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# Volume electron microscopy: taking the measure of cells in 3D

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Volume electron microscopy or volume EM (vEM) refers to a group of recently developed imaging approaches encompassing scanning EM (SEM), transmission EM (TEM) and X Ray based technologies that allow the interrogation of cells and tissue ultrastructure in 3D, at μm to mm volume scales and at nm level resolutions. The main approaches include the following: TEM tomography for the highest resolutions and smaller, often sub-cellular, volumes; serial block face SEM and FIB-SEM imaging for cell-level regions (although custom tools have vastly increased volumes that can be imaged); single- and multi-beam array tomography for larger samples; and X Ray microscopy or micro-CT for mm-sized volumes at relatively lower resolutions. While cryo EM approaches have dramatically altered the landscape of structural biology in the past decade, the science of volume EM and the community arising from the nascent field has helped make key discoveries in neuronal wiring diagrams (connectomics) and is beginning to have significant impacts on cell biological research. vEM sample preparation is largely compatible with traditional, room temperature EM protocols (vEM imaging is typically understood to operate at ambient temperatures), but often incorporates extra metallization of the sample for compatibility with imaging technologies available. Similarly, there is a focus on automation of image acquisition to capture larger volumes efficiently, albeit often at some cost to image resolution when compared to high resolution TEM. Similarly, the generation of large amounts of image data at high speed has created a need for sophisticated computational strategies to handle and analyze these data. For example, unlike fluorescence microscopy, where the feature of interest is specifically labeled, volume EM generates information rich and dense volumetric image datasets. Thus, segmentation, or the extraction of features from the grayscale data, is a step that needs to be performed accurately and efficiently. Long considered the bottleneck in the volume EM pipeline, newer machine learning and deep learning algorithms are making inroads into this problem, and are exciting frontiers for research in this space. Finally, vEM experiments are often executed in a correlative manner, combining multiple imaging modalities. These present their own sample preparation, imaging, and data processing problems that are active areas of research. Several laboratories around the world, often in close collaboration with industry partners, are at the forefront of vEM research: these and other groups are creating a variety of tools to push the limits of the technologies, and are sharing and applying them to a variety of experimental systems to reveal stunning new biology.