

## Publication

## Protein structure determination by electron diffraction using a single three-dimensional nanocrystal

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Three-dimensional nanometre-sized crystals of macromolecules currently resist structure elucidation by single-crystal X-ray crystallography. Here, a single nanocrystal with a diffracting volume of only 0.14  $\mu\text{m}^3$ , i.e. no more than 6  $\times 10^5$  unit cells, provided sufficient information to determine the structure of a rare dimeric polymorph of hen egg-white lysozyme by electron crystallography. This is at least an order of magnitude smaller than was previously possible. The molecular-replacement solution, based on a monomeric polyalanine model, provided sufficient phasing power to show side-chain density, and automated model building was used to reconstruct the side chains. Diffraction data were acquired using the rotation method with parallel beam diffraction on a Titan Krios transmission electron microscope equipped with a novel in-house-designed 1024  $\times$  1024 pixel Timepix hybrid pixel detector for low-dose diffraction data collection. Favourable detector characteristics include the ability to accurately discriminate single high-energy electrons from X-rays and count them, fast readout to finely sample reciprocal space and a high dynamic range. This work, together with other recent milestones, suggests that electron crystallography can provide an attractive alternative in determining biological structures.

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