School of Electrical, Computer and Energy Engineering

PhD Final Oral Defense
Three-dimensional morphological biosignatures for cancer by automated analysis of transmission-mode optical cell CT images
by
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Abstract
Despite significant advances in automation sciences and digital microscopy, current diagnostic practice for cancer detection primarily relies on a qualitative manual inspection of tissue architecture and cell and nuclear morphology in stained biopsies using low-magnification, two-dimensional (2D) brightfield microscopy. The efficacy of this process is limited by interoperator variations in sample preparation and imaging, and by interobserver variability in assessment. Further, the prognostic value over the past twenty years of predictive quantitative morphological signatures derived from computerized analysis of micrographs has been compromised by the inability of 2D microscopy to capture information in the third dimension, and by the anisotropic spatial resolution inherent to conventional 3D microscopy techniques that generate volumetric images by stacking 2D optical sections.

Single-cell optical computed tomography (cell CT) is a promising 3D imaging technique that uses white light excitation to image stained cells individually with sub-micron,
isotropic spatial resolution. This dissertation provides a scalable, automated computational framework to perform fully-automated 3D morphological analysis from transmission-mode optical cell CT images of hematoxylin-stained cells. The developed framework performs rapid and accurate quantification of 3D cell and nuclear morphology, facilitates assessment of morphological heterogeneity, and generates shape- and texture-based biosignatures predictive of cell health.

We have developed custom 3D image segmentation methods to precisely delineate volumes of interest (VOIs) from reconstructed cell images. Comparison with user-defined ground truth assessments yielded an average agreement (DICE coefficient) of 94% for the cell and its nucleus. We computed 75 biologically relevant morphological descriptors (features) from the segmented VOIs, and applied statistical classification methods to determine the subset of features that best predict cell health.

We demonstrate the efficacy of our proposed framework on an in vitro model of multistep carcinogenesis in human Barrett's esophagus (BE) and compare classifier performance using our 3D morphological analysis against computerized analysis of 2D image slices that reflect conventional cytological observation. Our results enable sensitive and specific nuclear grade classification for early cancer diagnosis and underline the value of the approach as an objective adjunctive tool to better understand morphological changes associated with malignant transformation.