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current events

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Promises of X-ray laser's power and potential for biology demonstrated with first publications

It has been a dream of researchers for over a decade to image complex biological molecules at high resolution without needing to crystallize them. Two studies published in the 3 February 2011 issue of *Nature* demonstrate how the unique capabilities of the world's first hard X-ray free-electron laser, the Linac Coherent Light Source (LCLS), located at SLAC in Stanford, USA, could revolutionize the structure–function studies of life-sustaining molecules. In view of the long-term importance of these papers, a full account is reproduced below from the press release of SLAC with only very minor modifications.

In one study an international research team used the LCLS to demonstrate a short-cut for determining the three-dimensional structures of proteins. The laser's brilliant pulses of X-ray light pulled structural data from tiny protein nanocrystals, avoiding the need to use large protein crystals that can be difficult or impossible to prepare. This could lop years off the structural analysis of some proteins and allow scientists to decipher tens of thousands of others that are out of reach today, including many involved in infectious disease.

In a separate paper the same team reported making the first single-shot images of intact viruses, paving the way for snapshots and movies of molecules, viruses and live microbes in action.

Led by Henry Chapman of the Center for Free-Electron Laser Science at the German national laboratory DESY and Janos Hajdu of Sweden's Uppsala University, the team of more than 80 researchers from 21 institutions performed these experiments in December 2009, just two months after the LCLS opened for research. Their studies are the first to demonstrate the power and potential of the LCLS for biology.

'The LCLS beam is a billion times brighter than previous X-ray sources, and so intense it can cut through steel', Chapman said. 'Yet these incredible X-ray bursts are used with surgical microscopic precision and exquisite control, and this is opening whole new realms of scientific possibilities', including the ability to observe atoms moving and chemical bonds forming and breaking in real time.

In the experiments, scientists sprayed viruses or nanocrystals into the path of the X-ray beam and zapped them with bursts of laser light. Each strobe-like laser pulse is so brief, a few millionths of a billionth of a second long, that it gathers all the information needed to make an image before the sample explodes.

Hajdu had proposed this method almost a decade earlier. Researchers at Arizona State University, Lawrence Livermore National Laboratory, SLAC and Uppsala spent years developing specialized equipment for injecting samples into the beam, and Germany's Max Planck Advanced Study Group brought in a 10-ton, $7 million instrument called CAMP to record every single photon of data with a fast ultra-sensitive X-ray camera for later analysis.

Tests at DESY and Lawrence Berkeley National Laboratory showed that the concept worked at lower X-ray energies. 'But as you go to higher energies, can you still outrun the damage?' asked team member Michael Bogan, a SLAC staff scientist and principal investigator at the PULSE Institute for Ultrafast Energy Science, jointly located at SLAC and Stanford University. The answer, he said, was yes: 'The physics still holds.'

The protein structure experiments were led by Chapman and Arizona State University's John Spence and Petra Fromme. They chose as their target Photosystem I, a biological factory in plant cells that converts sunlight into energy during photosynthesis. It is one of an important class of proteins known as membrane proteins that biologists and drug developers are eager to understand better.

Embedded in cell membranes, these proteins control traffic in and out of the cell and serve as docking points for infectious agents and disease-fighting drugs; in fact, they are the targets of more than 60% of the drugs on the market. Yet scientists know the structures of only a few of the membrane proteins, which are expected to make up some 40% of the protein universe, given the difficulty of turning them into big crystals for conventional X-ray analysis.

To get around this bottleneck, the researchers squirted millions of nanocrystals containing copies of Photosystem I across the X-ray beam. Laser pulses hit the crystals at various angles and scattered into the detector, forming the patterns needed to reconstitute images. Each crystal immediately vaporized, but by the time the next pulse arrived another crystal had moved into the bull's eye.

The team combined ten thousand of the three million snapshots they took to come up with a good match for the known molecular structure of Photosystem I.

'I attended several meetings this summer where this work was presented and I was extraordinarily excited by it', Michael Wiener of the University of Virginia, who was not involved in the research, said of the results. He leads one of nine institutes set up by the National Institutes of Health to decipher the structures of membrane proteins. 'Preparation of these nanocrystals is likely to be very very much easier than the larger crystals used to date', Wiener said, leaving scientists more time and money to find out how these important biomolecules work.

For the second experiment the team went a step beyond nanocrystals to no crystals at all. Led by Hajdu, they made single-shot portraits of individual virus particles. These snapshots are a step toward eventually producing stop-action movies of chemical changes taking place in molecules and within living cells.

Biologists have long dreamed of making images of viruses, whole microbes and living cells without freezing, slicing or otherwise disturbing them. This is one of the goals of the LCLS, and the researchers tested its capabilities on Mimivirus, the world's largest known virus, which infects amoebas.

Of the hundreds of Mimiviruses hit by the LCLS beam, two produced enough data to allow scientists to reconstitute their images. The images show the 20-sided structure of the Mimi's outer coat and an area of denser material inside, which may represent its genetic material. Shorter brighter pulses focused to a smaller area should greatly improve the resolution of these images to reveal details as small as 1 nm, the team wrote in their 3 February *Nature* report.

Obtaining a detailed picture of the internal structure of an individual virus 'would be a great achievement', said team member Jean-Michel Claverie, Director of the Structural and Genomic Information

Laboratory in Marseille, France, and one of the scientists who discovered Mimi's viral nature. 'This is a brand new way to look at a biological object', he said. 'This will allow us to address not only the questions related to the internal structure of the virus but its intrinsic variability from one individual virus particle to the next, a microscopic variability that might play a fundamental role in evolution.'

The team returned to the LCLS in January to look at the Mimivirus at X-ray wavelengths that should maximize the amount of contrast and detail in the images. They will be analyzing the results in the months to come.

SLAC Director Persis Drell, who sat in a control room packed with scientists as raw data from the two experiments came in, said the experience was thrilling, and so is the potential for biology and medicine. 'This first data and these first papers are really just the first view of a new research frontier', she said. 'They represent a turning point for the LCLS, demonstrating new technologies that will be great steps forward.'

LCLS-II conceptual design underway

In spring 2010 the US Department of Energy granted approval for SLAC to begin planning an upgrade to the Linac Coherent Light Source (LCLS). The LCLS-II team, led by Project Director John Galayda and Deputy Project Director David Schultz, is now in the process of writing a conceptual design report that details the project. This report, which is nearing completion, describes the use of another 1 km-long section of the SLAC linac, a second injector that would allow independent changes in beam parameters, a new tunnel with separate hard and soft undulator sources, and a new experimental hall. In all, LCLS-II would give investigators access to new regions of the X-ray spectrum and improved control over the X-ray beam while accommodating a larger number of research scientists working simultaneously.

The LCLS-II team will submit the conceptual design report to the Department of Energy in April 2011, at which point it will be reviewed and, if all goes well, awarded 'Critical Decision 1', which will allow the preliminary design to proceed.

Röntgen Prize for X-ray research goes to Christian David

In a ceremony held at the University of Giessen, Germany, on 26 November 2010, Christian David, a scientist at the Laboratory for Micro and Nanotechnology at the Paul Scherrer Institute, Switzerland, received the Röntgen Prize for research in radiation science. Christian pioneered a method for enhancing the quality of X-ray images. He developed an X-ray interferometer that allows the phase shift and scattering power of an object to be visualized, in addition to obtaining conventional radiographs produced by absorption. The interferometer is based on a set of diffraction gratings with micrometre-sized slits, developed and manufactured by David's group at the Laboratory for Micro and Nanotechnology. Christian David received the award jointly with Franz Pfeiffer from the Technische Universität München, who worked closely together with him.

Normal X-ray images are based on absorption contrast, which means that they show the shadow of the inner structure of the object being investigated. Therefore, materials with different absorption coefficients, such as bones and soft tissue in a medical examination, can be easily distinguished in an X-ray image. Materials with similar values of the absorption coefficient, however, look almost the same, which may be problematic in medical investigations, such as when a tumour has to be distinguished from the healthy tissue surrounding it.

Sine Larsen gives the first Barkla X-ray public lecture at Liverpool

Professor Sine Larsen, President of the International Union of Crystallography (IUCr), gave the first Barkla X-ray lecture at the University of Liverpool. This was also the University's first Science and Society Lecture for 2011. The series explores the beneficial relationship between science and society. Professor Larsen spoke about the impact of X-rays on society to a packed audience in the Victoria Gallery and Museum (VGM). Almost half of the audience were members of the public including a group of science students from a local high school.

Even though this was the first Barkla X-ray lecture, the University has held a series of Barkla lectures since 2006. The first Barkla lecture was given by the Nobel Prize winner Frank Anthony Wilczek on 3 February 2006. He talked about 'The Origin of Mass and the Feebleness of Gravity'. Other speakers in the series have included Nobel Laureates Martinus Justinus Godefriedus Veltman and Gerard Hooft, Wolf Prize Laureate Professor Francois Englert and the Lucasian Professor of Mathematics at Cambridge Michael Green.

Charles Glover Barkla (1877–1944) was awarded the 1917 Nobel Prize in Physics for his contributions to X-ray science. He was born on 7 June 1877 in Widnes, only about 12 miles from the University's VGM building where Sine Larsen gave her lecture. Barkla was educated at the Liverpool Institute and entered University College, Liverpool, in 1894 to study mathematics and physics, the latter under Oliver Lodge. He graduated with First Class Honours in Physics in 1898 and in the following year he obtained his Master's degree. Also in 1899, he was awarded a research scholarship by the Royal Commissioners for the Exhibition of 1851 and he proceeded to Trinity College, Cambridge, to work in the Cavendish Laboratory with J. J. Thomson. He returned to Liverpool in 1902 as Oliver Lodge Fellow. From 1905 to 1909 he was successively demonstrator, assistant lecturer in physics and special lecturer in advanced electricity at the university. Barkla's first researches concerned the velocity of electric waves along wires but in 1902 he commenced his investigations on Röntgen radiation which were to occupy almost his whole life. His discovery of homogeneous radiations characteristic of the elements

(Left to right) Michael Dacombe, Sine Larsen, Andy Cossins, Samar Hasnain, Ian Greer and Steve Holloway during the visit to Barkla X-ray Laboratory of Biophysics.

Sine Larsen with high school students after her lecture.

showed that these elements had their characteristic line spectra in X-ray and he was the first to show that secondary emission is of two kinds, one consisting of X-rays scattered unchanged and the other a fluorescent radiation peculiar to the particular substance. He discovered the polarization of X-rays, an experimental result of considerable importance for it meant that X-radiation could be regarded as similar to ordinary light. In a series of papers from 1906 onwards he reported many studies of X-rays and their interactions with matter, crucially showing that elements have characteristic X-ray line spectra.

Sine Larsen also visited the newly commissioned X-ray structural laboratory, which will be called the 'Barkla X-ray Laboratory of Biophysics' when it is opened in July by Sir Tom Blundell and Dame Louise Johnson. During the visit she met the Pro-Vice Chancellors of both the Science and Engineering (Professor Stephen Holloway) and Health and Life Science (Professor Ian Greer) faculties.

The University has been linked with the world of X-ray science almost from the time that William Röntgen made his discovery in November 1895. Only three months later Professor Oliver Lodge FRS (1851–1940) provided one of the earliest medical uses of X-rays by photographing a bullet embedded in the wrist of a 12-year old boy (*The Lancet*, 22nd February 1896, p. 497).

Symposium honours Edward A. Stern's contributions to the field of XAFS

A symposium and dinner honouring Ed Stern's contributions to the field of XAFS took place on 3 August 2010 during the opening day of the First North American Core Shell Spectroscopy conference, held concurrently with the Denver X-ray Conference. The symposium highlighted recent advances in XAFS experiment and theory, and emphasized how far XAFS has come since the discovery in the early 1970s by Sayers, Lytle and Stern that a Fourier transform of the XAFS oscillations can be used to determine local structure around a selected atom type, even in the absence of long-range order. Interestingly, the first correct short-range-order theory of XAFS was presented by these authors at the same Denver X-ray conference nearly three decades earlier. The symposium's dinner ended with a talk by Professor Daryl Crozier (Simon Fraser University) reminiscing on various aspects of Ed's distinguished career. This was timely as Ed reaches his 80th birthday this year. We would like to wish him well for his birthday and congratulate him for his achievements and leading the community worldwide to use and apply XAFS rigorously to whatever the applications might be. XAFS could have remained an esoteric technique if it was not for people like Ed.

Ed Stern at one of the recent international XAFS conferences, the first of which was held 30 years ago in March 1981 at Daresbury, UK.