International Report: BCA Spring Meeting 2014

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The 2014 Annual Spring Meeting of the British Crystallographic Association (BCA) took place at Loughborough University, from 7 to 10 April 2014. The theme of the meeting was "Crystallography@100: Looking to the Future, Learning from the Past." The plenary contributions from the Biological Structures Group (BSG), the Chemical Crystallography Group (CCG), the Industrial Group (IG), and the Physical Crystallography Group (PCG) followed the theme as did the Bragg and Lonsdale Lectures. The Young Crystallographers Group ran their sessions on the Monday and Tuesday morning before the main meeting and they are not reported here. The meeting was supported by 18 sponsors and 15 exhibitors.

The first section of this report concentrates on the above presentations and the meeting started with the Lonsdale lecture by Henry Chapman from DESY, Hamburg with the title "Macromolecular Crystallography with X-ray Laser Pulses." Free electron lasers (FELs) produce femtosecond pulses of coherent X-rays powerful enough to cut through steel and yet outrun radiation damage to crystals. These intense pulses are produced by self-amplified stimulated emission (SASE) through an undulator. A FEL pulse of full width at half maximum (FWHM) 30 femtoseconds and 10^{12} photon count has 50 GW peak power when compared with a typical synchrotron beam of 30 picoseconds half-width, 10^6 photon yield, and a peak power of 50 W. High radiation doses may cause changes in molecular structure, so these very short pulses will minimise the damage to the molecules. A tolerable dose is 30 MGy (megaGray) but this would heat water by 6200 K if no energy were able to escape, hence the need for very short pulse duration.

The ultrafast pulses from X-ray free-electron lasers (XFEL) have opened up a new form of nanocrystallography for structure determination of macromolecules. These pulses are of high-enough intensity and of sufficiently short duration that individual single-shot diffraction patterns can be obtained from a sample before significant radiation damage occurs.

In summary, diffraction before destruction holds good to approximately 1.9 Å resolution; experiments are conducted at room temperature; hundreds of thousands of two-dimensional (2D) diffraction measurements may be combined to yield average 3D structure factors; averaging, through the expectation maximization convergence (EMC) algorithm increases signal/noise ratios and favours the best crystals; high-throughput experiments are possible, as are time-resolved measurements.

The PCG Plenary Lecture was given by Malcolm McMahon from Edinburgh University and entitled "Extreme Crystallography in a Flash". The structure of iron at ambient conditions was determined to be *body centred cubic (bcc)* in 1917. Its structure at the centre of the earth, where the pressure is 3.5 million times atmospheric pressure (3.5 Mbar), or deep within exoplanets, where pressure may exceed 10 Mbar, is unknown. Until the 1990s, it was assumed that *all* materials would adopt high-symmetry structures at high densities, and that they would all become metals. The development of advanced powder diffraction techniques in the early 1990s, which enabled Rietveld refinement of high-pressure powder diffraction data for the first time, has since revealed that many initially simple systems (e.g. the elements) adopt very complex structural forms at high densities. Europium metal exhibits the *bcc* structure at ambient pressure which then transforms to the *hexagonal close packed (hcp)* structure at 12.5 Gpa and then, it was thought, to a new phase (Eu-III) at 18 GPa. In fact, Eu remains *hcp* up to 33 GPa and that extra diffraction peaks at 18 GPa are from an impurity phase with space group *R*-3*c*, possibly EuH_2. At 31.5 GPa Eu transforms to a phase (Eu-IV) with an incommensurately modulated monoclinic structure with superspace group *C*2/*c*. Eu-IV is the first phase in the lanthanide elements with an incommensurate crystal structure.

The CCG Plenary Lecture "Understanding the solid state into the next hundred years" was delivered by Paul Raithby from the University of Bath. He outlined the progress of X-ray crystallography from its origins with the early experiments of the Braggs to the present day. Small molecule crystallography in the 1960s and 1970s, with data collected on Weissenberg and Precession cameras, manual three-circle diffractometers, automated diffractometers controlled by punched cards or paper tape, gave way to four-circle instruments in the 1980s and 1990s and to the first macromolecular structures. Heavy atom phasing methods on mainframe computers progressed to automated direct methods and structure solution on personal computers. Synchrotron radiation in the UK, first at Daresbury and then at Diamond enabled shorter data collection times on smaller crystals.

X-ray crystallography yields a ground-state time-averaged structure, and this is its weakness. The future will involve synchrotron and XFEL sources, the latter enabling structure determination from single macromolecules, and femtosecond time-resolved diffraction experiments. Advances in X-ray sources, detectors, and computing power will allow observation of chemical/biological reactions as they happen. Total, as opposed to Bragg, scattering will bring a new perspective to the structure analysis, and the progress will be made in the analysis of non-crystalline materials, solutions, gels, and surfaces. Finally – will X-rays still be the radiation of choice?

The IG Plenary Lecture "Crystallography @100: Learning from the past and trying to look into the future"

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was given by Joel Bernstein from New York University, Abu Dhabi.

Joel's presentation was a journey through the last 100 years packed with interesting facts, quotes, and anecdotes. From the 1912 Friedrich and Knipping first X-ray diffraction (XRD) experiment through the contributions of artists in hand drawing 3D structures, the computing work at IBM and the work of many eminent scientists, too numerous to mention. As to the next 100 years he said that we are on the threshold of ever more exciting discoveries and applications of crystallography. He used an Eyring diagram to explain transition states and the control of reactions.

At the start he stated that there are four photographs of a phenomenon that led to paradigm changes in scientific thinking, but only revealed them at the end. They were: Roentgen 1895 (X-ray image of a hand); Becquerel 1896 (photographic plate fogged by uranium salt with an image of a metal Maltese cross); Friedrich & Knipping 1912 (first XRD image); and Franklin's 1952 (DNA X-ray plate).

The Bragg Lecture "Exploring a century of reciprocal space: same old theory – endless new results" was given by Judith Howard CBE, FRS from Durham.

Judith started with a review of the legacy of the two Braggs and went on to explore the work of other Nobel Laureates involved in crystallography, among them Dorothy Hodgkin and Max Perutz. Early crystal structures solved by the Braggs included diamond, which demonstrated the tetrahedral nature of the carbon–carbon bond, fluorspar (CaF_2), pyrites (FeS_2), and NaCl. The first successful X-ray photographs of a protein (pepsin) were obtained in 1934 by J.D. Bernal and Dorothy Crowfoot (Hodgkin) when Bernal realised that the crystal had to be kept in its mother-liquor to prevent disorder. Dorothy went on to solve the structures of Vitamin B_{12} and cholesterol iodide. In 1929, Kathleen Lonsdale proved that the benzene ring is hexagonal and flat when she solved the structure of hexamethylbenzene. She, together with W.T. Astbury, applied space group theories to the study of XRD patterns from crystals, work which resulted in the creation of the International Tables for Crystallography.

Judith covered the wider impact of crystallography through theory and computers, from Beevers–Lipson Strips, used by early crystallographers, including Dorothy Hodgkin to compute Fourier maps, to main frame computers and now laptops. She illustrated this with applications in industry and engineering, medicine and health, and education at all levels. In her Durham laboratory, diffraction experiments are performed on crystals at high pressure in a diamond anvil cell, spin state changes (magnetic to non-magnetic) are investigated, as are colour changes during temperature changes, and superconductivity at 2 K. She predicted a bright future for crystallography, with more intense X-ray sources such as the XFEL and faster acquisition of data, leading to time-resolved experiments showing how chemical reactions take place, and maybe even how protein molecules move and actually work.

The BSG Plenary was given by Neil Isaacs from the University of Glasgow and entitled "How times have changed."

Some 25 years after the first diffraction experiment the work of J. Monteath Robertson [Rep Prog Phys (1937) 4 332–367] at Glasgow laid the foundations for protein crystallography. The Sayre equation of 1951 for direct methods and in 1956 FORTRAN (from IBM) made programming easier. In the 1960s, Fred Sanger with insulin sequencing and the introduction of automation allowed the processing of one residue per hour instead of one a day. Fast Fourier transform (FFT) came in 1965. In 1975, the Protein database (PDB) had 13 entries and in 1976 a synchrotron was used for protein crystallography. In the 1980s, the PDB had 60 entries, BITNET (IBM) network for academics was set up with a single link CUNY to Yale, and Bricogne's maximum entropy method was used for solving crystal structures. VAX computers brought computation into the laboratory, and in 1988 the Jules Hendrix image plate was the death of film. The 1990s increased the PDB to 486 structures and saw the release of CCP4i interface to macromolecular software. In the 2000s, the PDB had 11395 structures, NIH began a protein structure initiative, the WWPDB bulletin board was established opening up a world of help, the Structural Genomics Consortium (SGC) started and in 2010 the PDB had 60789 structures. Neil summed up the future in four words; faster, smaller, larger, and better.

This second section reports on some of the meeting sessions. The IG ran an "XRD in the Pharmaceutical Industry" session with three presentations starting with Andrew Dobson of Astra Zeneca with the title "X-ray Powder Diffraction in context – Case studies in Pharmaceutical Solid Form Selection." Andrew stated that solid form selection is an important step in the development of pharmaceutical compounds impacting on downstream processes from early to late phase. X-ray powder diffraction (XRPD) is a key technique in solid form characterisation alongside other characterisation techniques. It provides rapid assessment (~4 min) of early phase compounds with simultaneous assessment of several compounds with a large number of samples generated for each compound. Hydrate characterization is an important part of the screening and single-crystal structures can be determined on crystals obtained using "Sublimus", an in-house developed instrument to grow crystals over a range of temperatures by sublimation. Structural Informatics is used through their "CFC" tool to estimate the likelihood of a particular interaction occurring based on the crystal structures of molecules similar to the target. This helps to increase confidence that the stable form has been discovered, guide and design experimental work, and support patent strategy and regulatory design.

The next talk from Philippe Fernandes of SAFC, Pharmorphix, Cambridge was entitled "Routine XRPD investigations on active pharmaceutical ingredients." Philippe explained that X-ray powder diffraction is a well established and recognised technique within the pharmaceutical industry to identify and quantify the polymorphic forms of a given active pharmaceutical ingredient (API), often in conjunction with other techniques, e.g. DSC. The use of indexing with DASH or TOPAZ and confirmation with Pawley fitting to confirm the cell parameters is an essential step in the identification of polymorphs. Variable temperature and variable

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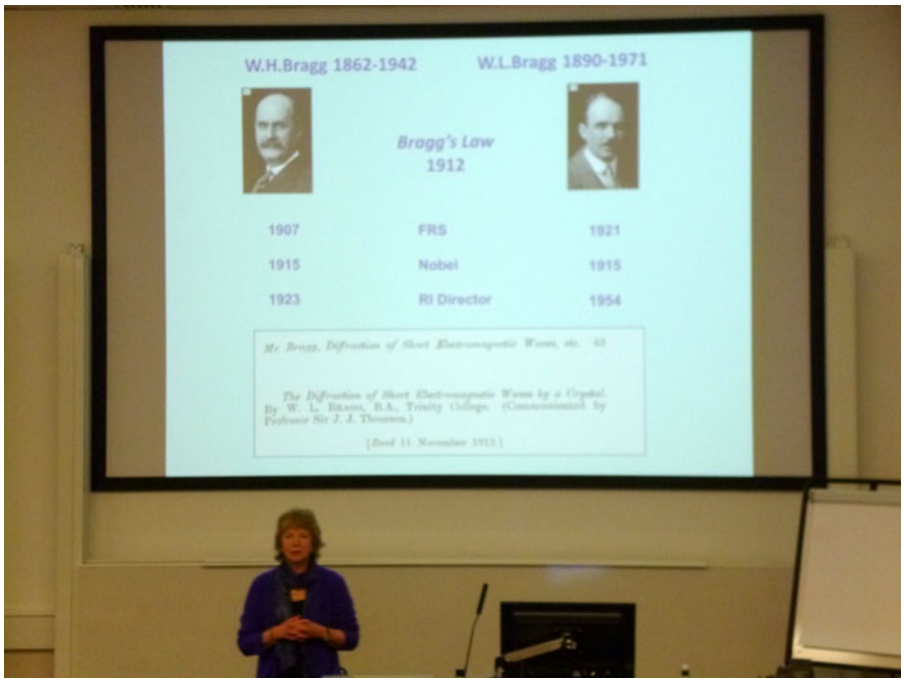

humidity XRPD are used to evaluate various physicochemical characteristics of pharmaceuticals. Structures are solved through simulated annealing with DASH or FOX.

The final talk of the session was given by Mark Eddleston, from the University of Cambridge with the title "Probing the Mechanism of Aspirin Degradation". A look at Aspirin degradation with time varies from batch to batch and under different temperature and humidity conditions. Cocrystallisation and the excipients present in the tablet can also affect degradation. Degradation rates at 40 °C and 95% RH were measured for different sample preparation methods, different crystal forms and the presence of excipients. The following observations were made: strong batch to batch and within batch variability, crystallisation of the degradant accelerates the rate of degradation and excipients can change the rate dramatically. Aspirin in the presence of water is converted into salicylic acid which initially forms a protective layer on the surface that remains until a crystal of salicylic acid has nucleated allowing degradation to continue.

A session of four prize lectures took place over Wednesday morning.

The first, the CCDC–CCG Prize lecture, was given by Lynne Thomas from the University of Bath and entitled "Molecular Disorder and Materials Function – a Marriage made in Confusion". Lynne stated that molecular disorder is dynamic correlated motion of atoms or molecules as shown in a fibre diffraction pattern of cellulose from wood (organic) or in inorganic materials such as semi-super conductors showing physical properties such as conductivity, ferroelectricity, and optical properties. Disorder has not been properly exploited in organic materials even though it is often present. It can be deliberately induced using crystal engineering principles. For example, the intergrowth of the two forms of aspirin can introduce increased solubility. Finally, thermochromic transitions were compared in 2-iodoaniline (form 2) and 2-bromoaniline (form 2) with the latter exhibiting a red-to-yellow and yellow-to-red reversible transition at 60 and 85 °C, respectively.

The BSG prize lecture was given by Simon Kolstoe from the University of Portsmouth and entitled "Targeting Transthyretin: X-ray Crystallography and Drug Design". He said that the first X-ray structure of Prealbumin was published over 30 years ago in the same month as the birth of the speaker. Now there are 231 structures of prealbumin (now called transthyretin) in the Protein Data Bank. It is interesting as a thyroxine carrier and because it is the main protein component in the hereditary disease transthyretin amyloidosis. In this type of amyloid, fibrillogenesis involves tetramer disassociation followed by structural changes within the monomer rendering the protein capable of misassembly to the crossed-β form of the fibre. Working with industry a new class of small-molecules that bind to globular transthyretin and prevent aggregation has been designed.

Next was the Institute of Physics sponsored PCG-SCMP Physical Crystallography Prize Lecture given by Roger Johnson from the University of Oxford and titled "Polarity, Chirality, and Axiality in Multiferroics". After a brief introduction to multiferroics, a revisited study of $MnSb_2O_6$ was discussed by Roger. It has a helical structure with scalar chirality related to a cycloidal polar magnetic structure by an axial rotation of spins. It is a multiferroic with novel 1-state/2-state switching. Next was the study of the new multiferroic $Cu_3Nb_2O_8$ with an axial structure coupled to chiral magnetism with low symmetry and ideal for theoretical studies of microscopic mechanisms. Multiferroics are fascinating materials that provide a wealth of new physics. New symmetry principles have been developed, such as the ferroaxial mechanism, which are being tested by state of the art experiments to find new and more exotic multiferroic materials.

Finally the Industrial Group-Young Crystallographers Group Prize lecture "Tuning the optical properties of new

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organometallic compounds", was presented by Mathew Bryant from the University of Bath. He reported the synthesis, spectroscopy, and structural investigation of new luminescent complexes of Pt(II) based on substituted tridentate 1,3-di (2-pyridyl)benzene(N^C^N) ligands was reported. Through variation in ligand, particularly in the fourth coordination position, the complexes display highly reversible vapochromic and solvatochromic effects in the solid state, along with dramatic changes in photoluminescent properties. Red (form 1), yellow (form 2), and blue (form 3) variants can be colour cycled by exposure to different atmospheres. Red to yellow is driven by vacuum, ethanol, or dry nitrogen and reversed in air. Yellow to blue is driven by methanol and reversed by dry nitrogen or vacuum. Blue to red is driven by air and reversed by methanol. Further development may lead to possible sensing applications.

Space limitations make it impossible to report here sessions on Crystal Engineering, Non-ambient Diffraction (two sessions), Application of Neutron Diffraction in Chemical Crystallography, Magnetic Structure determination, Dynamics Processes and Reactions, Complementary Non-Diffraction Techniques (two sessions), and Pushing the Limits; Faster and Slower, which between them covered many aspects of crystallography. However, reports of these sessions will appear on the BCA website in due course.

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