Cryo-Electron Microscopy and Tomography - The Past, the Present and the Future

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As a consequence of the 'resolution revolution' cryo-electron microscopy (cryo-EM) has become the most versatile method for structural biology. Advances made in instrumentation, in automation and in image processing over the recent past have expanded the capabilities of cryo-EM in a profound manner. Single particle cryo-EM (SPA) of isolated particles (ex situ) can deliver near-atomic resolution structures for large macromolecular complexes as well as for rather small proteins. SPA can be seen nowadays as an established method and has been awarded with the Nobel prize in chemistry in 2017. Although cryo-EM is not yet one of the high-throughput methods, the requirements in terms of user experience and measurement time are becoming ever less demanding. Equivalent to the beamlines in protein crystallography the first cryo-EM facilities/centers are being build up and put into operation. Of course, there is still room for further improvements in cryo-EM. The latest development of the Volta phase plate is a good example of this. The clear phase contrast improves the selection and classification of the individual particles and thus also enables the structural determination of very small proteins that were previously inaccessible.

However, proteins have their biological function in the complex environment of the cell and interact with other macromolecules. The exciting potential of cryo-EM therefore lies in cryo-electron tomography (CET), the three-dimensional analysis of macromolecular and supramolecular structures in their functional cellular context (i. e. in situ). This method closes the gap between molecular and cytological structural research.

After a brief look back this lecture will present our recent work in the field of cryo-electron microscopy/tomography and highlights technological developments, limitations and their opportunities. Furthermore, we will give a prospective towards obtaining structural insights from an in situ context at molecular resolution.