Cryo-scanning transmission electron microscopy for biology

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M. Elbaum[I]

[I]*Weizmann Institute of Science, Rehovot, Israel*

Electron microscopy of unstained cryogenic specimens provides the most faithful ultrastructural representation of biological material, from molecules to cells. Imaging of unstained material is challenging, however, because of the weak electron scattering. Typically the microscope operates in the wide field transmission mode with phase contrast. This mode offers the highest resolution for macromolecules, but also imposes severe constraints on the sample geometry. Most cellular samples are too thick to observe without sectioning. An alternative configuration is that of scanning transmission EM (STEM). Long considered incompatible with cryo-microscopy, STEM offers a number of advantages with respect to phase contrast TEM, including quantitative density measurements, suitability to thicker samples, and simple incorporation of spectroscopic tools. STEM contrast is ideal for tomography, and 3D reconstructions are obtained from cells and cell areas more than 1 micron thick. STEM is especially sensitive to relatively heavy elements, such as Ca, Fe, or Zn, on the organic background. New tools for image acquisition and processing are under development.