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John C. H. Spence and the Age of X-Ray Lasers

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John Spence's career spanned a great range of interests and he had an enormous impact on several communities by leading them into exciting new directions. He was an inventor in all the senses that that word evokes. He loved developing instrumentation and many of his innovations were the key for the introduction and development of new methods. His knowledge was broad and he readily and widely shared ideas in riveting talks and clearly written papers and books. I was fortunate to have collaborated with him for 20 years, when I teamed up with him in 2002 on a quest to develop coherent diffractive imaging with X-rays. Here, I discuss some of the history of John's work in coherent X-ray imaging, how it led to the birth of a new field of femtosecond imaging of macromolecules with X-ray free-electron lasers [1].

John spent a sabbatical at Lawrence Berkeley Laboratory in 1997, at a time just before the first demonstration of imaging a general objects by phasing its X-ray diffraction pattern [2]. At Berkeley, the Advanced Light Source (ALS) was among the first of a new generation of high-brightness (coherent) X-ray sources and there was a need for expertise and knowledge of how best to utilize them. John fulfilled this role perfectly, bringing with him many ideas from electron microscopy: STEM imaging modalities, ptychography, convergent-beam diffraction, point-projection holography, and phasing diffraction patterns. Together with Malcolm Howells, John designed and built beamline 9.0.1 at the ALS to explore this new territory. In 2001, John organized the first International Workshop on Phase Retrieval, bringing together people interested in coherent imaging from the electron and X-ray communities. This "Coherence" conference series continues to this day, and is still growing.

One idea presented at John's first Coherence Workshop was single-molecular imaging at X-ray free-electron lasers, using the short pulses to outrun radiation damage [3]. The idea of imaging exploding molecules had earlier been considered [4] at Lawrence Livermore National Lab where I worked, enabling me to start a project to explore the approach. While waiting for the world's first soft X-ray FEL in Hamburg to come on line to test these ideas, I got in touch with John who immediately invited me to join his efforts at Berkeley. There followed some of my most enjoyable times in experimental science overcoming challenges with John, Malcolm, Uwe Weierstall and Stefano Marchesini, to record a full three-dimensional diffraction dataset from a single object [5]. Exposure times were long enough for long lunches full of John's characteristic barrage of jokes, stories, and ideas sketched on napkins.

It was hard to attract funding for the work, but the NSF Center for Biophotonics Science and Technology took an interest. This was headed Dennis Matthews who demonstrated the first plasma-based X-ray laser at Livermore, who supported John's idea (with Bruce Doak) to measure the diffraction of laser-aligned molecules as they traversed a continuous X-ray or electron beam [6]. John recruited Petra Fromme of ASU into these efforts, who supplied beautiful 0.5 µm sized crystals of photosystem I complexes. These had a nice aspect ratio and polarizability for alignment and experiments at ALS accumulated diffraction of crystals in a liquid jet based on Bruce's expertise. The accumulated powder diffraction patterns of unaligned crystals could potentially be used directly for structure determination, using John's new approach of retrieving structures directly from powder diffraction using a version of iterative phasing called charge flipping [7]. However, the flow of crystals in jets solved one of the biggest challenges we were facing plans for the first experiments to be conducted at the Linac Coherent Light Source—the first hard X-ray FEL under construction at SLAC—which was how to get samples into the X-ray beam.

The first experiments at LCLS were carried out in 2009, by a group of collaborators who had coalesced around these efforts and who brought the necessary expertise on high frame-rate detectors, sample delivery, and all the experience developed at ALS and the Hamburg soft-X-ray FEL (by then called FLASH). The goal was to show whether "diffraction before destruction"—as John had coined it—could give structural information at the atomic scale. If a protein crystal showed high-angle Bragg diffraction this would imply all proteins structures had not vaporised in a cloud of atoms. This worked spectacularly well and all were gratified to see clear peaks to the edge of the detector, many of which showed fringes due to the finite crystal extent [8]. Thereafter followed intense developments into how to analyse the data, following John's suggestion of treating it as Monte Carlo integration, and to apply it to novel biological problems. It took time to convince review committees that our approach of serial crystallography could be extended to time-resolved structure determination to follow reactions triggered by a laser or by mixing crystals with a ligand on the fly.

In what perhaps is his greatest impact on X-ray FEL science, John founded the NSF BioXFEL Science and Technology Center in 2013. This continues to operate today and has enabled hundreds of XFEL experiments at all XFEL facilities now operating around the world [9]. The technique of serial femtosecond crystallography has also spread to many synchrotrons, with beamlines using liquid jet technologies developed in John's lab. By providing the ability to obtain structures free of radiation damage, at physiological temperatures, and with time resolutions from femtoseconds to milliseconds and beyond, these developments have maintained the relevance of X-ray crystallography alongside the superb capabilites of cryo-EM and deep learning. John got enormous joy from these pioneering experiments. As he himself wrote, "…the birth of a new field is the most exciting time to be involved in research." [1].

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Figure 1. John Spence, assisting Petra Fromme to load photosystem I nanocrystals in the first serial femtosecond crystallography experiments at LCLS, December 2009.

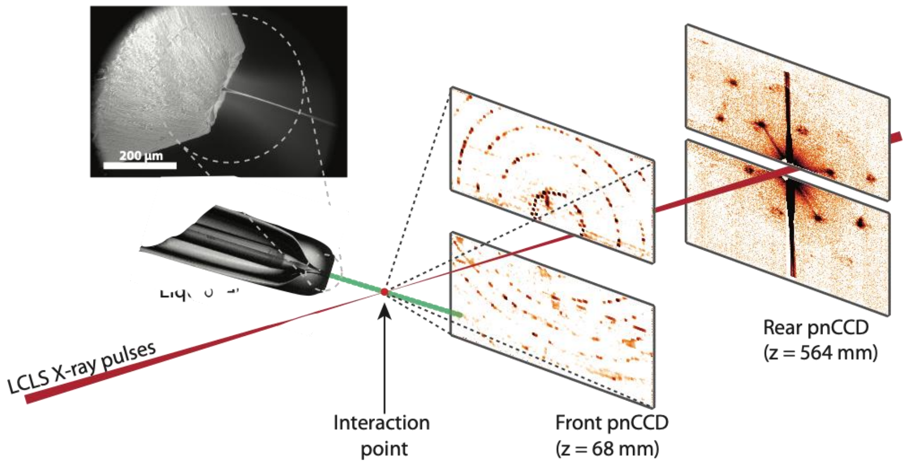

Figure 2. Serial femtosecond crystallography would not have taken off without several key ideas and instruments coming together just in time, including liquid nanojets, detectors, and algorithms.

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