Structure and Dynamics of Macromolecular Machines by Single Particle Cryo-EM

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Abstract

Most biological processes in all walks of life are performed by molecular machines better known as macromolecular complexes. In recent years electron microscopy has gone through a “resolution revolution” which has made cryogenic electron microscopy to a technique capable of elucidating the three-dimensional (3D) structure of large macromolecular complexes with an ever-improving level of detail. In favourable cases, a de-novo structure determination by cryo-EM alone has proved feasible. For example, the resolution levels achieved in determining the structure of the bacterial ribosome, already match or exceed those achieved by conventional X-ray crystallography. It is now even possible to obtain sets of atomic-resolution 3D reconstructions of macromolecular machinery in action from very large, noisy EM data sets (movies of 3D structures or: ‘4D’ structures). The improvements we have seen over the last decade include: better cryogenic handling of the specimen, computer-control of the ever better electron microscopes, direct recording of electrons in sensitive new digital cameras, as well as a vast array of powerful data-processing approaches. At the resolution level of around 3-4Å cryo-EM reaches an important threshold: we start seeing the side chains of proteins allowing for a better insight in their functioning. The giant hemoglobin of the common earthworm is one of our favourite test samples to illustrate the power of today’s