Single-cell analysis technologies for cell respiration rate and nuclear morphological changes in cancer

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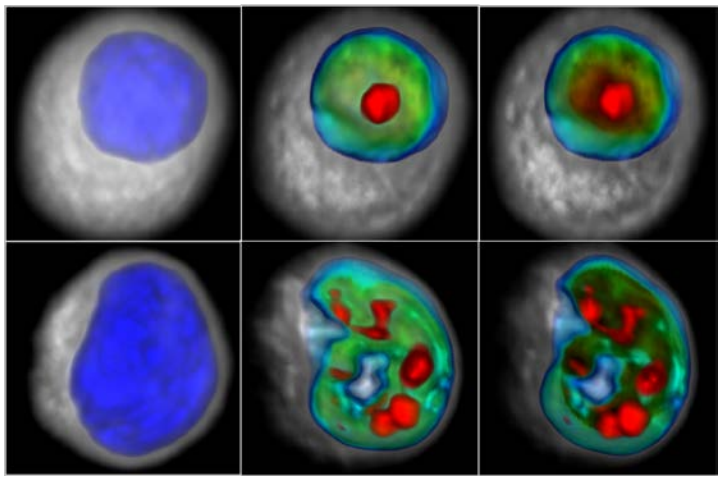
Engineering methods for microscale devices are being applied in fundamental and applied cancer research. We developed technologies for measuring physiological responses, genomics, transcriptomics (mRNA), protein function, and cytostructure at the few- and single-cell level. To accomplish these goals we adapted processes from the semiconductor industry to produce microfluidic devices, known as "labs on chips", for physiological measurements including oxygen consumption rate on individual cells or on a few interacting cells. We synthesized fluorescent optical sensors to measure oxygen concentration in the in vitro microenvironment surrounding an individual cell.

In parallel, we developed a capillary-based optical computed tomography (CT) imaging method called "cell CT" to perform 3D CT imaging on individual cells. Cell CT can image cell and nuclear structure by using absorption stains and it can image cell function using fluorescent dyes. We derive integrated biosignatures sensitive to cancer progression stage from this set of measurements, for eventual application to early cancer diagnosis. In this talk, I will briefly describe our technology and methods for single-cell physiological analysis, followed by a more in-depth presentation of our work on cell CT.

We perform optical tomographic imaging of single cells—"cell CT"—and automated 3D cytometry to quantify cell morphology, and investigate the power of our approach to distinguish between structural features of normal and abnormal cells. To produce 3D images of individual cells with the cell CT, we transport and rotate single, cultured, hematoxylin-stained cells in a special carrier gel within a 50-micron glass capillary. Then we produce 3D images with isotropic 350-nm resolution using optical projection tomography. We reconstruct cell images mathematically from 500 transmitted projections acquired over 360 degrees. We automatically process the data to extract quantitative morphometric descriptors (*features*) from the volumetric cell images. We segment the cell, the nucleus and the nucleoli (dense clumps of DNA) using robust computer vision techniques, then compute morphological and textural features from the segmented volumes. Finally, we evaluate the efficacy of using the statistical distribution of these chromatin architectural features in distinguishing between normal, metaplastic, dysplastic and cancer cells. We applied the method to human esophageal epithelial cell lines, analyzing hundreds of cells per line. Our results suggest that 3D cytomorphometry may prove efficacious in the future as a method for early cancer detection.



Volume renderings of suspended normal (top) and dysplastic (bottom) esophageal epithelial cells. Left images show the cell and nuclear surfaces, middle images reveal the nuclear interior and right images depict a 40-slice slab.