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Atomic resolution structure determination of larger macromolecular complexes by cryo-EM and X-ray crystallography

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The technological advances in electron microscopy hardware, in detector development and in available image processing tools made cryo-EM a highly successful and rapidly developing method for protein structure determination. Based on the exponentially growing numbers of protein structures determined by this method, cryo-EM is even likely to become the dominant method for protein structure determination within the next few years assuming the current growth in database deposition continues. Since cryo-EM does not require crystalline material, many structures of complexes have been solved in the last decade that were evasive targets to X-ray crystallography for a long time. In cryo-EM there is also an increasing level of automation that allows even beginners to obtain a high-resolution structure of a biochemically well-defined complex within days or weeks.
Furthermore, the resolution limits in cryo-EM have been pushed constantly over the last couple of years. For highly stable and rigid complexes, even true atomic resolution structures are now possible1. The image processing in cryo-EM also often allows the user to determine structures of several conformational states from one single dataset and therefore provides information about dynamic structural elements in a complex.
Because of the cryo-EM success story, the attention in structural biology has recently been shifted away from X-ray crystallography in spite of the long-term success and power of this technique. It is however noteworthy that several important developments were also made in the field of crystallography. Especially the possibilities to do time-resolved crystallographic experiments by XFEL but also by standard synchrotrons do provide access to detailed dynamic information in macromolecular complexes that is not yet obtainable by cryo-EM.
There is therefore absolutely no good reason to play the two techniques off against each other. Cryo-EM and crystallography have both advantages and disadvantages. Using both techniques in parallel indeed provides complementary information which greatly helps our structural and functional understanding of macromolecular complexes.

(1) Yip, K.M., Fischer, N., Paknia, E., Chari, A., and Stark, H. (2020). Atomic-resolution protein structure determination by cryo-EM. Nature 587, 157-161.