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Taking a Closer Look: Imaging Tumor Microenvironments with 3D FIB-SEM Reveals Complex Cellular Interactions

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Abstract:

As a part of the Serial Measurements of Molecular and Architectural Responses to Therapy (SMMART) precision medicine cancer trial, serial biopsies from cancer patients are collected and analyzed to inform treatment and advance the understanding of metastatic cancer. Within these analyses, advanced imaging is able to capture highly detailed spatial and structural information of the tumor microenvironment. Sections of the SMMART biopsies are imaged using electron microscopy (EM) which is able to capture up to 4nm of resolution. After preparing a 2D EM map of a biopsy, particular areas of interest are selected and imaged using 3D FIB-SEM (Focused Ion Beam-Scanning Electron Microscopy). The images are pre-processed to reduce noise and improve image alignment. Given the complexity of the images as well as the irregularity of cancer tissue, it is necessary to manually segment the EM images in order to gain meaningful information. Cells, organelles, and other structural features are identified and segmented in Microscopy Image Browser using brush tools, interpolation, and thresholding. The resulting models are rendered in Dragonfly and Amira to more easily visualize the structures and cellular interactions in 3D. Once rendered, stromal cells of various shapes and forms can be seen wrapping around nests of cancer cells. Additionally, fine structures such as filopodia and lamellipodia – thin protrusions from the cell membrane – are visible interlocking and interacting with other cells and the microenvironment. As of now, manual segmentation is a major time limiting factor in EM image analysis for cancer tissue. In order to combat this, there are projects underway to develop

machine learning algorithms to automate segmentation. Automation will hopefully allow electron microscope analysis to be a new and informative avenue for cancer research.