Universität Basel

Research Project

Single molecule electron diffraction

Third-party funded project

Project title Single molecule electron diffraction
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Organisation / Research unit
Departement Biozentrum / Nano-diffraction of Biological Specimen (Abrahams)
Department
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I propose establishing a technology platform for validating single molecule electron diffraction (simED) as an alternative, general method for structural studies of dynamic biomolecular complexes at atomic resolution. There is significant evidence that simED could boost the low signal-to-noise ratio of cryo-EM single particle analysis by an order of magnitude or more, potentially allowing structural studies beyond current capabilities and extending resolution in ongoing projects. The proposal plans developing simED by implementing unique instrumentation, automated data collection protocols and exploring phasing methods from protein crystallography. This development of hardware, software and automated data collection protocols also strongly supports nano-crystallographic applications, including pre-screening of nanocrystals for SwissFEL, polymorph screening in pharmaceutical research and further development of protein nanocrystallography within the EU-funded innovative training network “NaNED” (https://cordis.europa.eu/project/id/956099) kicking off in 2021. The proposal links the development of an advanced technology platform to the elucidation of important, fundamental process of life. Linking these goals ensures that the development of simED addresses real needs in biological research. The proposal builds upon the results of my previous SNF project grant, that focused on developing electron diffraction of crystalline samples for structural biology. In the last few years, electron crystallography became an established method for atomic structure determination. In September 2020, Basel University purchased an electron microscope for developing simED technology (delivery: spring 2021), that will initially be located at the PSI. It will be enhanced with a commercial post-column energy filter and a PSI JUNGFRAU direct electron detector. The new equipment is funded jointly by Basel University and the PSI and fully dedicated to electron diffraction studies, including the development of simED. It falls under responsibility of my joint research group located at these two institutions. If simED cannot produce data of the required quality, we will implement and further investigate cryo-electron ptychography using defocused convergent beam diffraction. This novel application in cryo-EM was published in June 2020 (Zhou, L et al. “Low-dose phase retrieval of biological specimens using cryo-electron ptychography”. Nat Commun 11, 2773 (2020)). Like in simED, this method scans the sample with a narrow beam, but this beam is convergent, and the diffraction data are measured as highly defocused images, whereas in simED the beam is essentially parallel, and the data are measured in the far field. The simED infrastructure can support both methods optimally. Following ideas developed at the LMB by Russo and colleagues, we will also explore simED at lower electron energies, as this may further boost the signal-to-noise ration by reducing radiation damage by up to 25%. As a second backup, we will consider implementing single particle cryo-EM imaging at lower energy on our simED instrumentation. Sample optimization, theory, algorithms and software concepts developed in the course of this project may contribute to extending

the resolution of single molecule XFEL X-ray diffraction beyond its current limits of approximately 100 nm.

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