CDCS
CENTER FOR DATA AND COMPUTING
IN NATURAL SCIENCES

OPENING SYMPOSIUM 2022

Universität Hamburg
DER FORSCHUNG | DER LEHRE | DER BILDUNG

DESY.

TUHH

Contribution ID: **103** Type: **Poster**

Towards Femtosecond Single-Particle Diffractive Imaging of Computationally Designed Photoactive Protein Complexes with XFEL Pulses

Outrunning radiation damage, femtosecond pulses of x-ray free-electron lasers (XFELs) open up the possibility of imaging the structure and dynamics of uncrystallized single-macromolecules, frozen in time at room-temperature, at ultrafast timescales. Imaging light-induced ultrafast dynamics in single-macromolecules in real-time is one of the key applications of XFELs. However, photoactive proteins exhibiting ultrafast dynamics are rare in nature, and they usually are quite small in the range of few tens to hundreds of KDa. Large photoactive proteins (~MDa) which scatter more photons than smaller proteins are desired for achieving the ultimate goals of single-particle imaging (SPI) with XFELs. Computational protein design provides the possibility of accurate designing of novel hyperstable MDa-sized protein complexes suitable for SPI with the flux of current generation FELs. Here, we propose to employ *AlphaFold* and *RosettaFold*-inspired inverse-design methods to generate sequences predicted to form novel photoactive protein complexes suitable for SPI, which can also be deployed to deliver drugs or genes and as probes in bio-imaging. In this poster, we present results from initial computational design efforts and SPI simulations of a designer protein-complex with hard X-ray FELs. We envisage that computationally designed protein complexes will likely help achieve the goals of time-resolved and holographic SPI, and in turn XFELs with their ability to image at ultrafast timescales will help iteratively optimize the design of de novo photoactive proteins by capturing the chromophore, protein side-chain interactions and collective motions of the designer-proteins at fs timescales.

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Session Classification: Poster session with buffet

Track Classification: CDL2 (Photon Science)