Cryoelectron microscopy: a dream for the microscopist and a primer for the non-microscopist

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Cryoelectron microscopy (cryo-EM) is a method for imaging frozen-hydrated specimens at cryogenic temperatures by electron microscopy. Specimens remain in their native state without the need for dyes or fixatives, allowing the study of fine cellular structures, viruses, and protein complexes at molecular resolution. Cryo-EM is increasingly becoming a mainstream technology for studying the architecture of cells, viruses, and protein assemblies at molecular resolution. In biology, applications of cryo-EM now span a wide spectrum, ranging from imaging intact tissue sections and plunge-frozen cells to individual bacteria, viruses, and protein molecules. Cryo-electron tomography, single-particle cryo-electron microscopy, and electron crystallography are all sub-disciplines of cryo-EM that have been used successfully to analyse biological structures in different contexts. Recent developments in microscope design and imaging hardware, paired with enhanced image processing and automation capabilities, appear poised to further advance the effectiveness of cryo-EM methods. These developments promise to increase the speed and extent of automation and to improve the resolutions that can be achieved, rendering this technology capable of determining a wide variety of biological structures. Additionally, established modalities for structure determination, such as X-ray crystallography and nuclear magnetic resonance spectroscopy, are being routinely integrated with cryo-EM density maps to achieve atomic-resolution models of complex, dynamic molecular assemblies. An overview of emerging themes in the application of this technology to the investigation of diverse questions in biology and medicine will be provided.