Measuring the nanoscale mass-density fluctuations within biological cells using optical and electron microscopy

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Partial wave spectroscopic (PWS) microscopy technique quantifies cellular nano-architecture (~ 20 nm) beyond the diffraction-limited resolution (~ 400 nm) of traditional microscopy or histopathology. These nanoscale alterations correspond to earliest morphological changes during cancer progression in cells. Specifically, PWS measures the nanoscale mass-density fluctuations within a cell, termed disorder strength. Herein, we describe in detail the PWS microscopy technique and its validation using rigorous 1-dimenstional (1D) finite difference time domain (FDTD) simulations. We also present results obtained from cell lines and lung cancer study (performed on 200 patients) which demonstrate disorder strength as a potential biomarker during early carcinogenesis.

Computational simulations depend heavily on the inputs and so it is critical to obtain the accurate native mass-density correlation function from an independent technique to validate PWS results and to understand light scattering from biological cells using FDTD simulations. To do this, we implemented the scanning transmission electron microscopy (STEM) technique (resolution ~ 1 Å) which unlike a conventional TEM, provides information about the native mass-density of isolated biological cells (herein, human cheek cell) without the need for sample sectioning or osmium staining. We demonstrate the quantification of these STEM gray-scale images to extract the statistical 3-D mass-density correlation function from the projected 2-D mass-density map. The original 3D-correlation function of mass-density can then be used to generate more accurate refractive-index models for FDTD simulations to explore light scattering from biological cells. This work is valuable for several areas including physics, biophotonics, clinical and numerical simulations.