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Towards more dose efficient cryogenic electron microscopy of biological samples

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Cryo-electron microscopy (cryo-EM) has become an indispensable tool for structural biologists studying the relationship between structure and function of various biomolecules. Recent advancements in transmission electron microscopy (TEM) hardware and data processing software have enabled atomic-level resolution for single particle cryo-EM. However, achieving near-atomic resolution for smaller (<100 kDa), more heterogeneous, and non-symmetric samples remains a significant challenge due to the limited scattering information provided by smaller particles, the high defocus required for image contrast enhancement, and the radiation damage that restricts the number of high-energy electrons per surface area, resulting in low signal-to-noise ratios. To address these challenges, we simulated single particle data sets using realistic parameters for ice layer, dose, detector performance, and beam characteristics for samples that were ideal in terms of homogeneity, distribution, and stability. Our simulations could help expand the size limits of cryo-EM. Meanwhile, we also reviewed alternative TEM techniques such as phase plate and ptychography that hold promise for providing complementary or additional structural information within the limited lifetime of the sample. Finally, we implemented a new event-based electron detector and show experimental data substantiating some of the promises we could simulate.

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