Report of the Helmholtz International Fellowship of Prof.!John!C.!H.!Spence FRS

Henry Chapman, DESY!
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Prof. John Spence received the Helmholtz International Fellow Award in 2016 and spread his Award over several visits to DESY and the European XFEL in 2017 to 2019. John Spence is a Fellow of the Royal Society and a Regent's Professor and the Richard Snell Professor of Physics at Arizona State University (ASU), with a joint appointment at the Lawrence Berkeley National Lab. He is the Director of Science of the "BioXFEL" a $50M Science and Technology Center funded by the US National Science Foundation, which is devoted to the development and application of hard X-ray lasers to Biology (see www.bioxfel.org). In this latter field, John has collaborated extensively with DESY and in particular his host Prof. Henry Chapman of the Center for Free-Electron Laser Science on the method of serial femtosecond crystallography. Indeed, this was one of the topics that John focused on during his Award, including experiments in establishing the method at the European XFEL. In his broader goal of tracking the dynamics of proteins over a large time spans (from femtoseconds to seconds), John also spent time at DESY evaluating the prospects and feasibility of using ultrafast electron di" raction for the study of protein dynamics, and collaborated on aspects of utilising compact X-ray laser sources such as the AXSIS facility that is under development at DESY as part of an ERC Synergy grant led by Prof. Franz Kärtner.!

The visits of John Spence as part of his Award are summarised in the table below.!

Date of visit	Place of Visit	Remarks
May-July 2017	DESY	Collaboration on serial crystallography analysis, and research into the feasibility of ultrafast electron di" raction for elucidation of protein dynamics
August 2018	DESY & European XFEL	Collaboration on first serial femtosecond crystallography experiments at megahertz rates
May-June 2019	DESY & European XFEL	Collaboration on first single-particle di" ractive imaging experiments at the European XFEL. Research and discussions on phasing dynamical di" raction in crystals.

The visits listed here were also used as a home base for productive trips to present colloquia at Uppsala and Gothenburg Universities in Sweden, the Humboldt University in Berlin, the Georg-August University in Goettingen, and the University of Manchester in UK. This was in addition to several colloquia he gave in CFEL DESY.!
During his visits John Spence initiated a collaboration together with Henry Chapman and Rolf Röhlsberger of DESY and Joachim van Zanthier of Erlangen University, on incoherent di" ractive imaging, a new concept for gaining atomic-resolution information that is sensitive to the electronic and chemical environment of atoms. The method applies ideas of quantum optics to X-ray imaging, to use intensity correlations of X-ray fluorescence to

extract the structural information. Measurements must be made within the coherence time of the fluorescence, which is about 1 femtosecond. This will be achieved using short-pulse X-ray pulses. The collaboration carried out first experiments at the Linac Coherent Light Source at the end of 2017, which failed to observe a convincing e" ect. Experiments will be carried out at the European XFEL in May 2020 using an improved geometry to gain an accurate measurement of the fluorescence coherence time using the correlation method.!

Considerable discussions and studies were led by John to examine the opportunities of ultrafast electron di" raction, in particular as enabled by the REGAE instrument at DESY. This electron gun and accelerator produces sub-picosecond pulses of electrons of MeV energy. John evaluated possible electron di" raction measurements from sub-micrometer protein crystals in a thin liquid cell. The required time scales to follow dynamics in biological catalytic processes (enzymatics) ranges from about 10 microseconds to seconds. The electron fluence available at REGAE would require exposure times longer than this, but the averaging methods employed in serial crystallography could be employed. Nevertheless, a challenge is to keep the crystal (which undergoes rotation in the liquid medium) still during the exposure. It appears to be more promising to adapt the instrument into an ultrafast microscope, using magnetic lenses, using annular illumination to make better use of the coherence and emittance of the source and achieve atomic resolution. These discussions are informing e" orts in the group of Franz Kärtner to utilise compact terahertz-driven electron guns and accelerators to produce beams with lower emittance (higher brightness) for such studies.!

Experiments at the European XFEL were carried out as part of a large collaboration led by scientists from CFEL DESY and Arizona State University. The great challenge facing any use of this facility for serial di" raction or imaging experiments is the means to pass fresh samples across the beam at high enough speed to match the megahertz rate of X-ray pulses. Samples need to move more than 100 µm so that the explosion of the sample induced by one pulse is cleared out in time for the next, 1 µs later. This means samples need to move at over 100 m/s. Methods established in John's lab to fabricate micro-nozzles by two-photon polymerisation 3D printing were key in making fast and small jets with the necessary speed. This was combined with method to mix ligands with protein crystals on the fly to carry out enzymatic studies.!

During his visits, John also established a collaboration with Prof. Robin Santra of CFEL DESY on simulating the e" ects of XFEL pulses on molecules and initiated another collaboration with Prof Christoph Koch at Humbolt University in Berlin on micro-electron di" raction from protein nanocrystals. He continued a collaboration with Carolin Seuring in Chapman's group (now at CSSB) on the use of patterned graphene substrates for imaging amyloid fibers with the EuXFEL. !

On his visits John wrote "I have found the research environment in Germany to be first-rate, with a most exciting range of scientific projects here at CFEL. The visit has initiated several scientific collaborations which will be continued with my laboratory in Arizona, USA. In addition, the supporting sta" have been most kind and helpful."