extract fingerprints in the form of color tones from a single photograph (Fig. 1d). We developed an efficient inverse search algorithm that works on the extracted colors (Fig. 1e) to recover the sample's structural information, namely thickness and refractive index. Panels (1f,g) show the extracted thickness (f) and refractive index (g) maps for the human colon-cancer cell (HCT116) shown on a panel (c).

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