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## 3D Electron Diffraction of Beam Sensitive Samples of Biological Interest: Proteins and Pharmaceuticals

*Wednesday, 14 September 2022 15:00 (30 minutes)*

The availability of a single crystal diffraction technique for crystals smaller than few microns is a breakthrough both in structural biology and in pharmaceutical sciences. In those disciplines it is quite common to have difficulties in crystallizing large single crystals, therefore the structural studies can be extremely challenging or even impossible. 3D electron diffraction (3D ED) has provided a valuable alternative [1]. Although proteins and pharmaceutical are usually quite beam sensitive, both hardware and methodological development allow to collect 3D ED data in low dose mode on crystals that can stand total doses of  $1 \text{ e}^-/\text{\AA}^2$  or less before their diffraction deteriorates below  $2 \text{ \AA}$  in resolution. This has been possible because new direct electron detectors became available and 3D ED data collection procedures have been improved allowing the total data collection time to be less than 1 minute [2]. During this presentation the different 3D ED methods will be discussed along with some significative examples. In particular the structure solution of important pharmaceutical compounds that remained unknown for decades will be presented: orthocetamol [3] and  $\delta$ -indometacine [4]. Their structure determination have been possible by combining low dose 3D ED techniques with nanobeam diffraction, avoiding to have contribution from different crystalline domains. The application of 3D ED to protein crystallography will be also discussed by highlighting the most recent development in the field.

[1] M. Gemmi, E. Mugnaioli, T.E. Gorelik, U. Kolb, L. Palatinus, P. Boullay, S. Hovmöller, J.P. Abrahams, *ACS Cent. Sci.* 2019, 5, 1315.

[2] M. Gemmi, A. E. Lanza *Acta Cryst.* 2019, B75, 495.

[3] I. Andrusenko, V. Hamilton, E. Mugnaioli, A.E. Lanza, C. Hall, J. Potticary, S.R. Hall, M. Gemmi *Angew. Chem. Int. Ed.* 2019, 58, 10919.

[4] I. Andrusenko, V. Hamilton, A.E. Lanza, C. L. Hall, E. Mugnaioli, J. Potticary, A. Buanz, S. Gaisford, A.M. Piras, Y. Zambito, S.R. Hall, M. Gemmi, *Int. J. Pharm.* 2021, 608, 121067.

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