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Hitting proteins with a sledgehammer – combining native mass spectrometry with an XFEL

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Native mass spectrometry (MS) enables the ionization and transfer of intact non-covalent protein complexes into the gas phase. As such, it is a perfect tool to study proteins and their assemblies in a mass and conformation specific manner. This enables MS to probe structural transitions which proteins and their complexes undergo, e.g. during a viral lifecycle. Such transient states are of high importance for structural biology, but most often cannot be purified and are inaccessible for crystallography.

Despite its remarkable sensitivity and selectivity, the structural resolution in native MS alone is limited. The amount of structural information could be vastly increased by its combination with powerful hard X ray free electron lasers (XFELs) such as the already established LCLS in Stanford or the European XFEL, the world's most intense light source so far, which has just become operational in Hamburg. These instruments promise an opportunity to obtain high resolution structures of single particles. Reciprocally, native MS could solve some of the issues with delivering sample into the beam and could also add another dimension of possibilities by manipulating and selecting charged molecules in the gas phase prior to their imaging.

This contribution will highlight the benefits of native MS for single particle imaging of transient protein intermediates at XFELs. It will also describe our plans and ongoing work to bring native MS to European XFEL single particle beamline as well as present our initial feasibility studies on achievable ion fluxes.

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