Crystallography News

British Crystallographic Association

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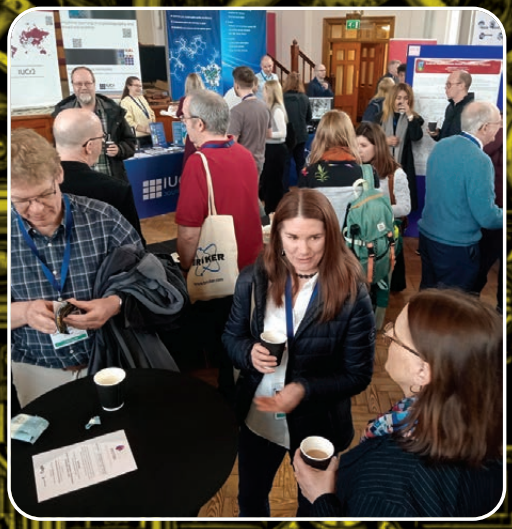

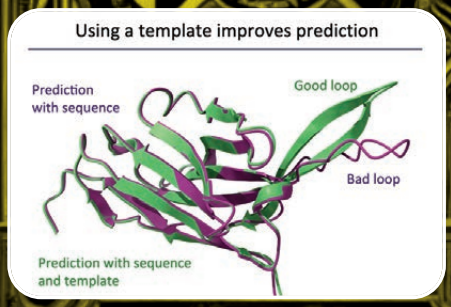

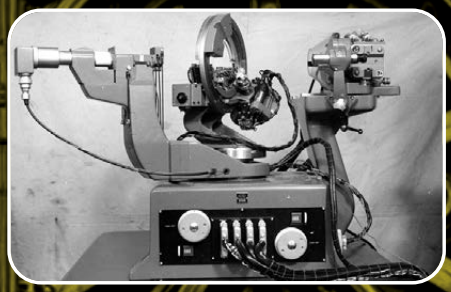

Scenes from the CCDC Science Day and the Leeds Spring Meeting

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Rigaku oxford diffraction

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Crystal LINE

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Control processes better with AI-based software analysis.

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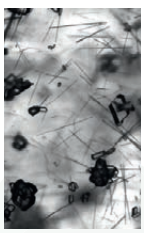
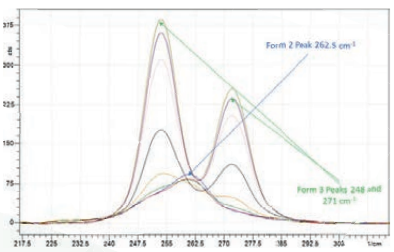
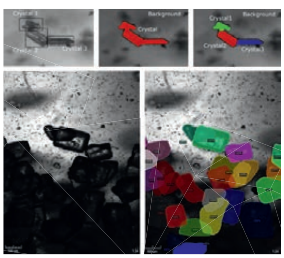
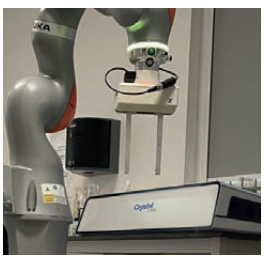


Polymorphic transformation

Coloured compounds







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Bursaries are available for BCA members to attend national/international crystallographic meetings in 2024/25.

Local meetings and virtual meetings (with no travel) are supported. Eligible members may apply every year.

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Please ensure that items for inclusion in the December 2024 issue are sent to the Editor to arrive before 25 October 2024.

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These details are not divulged to any others without your permission. You may inspect your entry during the Annual Meeting, or otherwise by application to the BCA Administrative Office. We will be happy to amend entries at any time.

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Contents

This month's cover:

Scenes from the CCDC Science Day and the Leeds Spring Meeting with a glimpse of technologies, new and old, below.

From the President

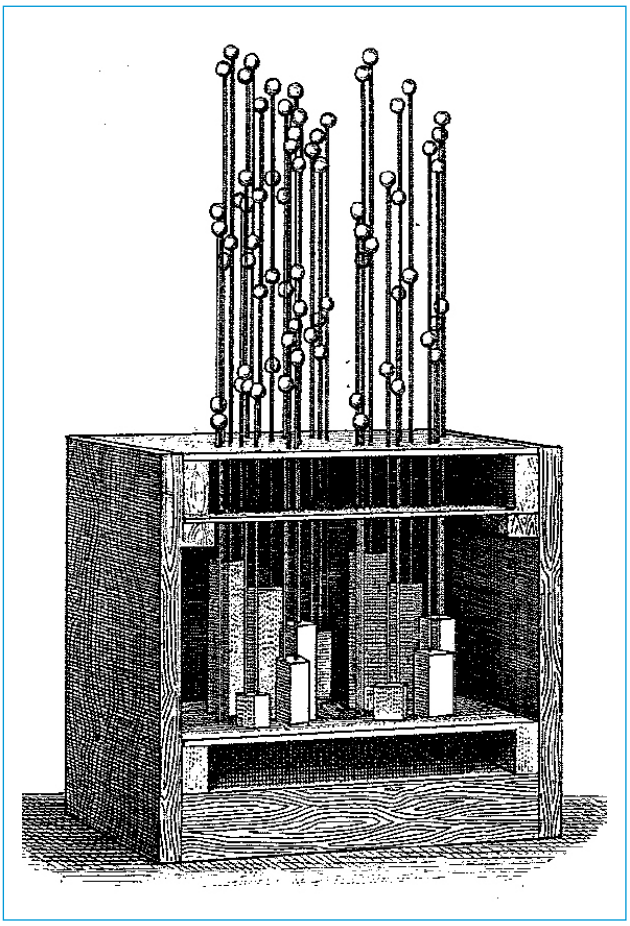
DESPITE the indications from the weather in St Andrews over the last few weeks it's summer time and I'm looking forward to going on holiday to Germany this weekend. It is supposed to be a break from thinking about crystals, but one thing I'm particularly looking forward to is visiting Terra Mineralia in Freiberg again (fortunately my family are too!). This is a wonderful collection of minerals – beautiful and rare display of specimens as well as the less dramatic members of the huge collection that the TU Bergakademie Freiberg holds.

Freiberg is a historical centre of mineralogy and crystallography due to its links to the nearby Erzgebirge/Krušnohoří (Ore Mountains), a Unesco World Heritage site straddling the Czech/German border. This area is a great place to visit old mines (including those specialised in silver and uranium) and see specimens of the many minerals whose discovery was first reported in the region, such as Zeunerite, $Cu(UO_2)_2(AsO_4)_2{\cdot}10\text{-}16H_2O$, Brassite $Mg(AsO_3OH){\cdot}_4(H_2O)$ and Koechlinite Bi_2MoO_6.

Incidentally, Koechlinite has a screw axis, which brings me to another German crystallographic link which has been occupying my mind of late. Chirality and its expression in crystal structures as enantiomorphism is a current interest. The 65 so-called Sohncke groups are central to this and, having read and written the name so many times over the last few months, I realised I didn't know anything about the person after whom the groups are named.

A little research led me to the fact that **Leonard Sohncke** (1842-1897), born in Halle was the first to consider crystallographic (as opposed to abstract) chirality in what came to be called space groups, and formalised the crystallographic screw axis (the glide plane was separately developed by **Barlow**, **Fedorov** and **Schoenflies** in their completion of the 230 space groups). Sohncke originally came up with 66 space groups which a chiral crystal structure may inhabit, but this was corrected down to 65 by Schoenflies. Another important contribution was the design of wooden models to demonstrate concepts such as screw axes when teaching (see picture), as published in his seminal 1879 work *Entwickelung einer Theorie der Krystallstruktur*. There is a fascinating short biography and explanation of the development of his work in **André Authier**'s *Early Days of X-ray Crystallography* (OUP, 2013), part of the IUCr book series.

On a more up-to-date topic, I have the pleasure of mentioning the poster prizes awarded at the Spring Meeting. **Lewis Williams** (University of Essex) won the ACA Judith Flippen-Anderson Structural Dynamics Prize for a poster entitled *"Visualising the Peroxidase Catalytic Cycle: Spectroscopically Verified Structures of Heme Intermediates from a Dye-decolorizing Peroxidase Catalytic Cycle Obtained Using Synchronous Time-resolved Crystallography and X-ray Emission Spectroscopy"*. The IUCr poster prizes were awarded to **Daniel Rainer** (University of Southampton) for



Source: Wikimedia.

"The National Electron Diffraction Facility – what, where, and how for 3DED now", **Cicely Tam** (Diamond Light Source) for *"Optimising and automating microcrystallisation methods for serial crystallography"* and **Shivani Grover** (University of Edinburgh) for *"Understanding the barocaloric effect in choline based plastic crystals from ab initio molecular dynamics"* – congratulations to all recipients and many thanks to the sponsors.

Finally, I note the sad news of the passing of **Richard Pauptit** (1954–2024), a stalwart of the community, who served as BSG President for many years. He made significant contributions to the field of protein crystallography and related areas throughout his career in academia and at AstraZeneca.

Alex Gibbs
University of St Andrews

BCA Council 2024

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Full committee details on the BCA website
www.crystallography.org.uk

From the Editor

IT is a great pleasure to bring you this issue of *Crystallography News* which begins with News from the CCDC as well as featuring the first of our Corporate Member Profiles, this time focussing on Molecular Dimensions. We continue reporting of the 2024 Spring Meeting in Leeds by covering the outstanding CCG, IG and BSG sessions and we have a bursary awardee report. We then have a fascinating report on the CCDC Science Day held in Cambridge in June this year as well as reports on the biologically-themed Astbury Conversation which was held in April in Leeds soon after the Spring Meeting and on the earlier CCP4 study weekend which was held in Nottingham in January. We have two subtly-related articles which come under the Down Memory Lane umbrella and should be of interest to members with a historical bent. We also celebrate the life of former BSG President, the late Dr Richard Pauptit.

In 1950, Alun Turing (now famous for having led the team which decoded German transmissions encrypted by the Enigma machine in WW2) initially conceived the idea of artificial intelligence in the form of a person exchanging messages with another person or a machine, but not knowing whether they were communicating with a computer or a human. If the tester could not reliably tell the messages from the machine from those of a person, the machine would be said to have passed the test[1]. Given the reputed strengths of the latest AI technologies, I thought I would call on them to help me write the remainder of this editorial and here are the virtually unedited results obtained from a few of the free online tools. All were given the string: "Editorial for Crystallography News."

ChatGPT

Crystallography is a fascinating and rapidly evolving field that plays a crucial role in numerous scientific disciplines, such as chemistry, physics, biology and materials science. Recent advancements in crystallography have led to groundbreaking discoveries and applications, showcasing the immense potential of this branch of science.

One of the most exciting developments in crystallography is the use of advanced structural determination techniques, such as X-ray crystallography, electron diffraction and neutron scattering. These methods allow researchers to study the atomic and molecular structure of crystalline materials with unprecedented detail and accuracy. By elucidating the arrangement of atoms in crystals, scientists can gain crucial insights into the properties and behaviour of materials, leading to the development of new drugs, advanced materials and cutting-edge technologies. Furthermore, crystallography has played a pivotal role in the discovery of novel drugs and therapeutic agents. By determining the three-dimensional structure of target proteins and enzymes, researchers can design more effective drugs with fewer side effects. This has revolutionized the field of drug discovery and paved the way for the development of personalized medicine tailored to individual patients' genetic makeup.

In addition, crystallography has also made significant contributions to the study of biological macromolecules, such as proteins and nucleic acids. By determining the structures of these complex molecules, scientists can better understand their function and role in various biological processes. This knowledge has profound implications for the fields of biochemistry, molecular biology and biotechnology, leading to advancements in areas such as drug design, enzyme engineering and genetic engineering.

Overall, the future of crystallography looks incredibly promising, with new techniques and technologies continually pushing the boundaries of what is possible. As researchers delve deeper into the atomic and molecular world, we can expect even more exciting discoveries and applications that will revolutionize science and technology. Crystallography News will continue to be a vital source of information for scientists, educators and enthusiasts alike, highlighting the latest developments and breakthroughs in this dynamic field.

Google Gemini (previously **Google Bard**) *Crystallography: Unveiling the Hidden World*

Crystallography, the science of determining the arrangement of atoms within a crystal structure, continues to be a powerful tool for unlocking the mysteries of the material world. From the development of new drugs and materials to the understanding of biological processes, crystallography plays a crucial role in scientific advancement.

In this issue of Crystallography News, we will explore some of the latest breakthroughs in the field. We will also highlight the work of crystallographers who are pushing the boundaries of our knowledge and developing new techniques to probe the hidden world of atoms. I am excited to share this issue with you and invite you to join the conversation. Crystallography is a dynamic and ever-evolving field and I believe that the best is yet to come. Let's delve deeper into the fascinating world of crystallography!

And finally, a more succinct one with an ecological flair for carbon-conscious members: **Ecosia Chat**

Crystallography is a fascinating field that plays a crucial role in various scientific disciplines. When writing an editorial for Crystallography News, you might want to highlight recent advancements, innovative research and the impact of crystallography on different industries. It's also essential to emphasize the importance of sustainability in crystallography practices to ensure a more eco-friendly approach to scientific research. If you're interested in exploring sustainable practices in crystallography further, I can provide you with some tips and resources. Just let me know!

What is clear with these tools is that their English is considerably less tongue-twisted than my own which would allow members to distinguish the work of the real-world CN editor from that of *the machine* very easily! Whilst ***Crystallographic Forteana*** will officially return in a future issue, I think there are some Fortean and ecological undertones in my contribution to this issue's Down Memory Lane. Finally, I must thank Philip Bradfield (Edinburgh) for submitting an excellent answer to last issue's quiz question. The quiz itself, along with a full appraisal of Philip's answer, will return, hopefully, in the next issue.

Jon Cooper, UCL

References:

1. Turing, Alan (1950). "Computing machinery and intelligence." *Mind* **LIX**, 433–460.

News from the CCDC

CCDC Scientist Awarded Prestigious BACG Young Scientists Award

Dr Pietro Sacchi, Research and Application Scientist at the CCDC, has been awarded the British Association for Crystal Growth (BACG) Young Scientists Award for his exceptional research on the HIV drug Ritonavir. The award is granted annually to a candidate who has made the most significant advance in the understanding of crystal growth processes. Pietro won based on his ground-breaking PNAS paper entitled "Crystal size, shape and conformational changes drive both the disappearance and reappearance of Ritonavir polymorphs in the mill." Read more at the CCDC website.

CSD Tools in Action: Cocrystal Design and Structural Features Analysis

Izabela Madura and co-workers from the Warsaw University of Technology used crystal structure analysis from the CCDC to design and study two cocrystals of caffeine and phenylboronic acid. This study investigates two cocrystal polymorphs composed of caffeine and 4-chlorophenylboronic acid using solid-state informatics tools. Read more at the CCDC website.

Check out all our blogs at the CCDC website.

User Webinar: Unlock the Potential of the CSD to Teach Chemistry and Crystallography

The CCDC hosted an external user webinar on the 6th of June featuring two academics from the US: Judith Currano, Head of the Chemistry Library at the University of Pennsylvania, and Diane Dickie, Senior Scientist for X-ray Diffraction and Crystallography at the University of Virginia.

During the webinar, both speakers emphasized how the CSD and associated software can be used to understand and gain experience in searching a scientific database, as well as to rapidly interrogate structure quality and re-interpret models – essential skills for any emerging structural scientist. If you missed the webinar, you can watch it on demand at the CCDC website.

CCDC Online Events: Free Virtual Workshops in October and November

First Steps in Protein-Ligand Docking With GOLD

8th October at 16:00–17:45 (BST)
This entry-level workshop on GOLD is designed for those working in drug discovery. You will learn the basics of performing protein-ligand docking using the CCDC's docking software GOLD. Register at the CCDC website.

ConQuest to Mercury – From Searching to Data Analysis

22nd October at 13:00–14:45 (BST)
We will explore a workflow using ConQuest and Mercury to have an in-depth look at trends and behaviours of defined 3D parameters, such as inter- and intra-molecular distances, angles and torsion angles as well as crystallographic parameters for relevant groups of structures in the CSD. Register at the CCDC website.

Introduction to Pharmacophore Searching Using CSD-CrossMiner

5th November at 10:30–12:15 (GMT)
This entry-level workshop on CSD-CrossMiner is designed for those working in drug discovery. You will learn how to perform pharmacophore searches to uncover new ligands using the CCDC's software CSD-CrossMiner. Register at the CCDC website.

All sessions are 90 minutes long and will include presentations and demonstrations by CCDC expert tutors and a hands-on part for you to try the software, with the tutors available to help you and answer your questions. The workshops will be recorded and all registered participants will have access to the recording.

CCDC Engagement Grant

Applications for the 2024/2025 round of CCDC Engagement Grants are now open! Awards are available to fund the creation of new STEM outreach activities and resources about crystallography or structural science to inspire non-specialist audiences, such as children and the general public.

Whether it's a video, social media content, game, poster, or any other related activity, we want to hear your ideas! You can explore the resources created by the winners of previous years' engagement grants at the CCDC website for inspiration. Applications close on 30th September 2024 (11:59 pm BST).

Follow us on Social Media

Want to learn more about CCDC events, blogs, case studies and software updates? Follow us on LinkedIn, Facebook and Twitter.

Sign up for the CCDC newsletter to receive inspiring content, the latest data updates, product releases and event announcements.

Ana Machado
CCDC

Corporate member profile: Molecular Dimensions

THE 1990s were a pivotal decade for structural biology. The emergence of several third generation synchrotron sources, along with the development of cryo-crystallography techniques marked significant milestones, shaping the field as we know it today[1].

In 1998, a budding crystallographer named Tony Savill identified a significant gap in the market: the field lacked products tailored to their specific needs. To address this, Tony founded Molecular Dimensions in Newmarket, England, with the vision of transforming it into one of the world's leading crystallography companies. This vision was propelled by significant milestones, for example an international collaborative research project in 2017. This project utilised our Free Interface Diffusion Plate and successfully reached the International Space Station, where it was used in a microgravity experiment to crystallise the Parkinson's disease protein LRRK2[2].

Over the years, we have developed key products in collaboration with leading scientists. For example, Morpheus Fusion, licensed by Fabrice Gorrec from the LMB Cambridge, is one of the most successful screens responsible for solving many novel proteins. While SG2, designed by Janet Newman, is an evolution of the popular and effective SG1 screen. Born from innovative chemical polymer research, Molecular Imprinted Polymers (MIPs), is a fascinating nucleating agent designed by Naomi Chayen. Our collaborations with crystallography experts have enabled us to commercialise and make accessible their innovative techniques to crystallographers around the world.

Now a part of the Calibre Scientific group, a diverse global provider of life science reagents, tools, instruments and other consumables to research laboratories, we partner with our sister companies, such as Protein Ark and Anatrace, to extend our scientific capabilities, allowing us to serve not only crystallographers but also the broader structural biology community with reliable methods for their work. For instance, one of our screens was used to solve one of the first structures of the COVID spike protein early in the pandemic.

Operating from our state-of-the-art manufacturing site at the UK headquarters in Sheffield, the technical team supports educational workshops by providing insightful talks and sharing tips and tricks. We actively engage with our customers by supporting local and international scientific conferences as well as readily assisting with technical queries by phone and via live web chat. Calibre Scientific's vision is to be your trusted partner for scientific discovery, so feedback from our customers and their success is always gratifying, especially when a scientist solves a new protein structure using our products.

Recently, Calibre Scientific opened an additional new distribution warehouse at the Advanced Manufacturing Park on the outskirts of Sheffield, expanding our operations with a brand new 20,000 square foot facility. This expansion has enabled us to offer more roles to local professionals and continue our work with Sheffield Hallam University supporting undergraduate and graduate students.

Looking ahead, our goals for the next 5-10 years include continuing to maintain high product standards, enhancing efficiency and developing new tools to streamline protein crystallisation. Calibre Scientific is undergoing an exciting period of growth and we remain focused on leveraging the talent within our company to stay at the forefront of this industry. Emily Parkinson, Production Scientist at Molecular Dimensions, shares the following.

"Work in the Molecular Dimensions lab focuses heavily on quality and consistency; it has taught me the importance of perfecting processes to maximise the reproducibility of results. My favourite part of working here is developing new products, keeping up with literature and evolving scientific techniques to come up with new screen formulations. Spending time bringing an idea to life is always rewarding when you see the product on the website or when the first order for it comes in. The spirit around the Sheffield Calibre Scientific site is always positive and collaborative (and there are always sweet treats waiting in the kitchen). Our team is rapidly expanding and there are more and more opportunities on site to learn something new."

We are a collaborative company open to new opportunities to enhance the structural biology field. Please get in touch with us to discuss further at **enquiries@moleculardimensions.com** or visit our website to learn more about our products.

Kira Fuller and **Paul Driver**
Calibre Scientific

References:

1. Jonathan C. Brooks-Bartlett and Elspeth F. Garman (2015). "The Nobel Science: One Hundred Years of Crystallography." *Interdisciplinary Science Reviews* 40, 244 – 264. https://doi.org/10.1179/0308018815z.000000000116.
2. Sebastian Mathea *et al.*, (2018). "Crystallizing the Parkinson's Disease Protein LRRK2 under Microgravity Conditions." *BioRxiv (Cold Spring Harbor Laboratory).* https://doi.org/10.1101/259655.

BCA Spring Meeting 2025 programme

The event will be held at the University of Leeds.

Early Stage Crystallographers Group (ESCG)

Monday 14 April 2025

13:00 – 21:00

The ESCG satellite meeting is an opportunity for all early-stage crystallography researchers, from across the BSG, CCG, PCG and IG, to present their work in a supportive and friendly environment, which will be run by fellow early career scientists.

13:00 – 13:30

ESCG Opening Plenary:

Session Chair: **Sam Lewis** (Cardiff University / Diamond Light Source)
Speaker: **Mark Warren** (Diamond Light Source)
Title TBC

13:30 – 17:15

ESCG Research Sessions

Contributed talks from the ESCG community.

Session 1 Chair: **Rebecca Clulow** (Uppsala University)
Session 2 Chair: **Ben Coulson** (Cardiff University)
Session 3 Chair: **Jake Hill** (University of Leeds)

17:15 – 17:45

ESCG Annual General Meeting

18:30 – 21:00

Flash Poster Presentations

Session Chairs: **Ellie Dempsey** (University of Edinburgh) and **Stephen Brown** (University of Warwick)

Researchers have an opportunity to present an overview of their poster in 30 seconds with one PowerPoint slide.

19:00

Poster Session with Dinner and Wine

21:00

Evening Concludes

Tuesday 15 April 2025

09:00 – 09:30

Parkin Lecture

Session Chair: TBC
Speaker: TBC

09:30 – 10:30

Session 4

Session Chair: **Stephen Brown** (University of Warwick)

10:30 – 11:00

Closing Plenary

Session Chair: **Jake Hill** (University of Leeds)
Speaker: **Jeremiah Tidey** (Warwick / NCS)
Title TBC

BCA Main Meeting

11:30 – 12:15

Lonsdale Lecture

Session Chair: **Thomas Hitchings** (University of Kent)
Speaker: TBC

13:00 – 13:45

BSG Plenary

Session Chair: TBC
Speaker: TBC
Title TBC

14:00 – 15:30

Parallel Sessions

PCG: Open session I
Session Chair: TBC

BSG: Engineering Biology
Session Chair: TBC

CCG/ESCG: Would you publish it? / interesting problems in chemical crystallography
Session Chair: TBC

16:15 – 17:45

Parallel Sessions

PCG: Computational Predictions
Session Chair: TBC

BSG: Open session
Session Chair: TBC

CCG: Polymorphism, hydrates and co-crystals
Session Chair: TBC

18:00 – 18:45
PCG Plenary
Session Chair: TBC
Speaker: **Robert Palgrave** (UCL)
Title TBC

19:00 – 21:00
Poster Session with Dinner and Wine

Wednesday 16 April 2025

09:00 – 09:45
IG Plenary
Session Chair: TBC
Keynote: **John Helliwell** (Manchester)
Title TBC

10:15 – 11:45
Parallel Sessions

IG: Amorphous modelling
Session Chair: TBC

BSG/CCG: In-situ crystallography
Session Chair: TBC

PCG: Complementary techniques
Session Chair: TBC

11:45 – 12:15
CCG Annual General Meeting
BSG Annual General Meeting
PCG Annual General Meeting

13:15 – 14:35
Early Career Prize Lectures

Biological Structures Group Early Career Prize
The BSG will award a prize to someone who has had an impact in the field of Structural Biology (with an emphasis on crystallography) and recently obtained a personal fellowship, a lectureship or equivalent position.

Chemical Crystallography Group Prize for Younger Scientists
The CCG will award a prize to a younger scientist who has performed original research in the field of chemical crystallography or the application of crystallographic information to structural chemistry.

Physical Crystallography Group Early Career Prize
The Physical Crystallography Prize is awarded for the best recently published work by a person in the early stages of their career, working in the field of Physical Crystallography, whose research is expected to make a significant impact in the field.

13:15 – 14:35
Exhibitor Forum
Session Chair: TBC

15:15 – 16:45
Parallel Workshops

Top tips on solving protein crystal structures (BSG/CCP4)
Session Chair: TBC

Outreach (CCG/ESCG)
Session Chairs: TBC

Rietveld refinement (PCG/IG)
Session Chair: TBC

17:15 – 18:00
Dorothy Hodgkin Prize Lecture:
Session Chair: TBC
Speaker: TBC
Title TBC

18:00 – 19:00
BCA Annual General Meeting

19:30 – 01:00
Conference Dinner & Ceilidh

Thursday 17 April 2025

09:00 – 09:45
CCG Plenary
Session Chair: TBC
Speaker: **Lucia Maini** (Bologna)
Title TBC

10:15 – 11:45
Parallel Sessions

CCG: Open session
Session Chair: TBC

PCG: Open session II
Session Chair: TBC

BSG: Integrative Structural Biology
Session Chair: TBC

12:15 – 13:45
Parallel Sessions

CCG/PCG: Coordinaton polymers and porous materials
Session Chair: TBC

PCG: Phase Transitions
Session Chair: TBC

BSG: Mechanisms and disease
Session Chair: TBC

CLOSE OF CONFERENCE

Reports on the BSG, CCG and IG sessions at the BCA Spring Meeting, Leeds, 2024

Chemical Crystallography Group (CCG) Sessions

Following hot on the heels of the ESCG satellite meeting, the CCG Plenary, which was given by **Aurora Cruz-Cabeza** (Durham), kick-started the entire BCA conference. Her talk, entitled "If you can't beat the laws of thermodynamics, join them: robust access routes to elusive polymorphs" began with defining a spectrum of polymorph types. This ranged from dominant ("happy chemist") polymorphs driven by thermodynamic and kinetic effects, through the thermodynamically-driven reluctant ("patient chemist") and kinetically-driven ready ("cautious chemist") to those elusive polymorphs which can cause chemists to quit in frustration and which formed the basis of her talk. The polymorphic behaviours of aspirin and theophylline were reviewed before the discussion turned to benzamide. Polymorphism of this compound has been known since the 19th century but it was only relatively recently and accidentally that diffraction quality crystals of form III were obtained by ball milling with catalytic amounts of nicotinamide. Aurora explained how computationally difficult this was to model but the result showed that it was possible to effect a thermodynamic switch during the milling process by controlling the amount of nicotinamide and so drive the growth of X-ray quality crystals of form III.

Following on from benzamide, Aurora reminded the audience of the Ritonavir controversy (when a stable and less effective Form II of the drug unexpectedly appeared). The speaker then went on to detail how relatively straightforward liquid-assisted grinding with isopropanol or water could effect easy conversion between Form I and Form II which was attributed to the effect of grinding on particle size, allowing for kinetic conversion between the two forms.

Dynamics and reactivity in solids

This session was chaired by **Erli Lu** (Newcastle) and began with the keynote speaker, **Hajime Ito** (Hokkaido) who got into solid-state reactivity entirely by accident when studying a gold cyano complex which turned out to have very sensitive luminescent mechanochromic properties. Hajime then applied his serendipitous interest in mechanochemistry to cross-coupling reactions in his talk entitled "From mechanochromism of organometallic crystals to mechanochemical organic synthesis." In the first example he demonstrated how applying the simplicity of ball-milling to Suzuki cross-coupling eliminates the need to reflux under an inert atmosphere with no loss of yield and how ball-milling allows for a degree of selectivity in Suzuki couplings, something not possible in the liquid phase. Ball-milling is equally useful for effecting reactivity of insoluble compounds; the "simmering stew" usually needed where a long, hot reflux results in low yield was replaced by hot ball milling. The ball mills have no thermal control but heat was quite easily applied by means of a simple heat gun. Hajime then turned his focus to catalytic applications of ball milling, which "kneads" catalysts that otherwise might phase-separate as part of the reaction. He also turned to calcium-based Grignard reagents which are very difficult to make in the liquid phase but almost quantitative in the ball mill. Finally, Hajime's most recent work focuses on trying to improve the synthetically-unpleasant Birch reduction with a ball mill process. Glucose is needed to help the sodium break down in the ball mill leading Hajime to dub this the "sweet Birch" reaction; given his use of cooking-based descriptions ("simmering stew," "kneading," "sweet Birch") one can assume that dinner chez Ito is a gourmet affair.

Following on, **John Wallis** (Nottingham Trent) explained how retirement had given him a new opportunity to revisit the Bürgi-Dunitz angle in his talk "New interactions between electrophilic and nucleophilic functional groups." Focusing on 1,8-substituted *peri*-naphthalenes, John described a series of new substituted *peri*-naphthalenes of varying steric bulk to explore the effect on the Bürgi-Dunitz angle and defined new parameters to model the torsional effect of substituents on the naphthalene unit. Additional strain can be, in effect, imposed on the naphthalene unit by the synthesis of very strained bis-*peri*-naphthalene compounds and further work will focus on the synthesis of molecules containing dicarbonyl groups for the purpose of metal coordination to induce further structural strain and change.

Following an unfortunately protracted period of "computer say no" (of course, this always happens at a conference) **Petra Bombicz** (CSC, Hungary) reminded us that IUPAC define a carbocation as any ion with a positively charged carbon but with no actual structure implied. This is important since the carbocations she described in "Structural characterisation of tricyclic and bicyclic guanidinium-type carbocations in their cocrystal" contain significant flexibility. Using guanidinium as a skeleton she described tri- and bi-substituted carbocations shaped as conjoined, semi-flexible 6-membered envelope-shaped rings and presented co-crystals of differing stoichiometry with the tosylate anion. Persistent structural features are alternating columns of cations and anions which form distinct layers in the broader crystal packing.

Ben Coulson (Cardiff) rounded off the session with a lecture entitled "A photocrystallographic study of packing effects on linkage isomerism." He began by reminding us of linkage isomerism in nitro complexes and then detailed how it was applied to a series of strut-like palladium $PdL(NO_2)_2$-type complexes where L is a 2,2-bipyridine-based ligand with alkyl chains of varying lengths. These complexes reliably dimerise, forming sheet structures with short chains and herringbone-type structures with long chains. Irradiation of these compounds with 470 nm light at 150 K effects isomerism of the nitro groups into excited states favoured by bulkier ligands and this was attributed to the longer-chain compounds having more "wiggle room" in the crystal to support the nitro isomerism. XPS measurements demonstrate that the population of excited states is uniform throughout the crystal.

Crystallography and Systems under Mechanical Stress (with IG)

The Plenary talk, "Under pressure: rational design of complex mechanical phenomena in molecular crystals" by **Sarah Guerin** (Limerick) was not given as the speaker was absent due to illness. The session then started with two excellent

presentations from the Hobday group at the University of Edinburgh. These were on solid-state barocaloric materials – potential replacements for refrigerant liquids that are currently in use and which have high global warming potentials.

First **Joshua Levinsky** (Edinburgh) presented "The barocaloric and structural properties of choline-based plastic crystals" in which the effect of substituting halides in two choline-based ionic plastic crystals was studied. These materials undergo pressure-induced solid-solid phase transitions, with a large change in entropy. The barocaloric properties of the materials were investigated using high pressure differential scanning calorimetry (DSC) to look for phase transitions by changes in pressure, alongside using single crystal and powder diffraction techniques as well as *ab initio* molecular dynamics simulations. In these materials, the high temperature phase is disordered with a high symmetry crystal structure, the corresponding low temperature phase is ordered with a low symmetry crystal structure. Substituting halides resulted in a difference in transition temperature and entropy, highlighting the role of element choice in continuing to design future solid-state refrigerants.

Phillippa Partridge (Edinburgh) then presented "Investigating the phase space of hexamethyl guanidinium hexafluorophosphate." This looked at the pressure induced phase transitions in a different barocaloric material. Variable temperature and high-pressure crystallography along with high-pressure DSC were performed to understand if this compound has the desired characteristics of a barocaloric material and to construct a full phase diagram. The room temperature structure is ordered primitive cubic but on heating to 336 K there is a phase transition to a disordered face-centred cubic structure with a large volume increase. Interesting effects in the phase transition of the material were also seen at lower pressures (below 500 bar).

The final presentation was given by **Xiaojiao Liu** (DLS) in collaboration with Colin Pulham, also from the University of Edinburgh. This presentation was on "Pressure-induced phase separation of miscible liquids: 1:1 n-pentane/iso-pentane." These materials are miscible and amorphous at room temperature and have very similar boiling points, therefore separation of the two isomers is very difficult. However, with the application of pressure, n-pentane crystallised out at 3.3 GPa, which could allow the separation of the pure solid from the mixture. This study showed that pressure-induced crystallisation could have great potential in the separation of mixtures. Additionally, as this mixture is often used as a pressure transmitting medium for high-pressure crystallography experiments, the observed crystallisation of n-pentane could indicate that in such experiments there may be the appearance of unexpected diffraction peaks.

Mechanochemistry

This session was chaired by **Giulio Lampronti** (Cambridge) and began with a keynote lecture entitled "Mechanochemistry: from curiosity to commercialisation" which was given by **Stuart James** (Queen's, Belfast). The speaker explained how inducing reactions through mechanical energy, is undergoing a remarkable renaissance in academia and increasingly in industry since it allows chemical synthesis without the need for solvents. The speaker covered the continuous scale-up through the use of twin screw extrusion techniques which is the basis of a spin-out company (MOF Technologies Ltd., now Nuada Ltd.) which manufactures MOFs (metal-organic frameworks) mechanochemically on a commercial basis. Order-of-magnitude reductions in carbon footprint can be achieved by applying catalytic Pd coatings to extrusion equipment to enable continuous solvent-free cross-coupling reactions and continuous delamination of layered materials. The next lecture, entitled "Mechanochemically-accessible cocrystals assembled using halogen bonds to carbon" was presented by **Jogirdas Vainauskas** (Birmingham and McGill). This speaker outlined several cocrystal design considerations based on halogen bonds to carbon, which provide an opportunity to reliably arrange a wide variety of polycyclic aromatic hydrocarbons (PAHs) into predictable ladder-like solid-state architectures, including halogen bonds to "latent" π-systems. Cocrystal screening by mechanochemical ball-milling has enabled the discovery of previously overlooked cocrystal stoichiometries and combinations, as well as pathways for conversion from binary to ternary cocrystals. Next up, **Mihails Arhangelskis** (Warsaw) spoke on "Computational prediction of mechanochemical reactivity of molecular crystalline materials." The speaker covered the successful use of periodic density functional theory (DFT) calculations to predict the outcomes of a series of interconversion reactions between halogen- and hydrogen-bonded cocrystals. Periodic DFT calculations were also used for the interpretation of *in situ* solid-state Raman and fluorescence monitoring of mechanochemical transformations. **Farshid Effaty** (Birmingham and Concordia) gave the final presentation in this session which was entitled "Rapid and scalable synthesis of boroxine-based covalent-organic frameworks via mechanochemistry." The lecture covered 1,2 boroxine-linked covalent-organic frameworks (COFs) which are typically obtained via solvo-thermal methods. The speaker described how ground-breaking mechanochemistry can be used in the synthesis of 2- and 3-dimensional boroxine COFs at room-temperature using trimethylboroxine (TMB) as a dehydration additive.

This year the IG Plenary was given by the CCG supremo **Simon Coles** (Southampton) and was chaired by **Tony Bell** (Sheffield Hallam). Simon's lecture was entitled "A step change for single crystal structure determination: the new capabilities of electron crystallography." For many years the National Crystallography Service has been helping crystallographers with difficult single-crystal structure determinations with their facilities at the Universities of Newcastle and Southampton along with beamline I-19 at DLS.

The NCS has now expanded its horizons by adding electrons to X-rays as a method of structure determination. Crystal structure determination using transmission electron microscopy (TEM) has been known for many years. However, the NCS now has a dedicated electron diffractometer optimised for crystal structure determinations. The NCS could previously analyse micron sized crystals using X-rays. Using electrons, crystal structure determinations can now be done with crystals on the scale of nanometres. As an old powder diffractionist it is fascinating that crystal structures can now be done on powder grains!

Professor Coles gave a fascinating presentation giving examples of work done with the electron diffractometer and speculated on future work.

The CCG session on Framework materials, expertly chaired by **Georgia Orton** (Birmingham), was covered by several of the AB bursary awardee reports in the last issue (No. 169), to which interested members are referred.

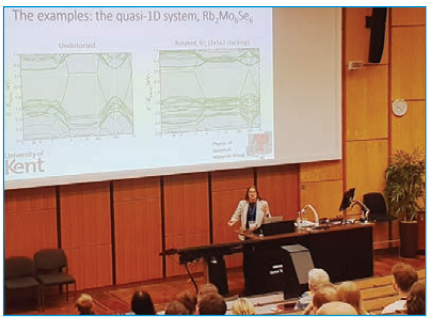
Molecular interactions and supramolecular chemistry

This CCG session was chaired by **Krešo Bučar** (UCL) and began with a keynote lecture entitled "Drug/co-former assembly in solution and the solid – from predicting co-crystallisation to taste masking" which was given by **Katharina Edkins** (Strathclyde). The speaker began by emphasising how supramolecular interactions are amongst the strongest in molecular crystals and how hydrogen bonds can be used to predict the interactions of molecules in different crystal forms and in co-crystallisation. The results of recent studies investigating aggregation and co-crystal nucleation from a specific solvent in the presence of a hydrotrope which affected solubility were presented. The efficiency of co-crystallisation as a taste-masking method has also been actively studied. The next lecture, entitled "A seventh blind test of crystal structure prediction (CSP): challenging use cases" was given by **Lily Hunnisett** (CCDC). The speaker described this community-based initiative, which involves 28 groups from both academia and industry across 14 countries. A number of complex cases not only highlighted where CSP excels, but revealed where these methods struggle and indicated urgent paths for future CSP research. "Structure of the caffeine-pyrogallol complex: revisiting the pioneering structural analysis of a model pharmaceutical cocrystal" was the title of the next lecture given by **Okba Al Rahal** (Birmingham). The speaker described a recent re-investigation of this historically important cocrystal system along with the discovery of new cocrystal phases. In contrast to the original study in the 1960's, the revised structural model determined by XRD and validated by DFT shows that caffeine and pyrogallol do interact directly through O-H···N hydrogen bonds. The last lecture in this session was entitled "Investigation of non-covalent interactions in cocrystal derivatives of the classic adduct C_6H_6:C_6F_6 using the complementary techniques of DSC, PXRD and SXD" and was presented by **Jeremy Cockcroft** (UCL). The speaker covered a multi-disciplinary approach to understanding the solid-state behaviour of these very interesting adducts. The samples need to be handled in X-ray capillaries due to their volatile nature. Cooling to the solid phase allowed their structures to be determined from what initially looked like very poor data.

Open Session

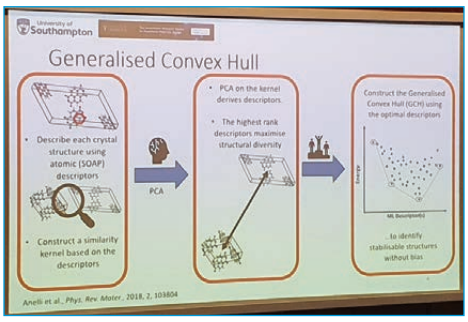
This session was chaired by **Sam Chong** (Liverpool) and began with a keynote lecture by **Andrew Peel** (CCDC) entitled: "Harnessing the Cambridge Structural Database for teaching symmetry." The speaker explained how the CCDC has a teaching subset of 850 structures which are free to download and how the Mercury program can be used to visualise, 3D-print and animate them. The structures are useful for training students in basic chemical valency and bonding geometry as well as more advanced topics such as Laue and point group symmetry, which have implications for the vibrational modes encountered in spectroscopy. The next lecture entitled "Investigating Tranilast hydrates: a comprehensive analysis through DVS screening and ssNMR characterisation" was given by **Yichun Shen** (Manchester). The speaker described the general issues of hydration in pharmaceuticals before describing her work on the discovery of numerous interesting hydrates and solvates of the anti-allergy drug Tranilast which were characterised by crystallography and solid-state NMR. "Deconstructing the full 3D faceted growth rates from the temporal capture of crystal growth through *in-situ* optical microscopy" was the subject of the lecture by **Cai Ma** (Leeds). The speaker emphasised the need for desirable crystal size and shape in the manufacture and formulation of agrichemicals, which are produced on the tonne scale. The speaker described microscopic work on measurement of the growth rate of the B-form of L-glutamic acid crystals using machine learning to map 2D images to models of the 3D crystal shape. "Meaningful structural comparisons to describe and rank predicted molecular crystal structures" was the title of the lecture by **Jennie Martin** (Southampton) who summarised the current state of the crystal structure prediction field and outlined work using a generalised convex hull model (a concept from set theory) and machine learning.

Tony Bell, Sheffield Hallam
Jon Cooper, UCL
Natalie Johnson, CCDC
Mark Montgomery, Syngenta
Gary Nichol, Edinburgh



Silvia Ramos (Kent) delivering the PCG Plenary at the 2024 Spring Meeting in Leeds.

David Aragao (DLS) flying the flag in style for the next IUCr in Calgary, Canada in 2026.



*A slide by **Jennie Martin** (Southampton) whose research on crystal structure prediction involves use of a generalised convex hull model (a concept from set theory) and machine learning.*

Biological Structures Group (BSG) and BCA prize lectures

The BSG session entitled "Getting the most from your protein crystals at the synchrotron" was chaired by **Adam Crawshaw** (DLS) and began with a keynote lecture entitled "Precision, power and progress: mastering synchrotron experiments" by **David Aragao** (DLS). The speaker covered how crystal alignment, fine slicing, oscillation range, matching the size of the beam to that of the crystal and multi-axis goniometry can be optimised in an experiment along with the importance of considering the dose. Increasing the resolution of a dataset is probably better done by collecting on more crystals rather than increasing exposure time. The next lecture entitled "VMXm – getting the most from very small crystals" was given by **Anna Warren** (DLS) who covered methods for improving data quality such as reducing the background, partly through cleaner sample mounting and considerations of dose to take advantage of photoelectron escape to increase crystal lifespan in the beam. The VMXm (versatile macromolecular crystallography microfocus) beamline can collect data from crystals as small as 0.5 µm in each dimension and operates with the sample *in vacuo* at low temperature with a high energy beam, thus making it suitable for both protein and small molecule crystallography. The speaker then covered a number of fascinating success stories. "New dogs, old tricks: VMXi, an *in-situ* room temperature MX beamline at the Diamond Light Source" was the intriguing title of the talk given by **James Sandy** (DLS) who covered the renaissance in room temperatures studies. James told us how one can collect 6,000 datasets within 24 hours on this beamline. The speaker described the new AI crystal finding tool CHIMP (Crystal Hits In My Plates) which allows highly redundant data to be collected automatically from clusters of crystals. **Ramona Duman** (DLS) then spoke on "Light ion identification by X-ray anomalous scattering" using the I23 beamline which has a tunable wavelength range from 1.1 to 5.9 Å. The beamline allows discrimination between different light elements such as the alkali and alkali earth metals, halides, etc, in very large macromolecular complexes such as the ribosome, as well as defining the orientation of heteroaromatic groups in fragment screening studies.

The BSG plenary lecture was given by **Syma Khalid** (Oxford) and was entitled "When structural data gets messy: insights from molecular simulations." In this lecture, which was chaired by **Rachael Wilkinson** (Oxford), the speaker outlined theoretical molecular dynamics and integrative modelling studies of the bacterial cell wall and outer membrane proteins, incorporating experimental data from various sources.

The IG Plenary, chaired by **Tony Bell** (Sheffield Hallam), was given by **Simon Coles** (Southampton) and was entitled "A step change for single crystal structure determination: the new capabilities of electron crystallography." Simon began by emphasising how we appear to have reached the limit with X-rays in terms of minimum crystal size and how electron diffraction (ED) allows us to analyse ever smaller samples.The speaker described the Rigaku Jeol instrument which operates at 200 kV and generates electrons with a wavelength of 0.025 Å. The samples are mounted on grids and rotated about a single axis during data collection. Currently his group has been determining several ED structures per week, or indeed per day, with samples as small as 0.1 – 0.2 µm. The EPSRC-funded facility supports work across a range of disciplines including pharmaceuticals, material science, electronics and catalysis, as well as food science and agrichemicals. The speaker emphasised how currently ED data and refinement statistics are not comparable with those of X-ray studies due to a various factors including sample damage caused by the high vacuum and the strong dynamic scattering which electrons undergo. The use of cryocooling to mitigate some of these effects is available as an upgrade to the instrument.

The joint IG/BSG session entitled "Exploring synergies at the small molecule-biomolecule boundary" was chaired by **Tony Bell** (Sheffield Hallam) and **Raquel Bessa** (Johnson Matthey). The session began with a keynote lecture entitled "Synergising diffraction sciences - an industrial perspective" which was given by **Chun-wa Chung** (GSK). The speaker outlined the broad aims of protein and chemical crystallographic studies in the pharmaceutical sector. These range from screening for ligands bound to a target protein, lead generation, optimisation and studies of antibody epitopes on the biological side, through to absolute structure determinations, polymorphs, solvates and active pharmacological ingredient (API) tablet assessment on the chemical side. The speaker described the discovery of the antibiotic penicillin and how GSK was responsible for producing 80 % of the UK supply by 1944. One of the relatively few new classes of antibiotic which have been discovered in the intervening decades are the DNA topoisomerase inhibitors. The speaker explained how inhibitors which stabilise intermediates have been easier to develop than ligands which block DNA binding to the enzyme. The speaker outlined work on moxifloxacin and gepotidacin – the latter being the first new antibiotic in 20 years, which is currently in phase III trials. Chun-wa explained how synchrotron beam time has proved to be more cost effective than in-house X-ray facilities for PX work in an industrial setting whereas the situation is the other way round for small molecule studies. In the questions the speaker indicated that surface plasmon resonance was probably the best technique for initial fragment screening studies, prior to crystallographic characterisation. The next lecture was given by **Natalie Tatum** (Newcastle) and was entitled: "FragLites map sites of protein-protein interaction: crystallographic fragment screening of CDK2-cyclin A." The speaker described the FragLites fragment screening library which the Newcastle group has developed. It consists of halogen containing compounds to aid identifying the orientation of the bound ligand in electron density maps. The group undertakes work on a range of cell-cycle proteins and cancer drug targets in collaboration with Astex Therapeutics in Cambridge. Studies of the CDK2-cyclin A2 complex suggest that the fragments are excellent indicators of protein-protein interaction sites. The next lecture was entitled "3D crystal shape detection from single images using paired neural network auto-encoders" and was given by **Thomas Ilett** (Leeds). The speaker described the use of computer vision and AI to study crystal shape in a project which involved images of synthetic crystal shapes being used to train a neural network. Whilst refraction and reflection make the optimisation difficult, the model can extract morphology parameters from single images of real crystals and these have good correspondence with observed images. Last but not least, the final lecture in this session was given by **Abhinav Vadakkepat** (Birkbeck/ Leicester) and was entitled: "Structural studies on the conjugative type IV secretion system." The speaker explained how bacteria use long thin tubules (pili) to transfer plasmid DNA between one another and this allows antibiotic resistance to spread. The first step in conjugation is the formation of a relaxosome which squeezes the DNA into the pilus which then extends outwards until it makes contact with another bacterium. The speaker described the 3.2 Å resolution cryo-EM structure of the secretion system with a number of impressive videos and reconstructions of the pilus in action. Current work includes the study of mutants which are known to form pili but are defective in DNA transfer. These suggest that small

changes can inactivate the system and that discovering compounds which could inhibit secretion by the pilus as antimicrobial drugs is a strong possibility.

The CCG early career prize lecture was presented by **Patrick Doheny** (Birmingham) and was entitled "A journey through MOFs, charge transfer and thermal expansion." Patrick spoke on the subject of electroactive MOF's as redox active metal sensors, as well as their use in energy storage devices and in electrocatalysis. Patrick then moved on to describe crystallographic and solid state EPR studies of Cd-DMF complexes within thiazolo-[5,4-d]-thiazole (TzTz) frameworks. The EPR hyperfine splitting indicated delocalisation of electrons along the ligand length. Patrick also described studies of electrochromism in which the sample changes from colour from green to yellow due to intervalance charge transfer (IVCT). The speaker described studies of Prussian blue pigments – intensely coloured MOF's with many applications and mentioned how the steric bulk of TzTz compounds affects their charge transfer properties. Patrick finished by describing some very interesting work on the thermal expansion and contraction of Gd-Er adipic acid complexes and how these effects correlate with structural changes in the crystal. The first of two PCG prize lectures was given by **Hanna Boström** (Stockholm) and was entitled "Degrees of freedom in Prussian blue analogues." The speaker described how Prussian blue compounds are an important family of cyano-metal complexes which have very interesting charge-transfer and spin-crossover properties, as well as exhibiting both piezo- and photo-magnetism. The speaker covered the Jahn Teller distortions which are encountered in these octahedral transition metal complexes. The next PCG prize lecture was entitled "A tale of two effects" and was given by **Lewis Owen** (Sheffield) who described short range order and disorder in the distortion of lattices. Lewis described modelling these systems with DFT and Monte Carlo methods as well as experimental studies using Bragg- and diffuse-scattering measurements which yield a pairwise distribution function. The speaker described the theoretical Clapp configurations of nearest neighbour atoms in cubic binary alloys and how similar atomic arrangements might arise from one another during distortion of the lattice. The speaker concluded by describing the Royce access scheme for facilitating the use of materials science equipment by postgraduates and small market enterprises. The session concluded with three commercial presentations chaired by **Peter Moody** (Leicester), the first of which was given by **Patrick Shaw-Stewart** (Douglas Instruments) and concerned robotic microbatch crystallisation under oil. This format is very good for establishing a phase diagram for a given protein and involves making a seed stock to define the metastable zone. The setup is also good for scaling up. **Peter Mills** (Photonic Science) then spoke on a system for crystal alignment using Laue diffraction and, last but not least, **John Kollath** (Stoe) presented the StadiP powder diffraction system which facilitates high pressure, as well as high and low temperature studies. The speaker also described a new profile fitting algorithm incorporated in the integrate3D software.

Following coffee and posters, the BSG session on "Artificial Intelligence in Structural Biology", chaired by **Georgina Menzies** (Cardiff) began with a keynote lecture entitled: "Integrative Structural Biology with AI" which was given by **Isabel Moraes** (Google DeepMind). The speaker described how AlphaFold2 delivers significantly improved side chain predictions and how a collaboration between the DeepMind team and EMBL has resulted in significantly better domain predictions which are provided with a heat map to enable the user to discern the regions of highest and lowest confidence. Isabel emphasised the importance of experimental work in structural biology but also mentioned that we are at the beginning of a very exciting era in which it is likely that AI will be able to predict protein dynamics and the effects of mutations. The next talk was given by **Jennifer Miles** (Leeds) and was entitled "Adaptability is important, in crystallography, mitosis and the lab." Jennifer described the tightly regulated mitotic kinase: aurora-A which is inhibited by the largely disordered centrosomal protein CEP192. To facilitate co-expression, crystallisation and structural studies of the aurora-A-CEP192 complex, 1D-NMR was used to define the disordered regions of CEP192 and to narrow down the region which binds to aurora-A as being residues 468-533. Further work was required to obtain co-crystals of the complex by mutating away the residues of aurora-A which are involved in crystal contacts of the native protein, and use of a nanobody against aurora-A was also needed. The structure of the complex revealed that the CEP peptide wraps around the N-terminal lobe of aurora-A and blocks the binding site for activator proteins. The peptide itself is slightly activating. The next lecture was entitled "Error estimates in atom coordinates and B factors in macromolecular crystallography" and was given by **John Helliwell** (Manchester). John explained how the method of full-matrix inversion is used to derive error estimates for refinement parameters in small molecule crystallography. However, this approach is of limited value in macromolecular studies and even with small molecule structures it under-estimates coordinate errors by a factor of around 1.4. These concerns led Durward Cruickshank to derive improved error estimates by using the atomic B-factors to scale the coordinate uncertainties and his approach (known as the diffraction-component precision index, or DPI for short) was subsequently reformulated by David Blow. The speaker emphasised how better error estimates may be obtained by using multiple datasets arising from parallel data processing work-flows at synchrotron sources and how this approach may allow macromolecular B-factor ESD's to be determined reliably.

This year the Bragg Prize Lecture was entitled "The future of macromolecular crystallography in the age of machine learning" and was given by **Arwen Pearson** (Hamburg) in a session that was chaired by **Richard Cooper** (Oxford). The speaker began by outlining the spectacular advances in AI prediction of protein structure and went on to discuss areas where experimental work still remains pivotal, most notably dynamic processes including catalysis, allostery and transport. Arwen outlined the range of time- and length-scales on which crystallographic work still excels in structural biology and described some of the facilities where these studies can be undertaken such as 4th generation synchrotrons and XFEL sources. The speaker posed the question of whether we can get all the way to actually see chemistry in action. Arwen outlined a range of low temperature studies to trap intermediates as well as time-resolved pump-probe work, including photo-isomerisation, the use of photolabile reagents and temperature-jump studies.

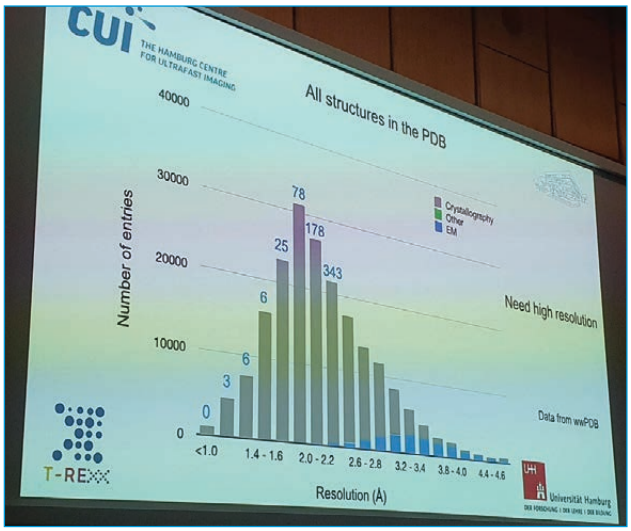
The BSG session entitled "Breaking barriers with emerging technology in structural biology" was chaired by **Hanna Kwon** (Leicester) and began with a keynote lecture by **Pedro Nunes** (DLS) on "The high-energy electron crystallography instrument: a new tool for macromolecular structure determination." The speaker covered the construction of the HEXI instrument which is designed to deliver MeV electrons so as to allow the use of thicker crystals in the 0.3 to 3.0 μm range. The instrument will incorporate goniometry to allow fast rotation data to be collected at room temperature or at cryo-temperatures and to allow serial crystallography studies.

HEXI will have a CMOS detector and will require lead shielding between 5 and 15 cm thick. The unit cell size is estimated to have an upper limit of 250 Å and the instrument is likely to be available in 2026. "Challenges and prospects of electron diffraction for protein nanocrystallography" was the title of the presentation by **Marcus Gallagher-Jones** (Rosalind Franklin Institute) who discussed the fact that small crystals of macromolecules possess relatively few unit cells and therefore suffer from weak diffraction compared to crystals of small molecules. Some nanocrystals are even formed biologically, such as by the bacterium *Bacillus thuringiensis* during sporulation, whereas others can be obtained from crystallisation experiments e.g. those which do not yield crystals of sufficient size for X-ray work. The nanocrystalline slurry can be mounted in much the same way as samples for EM work and crystals which are actually too big for ED analysis can be cut to size by focussed ion beam milling. In spite of this the low number of protein structures determined thus far by ED is attributable to difficulties in sample preparation. Clearer diffraction spots can be obtained by energy filtering the beam which helps to reduce inelastic scattering. The next speaker, **Samuel Rose** (ESRF), gave a presentation entitled "Time-resolved microsecond crystallography and time-resolved optical in crystallo spectroscopy at a synchrotron (ESRF-EBS)." The speaker described how the source at the ESRF is now 100 times more brilliant than before as well as having 50 times greater coherence. The ID29 beamline is designed to perform synchronised X-ray diffraction and optical spectroscopy experiments with micro- to milli-second time resolution, which is ideal for studies of enzyme mechanisms. The beamline has a comprehensive range of facilities for time-resolved serial work such as injectors and viscous extruders as well as a sample delivery tape drive device for rapid addition of enzyme substrates and a nanosecond laser for light activation. The final lecture in this session entitled "Spherical crystals: laser shaping of biological and chemical materials under cryogenic conditions" was given by **Christian Orr** (DLS). Christian described a laser-shaping system applicable to protein or small molecule crystals and other samples which operates at room or cryo-temperatures on the I23 long wavelength beamline. Use of spherical crystals removes the need for an absorption correction and enhances the quality of anomalous scattering measurements which greatly aids the identification of light elements such as Na^+ and Mg^{2+} ions in protein structures. A femtosecond laser is used to ablate the surface material of the crystal without loss of diffraction quality and much of the surrounding solvent and mounting material can also be removed to reduce the background scatter. The speaker outlined a number of very interesting case studies.

The final part of the Spring Meeting which was organised by the BSG was the "Open Session" which was chaired by **Georgia Isom** (Oxford). The keynote lecture, entitled "Solving structures of crystals in cells using electron tomography," was given by **Tanmay Bharat** (MRC Cambridge) who described the outer layer of the bacterial cell wall, the S-layer, which consists of repeating sheet-forming proteins that form a paracrystalline array. The S-layer proteins perform a wide range of functions including cellular defence, cell-shape maintenance and transport. The speaker emphasised how electron cryotomography and subtomogram averaging methods are being used to derive molecular models of S-layer components and other macromolecules in the native environment of cells. This work has led to biological insights into the S-layer structure, biogenesis and distribution across the microbial tree of life. The next lecture was given by **Augustinas Silale** (Newcastle) and concerned the "Structural basis of iron piracy by a prominent human gut symbiont."

Bacteria often acquire iron from the environment by producing siderophores to chelate Fe^{3+} and absorb it via transporter proteins. The dominant human gut symbiont, *Bacteroides thetaiotaomicron*, does not produce siderophores itself but has been recently shown to acquire iron from siderphores produced by other bacteria via a dedicated xenosiderophore utilisation system (Xus), which consists of an outer membrane TonB-dependent transporter (XusA), a cell surface-exposed lipoprotein (XusB), and an inner membrane iron reductase. The structures of a siderophore bound to XusB and the XusAB complex have been studied by crystallography and cryo-EM, providing many insights into symbiont-pathogen interactions in the gut. The next lecture on the "Cryo-EM structure of the CDK2-cyclin A-CDC25A complex" was given by **Rhianna Rowland** (Newcastle) who spoke on phosphatases which regulate the cell cycle. These cancer-related enzymes remove inhibitory phosphorylation sites on the glycine-rich motif of cyclin-dependent protein kinases (CDKs) to activate them. The speaker presented the cryo-EM structure of the 86 kDa CDC25A-CDK2-cyclin A complex at 2.7 Å resolution, highlighting key protein-protein interactions that could be targeted to disrupt complex formation. The conserved CDK GDSEID motif makes important contacts with the phosphatase and likewise the C-terminal helix of the phosphatase makes crucial contacts with the cyclin. "An octameric PqiC toroid stabilises the outer-membrane interaction of the PqiABC transport system" was the title of the final presentation in this session which was given by **Benjamin Cooper** (Oxford). The *E. coli* paraquat inducible (Pqi) pathway is a putative Gram-negative phospholipid transport system consisting of an integral inner membrane protein (PqiA), a periplasmic spanning MCE (mammalian cell entry) family protein (PqiB) and an outer membrane lipoprotein (PqiC). The X-ray structures of both the native and a truncated soluble construct of the PqiC lipoprotein have been determined and neutron reflectometry has been used to study numerous further details of the complex.

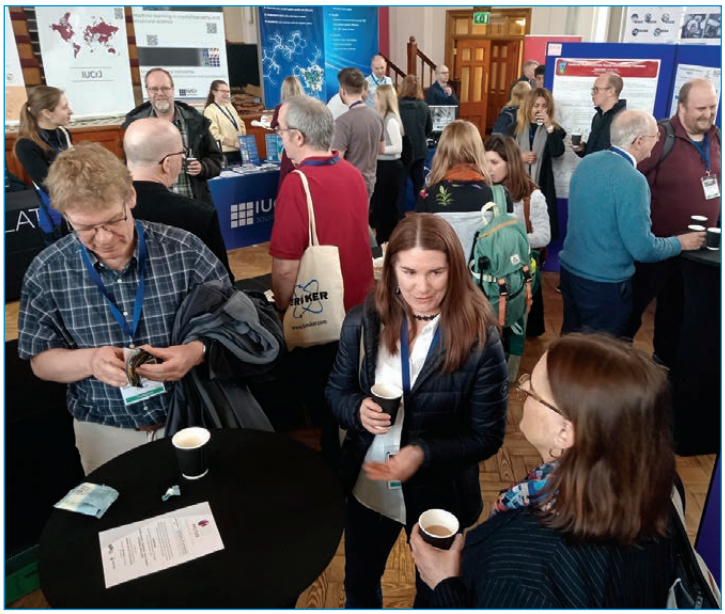
Jon Cooper, UCL
Mark Montgomery, Syngenta



Arwen Pearson (Hamburg) provided convincing evidence that X-ray crystallography remains the dominant tool for delivering the resolutions required for time-resolved structural studies.

An evening scene from the 2024 BCA Spring Meeting in Leeds.

Look carefully and one of the many campus rabbits can be seen crossing the road.



Poster presenters, exhibitors and other delegates mingle at one of the many coffee breaks.

Bursary awardee report

I arrived in the University of Leeds for the BCA Spring Meeting 2024 on a sunny Monday 25th March. It was my third time attending the BCA conference and my second visit to Leeds. I had a fantastic experience there, not only because of the lovely rabbits on campus, which we do not have in Manchester, but also due to the thrilling presentations on cutting-edge science and technology.

The conference included two meetings. The first was the ESCG Early Career Satellite Meeting, which started on Monday afternoon. **Lukáš Palatinus** (Czech Academy of Sciences) gave a wonderful talk on the limits and prospects of electron crystallography, as an opening lecture. The ESCG meeting concluded at noon on 26th March with an interesting and enjoyable closing plenary talk on protein dynamics given by **Helen Ginn** (Hamburg). The ESCG meeting offered a fantastic opportunity for young crystallographers to present their impressive work, network and freely make new friends.

The next three days followed with the main meeting, consisting of three parallel sessions, the most impressive being the CCG session on "Dynamics and Reactivity in Solids." The keynote speaker **Hajime Ito** (Hokkaido) gave a talk on mechanochemical organic synthesis. Using ball milling, free from organic solvents, offers a green approach to organic reactions, attracting considerable attention due to its high efficiency. Additionally, his research group concentrates on pioneering reactions achievable solely through ball milling, as well as innovating new environmentally friendly synthetic methods. I have used ball milling for crystallisation before, but discovering its application in chemical synthesis for the first time has significantly expanded my perspective. Another highlight for me in this session was the lecture given by **Petra Bombicz** (Budapest) about the structural characterisation of tricyclic and bicyclic guanidinium-type carbocations in their co-crystals. The presentation provided insight into the structure characterisation of the co-crystals in my PhD research.

I felt very honoured to give an oral presentation on the final day of the meeting, showcasing my research on the characterisation of hydrates. I was also delighted to find that many researchers showed interest in my work, having discussions with me after the presentation and offering valuable suggestions.

There was ample time for networking, with well-planned events such as coffee breaks during each session and poster sessions, accompanied by lunch, dinner and wine. Additionally, a grand conference dinner was held at the refectory on the final evening, offering more space and a better atmosphere for networking. Additionally, the exhibition by the commercial sponsors of the meeting provided great opportunities to discuss new technologies and equipment with these companies, as well as to pick up some freebies.

The conference concluded on 28th March. It was an invaluable opportunity for me to attend before my graduation and my final chance to attend as a PhD candidate. I have attended the BCA spring meetings for three years and they have broadened my research horizons, boosted my confidence in my own research and improved my presentation skills. Additionally, I have made many friends here. I will always cherish the wonderful memories from the BCA.

Yichun Shen
Manchester

CCDC Science Day – the most inspiring day of the year for our scientific community

THE Cambridge Crystallographic Data Centre sponsors numerous PhD and Masters students each year and co-supervises them alongside leading scientists from academic and commercial institutions. As a charitable institution, our mission is to support the development of the next generation of scientists. Every year, we invite them and their external supervisors to the CCDC office in Cambridge, UK, to spend a day presenting their research, listening to their peers and sharing knowledge and ideas.

This year would not be any different. CCDC Science Day 2024 started with **Nathan Hennessy** (Leeds) a 3rd-year student, presenting on "Cooling crystallisation from binary solvent mixtures: relationships between solvent composition and activation barriers for nucleation." Nathan presented crystallization at the molecular level, focusing on the example of L-histidine and explained the processes of dissolution and crystallization, emphasizing the importance of factors such as Gibbs free energy, enthalpy, entropy and solvent composition. His research goals involve determining activation barriers for these processes, correlating them to solvent composition and analyzing trends using computational data. The workflow created by Nathan involves assessing solubility profiles to determine the feasibility of crystallization using different solvent mixtures and he is exploring how data from the Cambridge Structural Database (CSD) can be used to understand these processes.

Dori Gasparikova (Durham), a final year student, presented her research on glucokinase (GK) and its role in the body, particularly in the liver where it converts glucose into glycogen and in the pancreas where it is involved in glucose-stimulated insulin release. The importance of studying GK concerning diabetes management was emphasized, considering the adverse effects of current therapeutics. Dori also referred to potential binders of GK, including activators and inhibitors. Her project goals were divided into experimental and computational methods, involving protein expression and purification, as well as docking experiments to guide the design of molecules. The optimization of GK expression, purification and validation were described, along with the initial steps in protein purification using affinity chromatography with a HisTrap HP column.

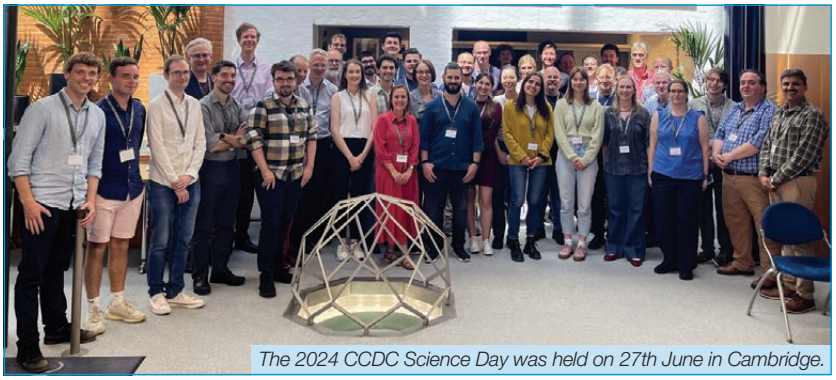
Harry Nash (Sheffield) is in his final year and he presented his work on exploring and predicting sigma-hole interactions in the CSD using machine learning techniques to predict interaction energies. Harry explained the nature and characteristics of sigma-hole interactions, the expected trends and the reasons for the interest in these interactions. The workflow involves searching the CSD with ConQuest, using the CSD Python API for automation of searches, geometric trend analysis of the data and machine learning using a database of sigma-hole interactions and their calculated energies, as well as final validation against a dataset of molecular cutouts from the CSD.

Emilia Prandini (Politecnico di Torino in Italy) who is in her 2nd year was up next to present her project: "Predicting particle quality attributes of organic crystalline materials using particle informatics". Her main topic was predicting the particle quality of crystalline materials using informatics methods, focusing on a case study of a quercetin dimethyl formamide (DMF) solvate. Her presentation covered crystal engineering, particle informatics methods and the impact of crystal properties on particle quality attributes. The methodology combines computational and experimental approaches, including XRD, molecular modelling, surface analysis, thermal stability studies, crystal phase determination and crystal growth analysis. Emilia's research aims to correlate crystal structure with surface properties, particularly focusing on the desolvation behaviour of this complex quercetin-DMF system.

As usual, we wrapped up the day with engaging lightning talks from our first and second-year students. We started with **Aaron Horner** (Southampton) who is evaluating new methods to quantify complex molecular models. **Henry Holleb** (Durham) is researching the hydration of pharmaceutical salts and **James Broster** (Oxford) is studying physics-based and machine-learning docking methods. **Alex Lee** (Durham) is researching high-throughput conglomerate synthesis and analysis while **William Midgley** (Durham) aims to use GOLD to aid PROTAC linker design and **Omar El-Habbak** (Strathclyde) is focused on correlating digital and experimental chemical space to pharmaceutical manufacturing processes.

The presentations covered a wide range of topics, from molecular level crystallization to predicting particle quality attributes of organic crystalline materials, showcasing the depth and breadth of scientific inquiry being pursued. The engagement and enthusiasm of both the students and their supervisors were evident throughout the day, highlighting the collaborative and supportive environment fostered by the CCDC. It was truly a day of knowledge sharing, inspiration and celebration of scientific inquiry.

Ana Machado, CCDC



The 2024 CCDC Science Day was held on 27th June in Cambridge.

Astbury Conversation, University of Leeds, 8th – 9th April 2024

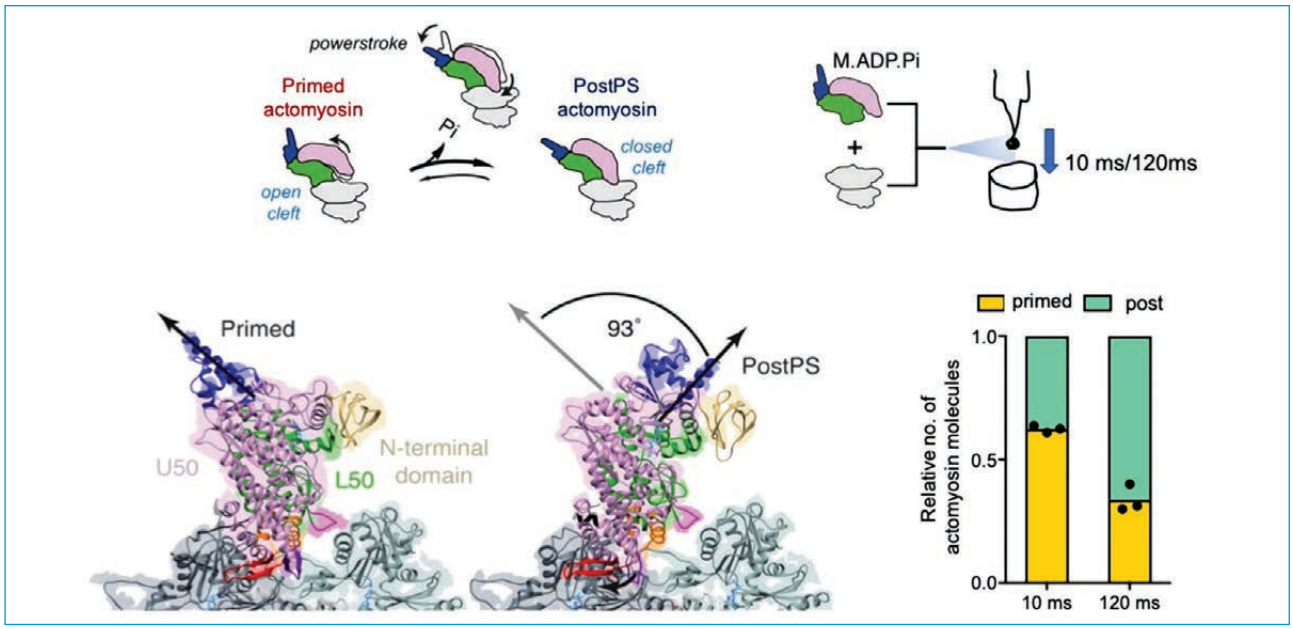
THE 2024 Astbury Conversation 'Illuminating Life' brought together scientists from around the world to showcase a fascinating selection of cutting-edge research in molecular biology. The Astbury Centre for Structural Molecular Biology is an interdisciplinary institute based at the University of Leeds that brings together experts in biology, chemistry and physics with a common goal of understanding the molecular basis of biological mechanisms in living cells. The namesake of the centre, William Astbury, is best known for his work on fibre diffraction, the threads of which still run through the research of the Astbury Centre. Of particular note is the work of Sheena Radford, who was recently awarded the Centenary Award from the Biochemical Society, recognising the impact of her research into protein folding and misfolding.

The meeting was attended by ~300 participants with a diverse array of speakers from around the world. The Conversation was composed of longer talks punctuated by flash presentations, giving early career researchers an opportunity to share their results and direct attendees to their posters for more in-depth discussions during the popular poster/pizza/beer session on the first evening. Highlights from the first day included a beautiful demonstration of the application of time-resolved cryo-EM in the investigation of myosin dynamics by **Charlie Scarff** (Leeds). The theme of 'illuminating biology' was encapsulated wonderfully by **Kimberly Bonger** (Radboud, NL) whose development of chemoenzymatic fluorescent labels allows the visualisation of proteins inside cells. The transport/translocation paradox was discussed by **Dirk Görlich** (Max Planck Institute for Multidisciplinary Sciences) from the perspective of investigating phenylalanine-glycine motifs involved in binding nuclear transport receptors and the selective phase model.

The second day kicked off with a fascinating insight into the real-life applications of protease activated fluorescent probes for enzyme targets in cancer and infectious disease. Used in combination with surgical imaging, these probes allow real-time fluorescent imaging of tumours during surgery and the talk included several detailed examples of this application. **Jason Chin** (MRC-LMB) presented his on-going exploration of the limits of synthetic ribosomes in the production of non-canonical biopolymers inside living cells using new aminoacyl-tRNA synthetase/tRNA pairs that may enable the synthesis of drug-like molecules in-situ. **Arwen Pearson** (Hamburg) discussed the fundamental motivations of the use of time-resolved X-ray crystallography to investigate molecular mechanisms. Preliminary results were presented highlighting the use of sub-Ångström resolution structures in the determination of hydrogen positions.

The Conversation culminated with a public lecture by key note speaker **Xiaowei Zhuang** (Harvard) covering her work on spatially resolved single cell genomics, the development of multiplexed error-robust fluorescence in situ hybridisation (MERFISH). This was discussed in the broader context of the impact of her work on our ability to see inside the cell. Several students from the University of Leeds 'Reach for Excellence' scheme were in attendance. This scheme provides opportunities for those from diverse backgrounds to take part in higher education activities. The students were also given the opportunity to meet with Xiaowei, perhaps inspiring a future key note speaker at the Astbury Conversation!

Briony Yorke
Leeds



The swinging lever hypothesis of myosin directly demonstrated by time-resolved cryo-EM https://www.biorxiv.org/content/10.1101/2024.01.05.574365v1 *with permission of* **Charlie Scarff** *(Leeds).*

CCP4 Study Weekend, 3rd – 5th January 2024, Nottingham

Decision making in MX – how to be a productive structural biologist

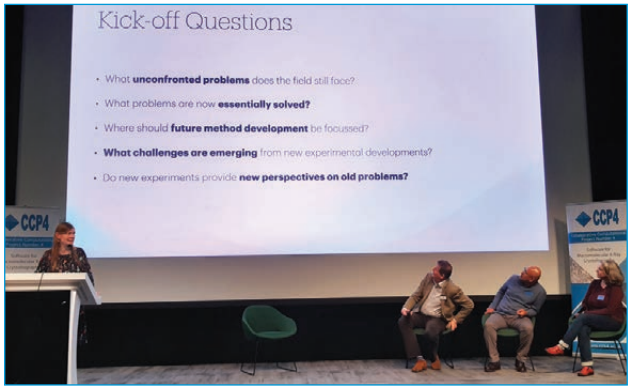
TO be or not to be. To do or not to do this or that. These are the questions raised when tackling the many facets of structural biology and which were addressed in this study weekend, held during the week!

As has become customary, **Dave Hall** (the first of a series of DLS speakers) started the proceedings with the Diamond Users Meeting, giving an MX beamline overview and the latest on Diamond II / Alternatives & MX-Bridge. The lecturer placed an emphasis on the automation and software developments occurring on I03 and I04 as we move towards the MX-Bridge phase during the planned shutdown from December 2027 until September 2029, when all samples sent to Diamond will be sent on to APS. The rest of the sessions were dedicated to the many facilities that are available at Diamond and how they are continually being updated. **Felicity Bertram** gave a talk on "Diamond isn't hard: how to access Diamond MX beamlines and training opportunities." **Craig Bull** talked about the "Future of MX Crystallography at the ISIS Neutron and Muon Source" followed by **Lizbe Koekemoer** who gave "An update on XChem activities." **Alistair Siebert** gave "A progress update on the High energy Xtallography Instrument (HeXI) at DLS," **Anna Warren** spoke on "Getting the most from micron sized crystals" at VMXm and **Andrew Quigley** informed us about what is needed for "Working with membrane proteins at Diamond." **Graeme Winter** spoke on "Current software activities on MX beamlines," **Danny Axford** talked about a range of subjects "From micro-crystals to macro-data – micro and serial crystallography at beamline I24" and **Jos Kamps** spoke remotely on "Exploring enzyme dynamics using a combination of synchrotron and XFEL methods." Finally we heard about "Routine room temperature structure determination at VMXi" from **Mike Hough**. The session was finished with a Diamond User Committee discussion led by **David Briggs** and **Colin Levy**. The overwhelming message is that whatever state-of-the-art experiment on structural biology one would like to perform, one is only an email away from the user office or any of the Diamond personnel for best guidance.

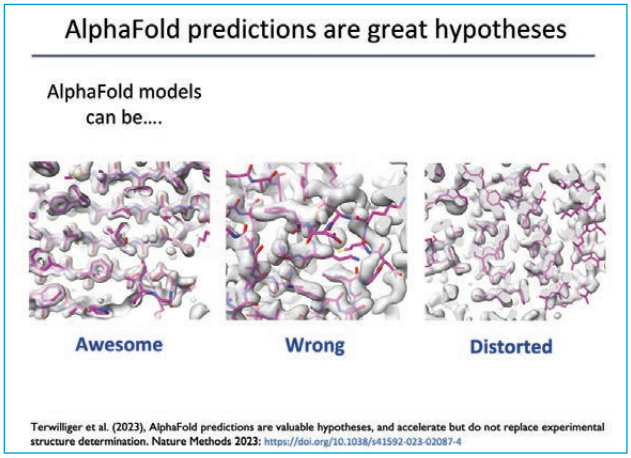
The first session of the main conference started with a keynote lecture by **Patrick Reinke** (DESY, Hamburg) on "Lessons learned from SARS-CoV2 drug screening campaigns: harvesting all existing MX tools/pipelines at the time by a collaborative group of users." The speaker described fragment screening of the SARS-CoV-2 main protease at PETRA III and the associated software developments which led to the finding that an aldehyde cysteine protease inhibitor was the best candidate compound for further study.

The day was nicely rounded off with an enjoyable round table discussion "Crystallography is dead – long live Crystallography!" led by **Elspeth Garman** (Oxford, Chair) with **David Brown** (Servier, France), **Ashwin Chari** (Max Planck Institute, Germany) and **Arwen Pearson** (CFEL, Germany). The over-riding feeling was that despite all the advancements made in technology and the advent of AlphaFold, crystallography is still a relevant and major force in structural determination and for understanding key issues in biology. The day's proceedings finished nicely with an informal networking event, a poster session over some tasty food and a hearty cèilidh for all to relax their brains for the next day.

The second day began with a lecture entitled "What's new in CCP4?" by **Ville Uski** (UKRI-STFC CCP4) which was followed by a presentation entitled "Dials User Interface 2" by **Luis Fuentes-Montero** (DLS) covering software developments in data processing. The next lecture entitled "Moorhen: interactive model building on the web" by **Filomeno Sánchez Rodríguez** (York) who described the new web-based protein modelling and refinement tool (moorhen.org) which is written in React and uses the libcoot API. The final talk in this session was entitled "Developments in multi-crystal data processing" and was given by **Amy Thompson** (DLS) who described this computationally demanding technique for combating the challenges associated with room temperature collection and radiation damage. Clustering methods which are applied by the program *xia2.multiplex* can be used to significantly improve



*Elspeth Garman (Oxford) chairing a panel discussion entitled "Crystallography is dead – long live Crystallography!" at the 2024 CCP4 study weekend with **David Brown** (Servier, France), **Ashwin Chari** (Max Planck Institute, Germany) and **Arwen Pearson** (CFEL, Germany) straining attentively to glimpse the screen behind!*



*AlphaFold predictions are great hypotheses, but they can be wrong or distorted. Slide by **Dorothee Liebschner** (LBNL, USA).*

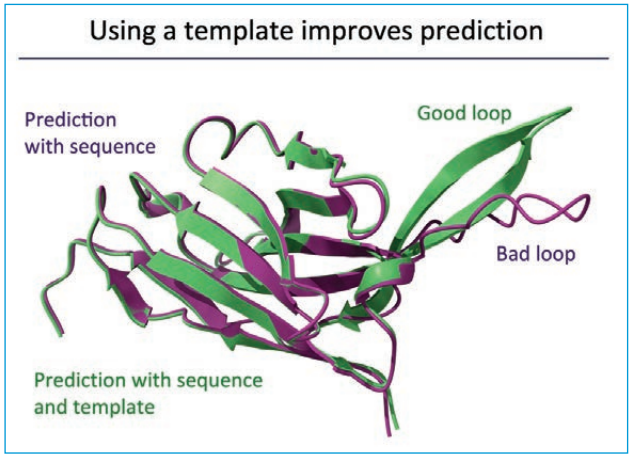
data quality and to visualise distinct states within a multi-crystal dataset.

The second session: "Preparation and data collection: planning and execution of the diffraction experiment" started with **Elspeth Garman** (Oxford) talking about "Identifying radiation damage and avoiding it in the first place." Elspeth gave a wonderful overview on the effects of radiation damage during data collection resulting in fading of data quality and leading to pathologies in structures. The program RADDOSE-3D is now routinely used in many beamlines, including I03, I04 and I04.1 at Diamond, to minimise radiation damage in the first place. Then **Graeme Winter** (DLS) emphasised "Use the right tool, right: making the best use of the right X-ray facility for your science" and never be afraid to ask questions and to discuss your experiments with experts. The session was concluded by **Rasmus Fogh** (Global Phasing) who told us about "Automated workflows for strategy computation and data collection at synchrotron beamlines." The GΦL expert decision-making software for multi-orientation data collection achieves optimum redundancy with minimum radiation damage and is used at an ever growing number of synchrotron sources.

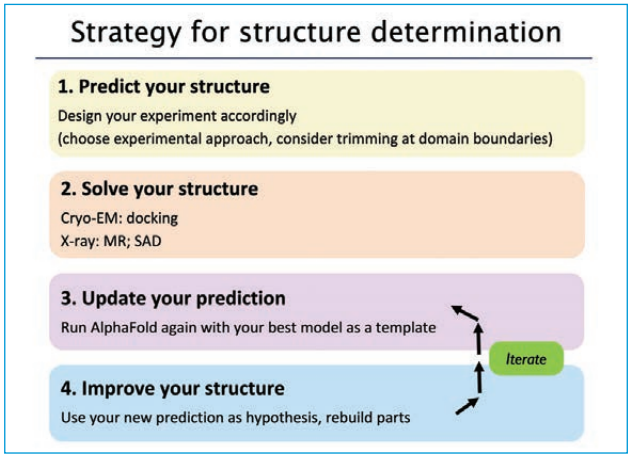
Session 3 entitled "Structure solution & model building (post-AlphaFold)" started with **Dorothee Liebschner** (LBNL, USA) who talked about "AlphaFold and its impact on streamlining structure solution." Dorothee highlighted how predictive models generated by AlphaFold, OpenFold and RosettaFold not only speed up structure determination, but how a new iterative model-improvement procedure (*phenix.predict_and_build*) that generates predicted models can be used to solve an X-ray structure by MR or to interpret a cryo-EM map. **Kamel el Omari** (DLS) talked about "Light atoms identification and location by anomalous scattering" using the unique wavelength range from 1.1 to 5.9 Å available at the beamline I23 (DLS). This enables experimental identification and location of metal ions and lighter atoms of biological relevance (Ca, K, S, P and Cl), especially in important enzymes such as polymerases, by their anomalous scattering. **Paul Emsley** (UKRI MRC-LMB) told us about "Being efficient (or lazy) in Coot" by finding short-cuts and using them. The new version of the program has significant improvements such as interactive navigation and validation during real space refinement.

Session 4 with its intriguing title "The important final touches: modelling subtle / difficult structural features" began with **Tristan Croll** (Altos Labs, UK) who, despite being locked down with Covid, was able to remotely talk us through "Five years of ISOLDE: lessons learned and paths forward." The speaker described how interactive molecular dynamics can now be performed in structure analysis due to the availability of affordable GPU's which also allow parallelisation of structure factor calculations so that the electron density can be updated constantly. The speaker concluded by considering ways ahead for coping with the inevitable data-deluge from the cryo-EM revolution. **Lucy Schofield** (York) highlighted the issues and new approaches involved in "Building atomic models of glycans with confidence" as sugars are very heterogeneous, flexible and stereochemically complex, even though pyranose rings have clear conformational preferences. Bringing structural glycobiology up to a speed comparable with that of proteins and nucleic acids has required new methods to be developed. New software, such as PRIVATEER, is continually being updated to address these issues. **Garib Murshudov** (UKRI MRC-LMB) informed us on "Dealing with metal-containing ligands" which remains a surprisingly difficult subject despite the remarkable improvements in ligand building and validation tools over the last two decades. Problems arise with difficult coordination geometry and ionisation state. The speaker described tools for improved treatment of metal-containing ligands with special attention to heme-like ligands and iron-sulphur clusters, as they form a substantial portion of the wwPDB's chemical components dictionary (CCD).

Day three began with Session 5 on the subject of "Weak signal/large datasets: partial data and partial occupancies" commencing with a lecture by **Arwen Pearson** (CFEL) entitled "Same but different: serial data collection and processing." The speaker compared the now well-established pipelines for routine data collection and processing with the different flavours of serial and multi-crystal methods, focussing on the T-REXX endstation on beamline P14 at the PETRA III synchrotron in Hamburg and the handling of the associated metadata. Next up, **Elke de Zitter** (IBS, Grenoble) gave a presentation entitled "Xtrapol8: identifying and modelling low-occupancy states in macromolecular crystallography." The speaker described how the program Xtrapol8 was originally written for the analysis of time-resolved crystallography data, to compare electron density maps and structures acquired before and after the application of a trigger, but it can also be applied to other studies in which a low-occupancy state is of interest. The final talk of this session "Everything, everywhere, all at once: multi-state, multi-dataset, multi-model refinement" was given by **Nicholas Pearce** (Linköping, Sweden). The speaker covered the generation, refinement and validation of multi-state models in multi-dataset experiments with automatically generated



Using a data-based template improves AlphaFold prediction. Slide by ***Dorothee Liebschner*** *(LBNL, USA).*



A modern strategy for structure determination that includes AlphaFold prediction. Slide by ***Dorothee Liebschner*** *(LBNL, USA).*

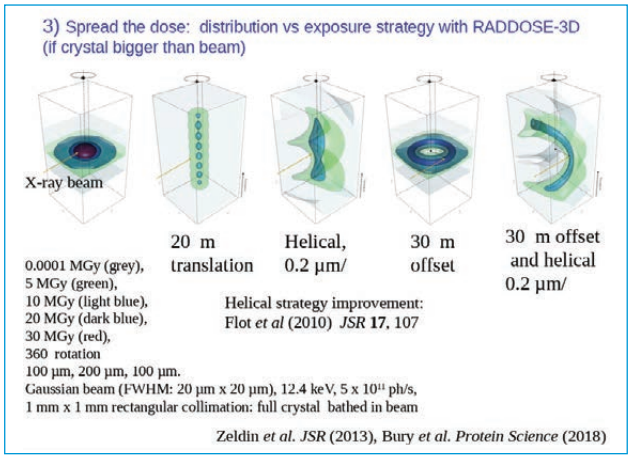
structural restraints which aid convergence. This method was applied to fragment screening of the SARS-CoV-2 protease.

The 6th session entitled "Experimental interactions: ligands, everywhere, all at once" began with a lecture by **Judit Debreczeni** (AstraZeneca) who gave an excellent overview of "Decision making in MX – how to be a productive structural biologist" from an industrial structural biologist's perspective. **Ed Daniel** (Oulu, Finland) then talked about "Managing your data with LIMS systems" covering the use of the IceBear software – a laboratory information management systems (LIMS) tool to ensure complete tracking from protein sequence through to structure deposition and raw data archival. Next, **Oliver Smart** (Global Phasing) talked about "Validation of ligands: making decisions while modelling" focussing particularly on how mistakes can arise during structure determination. The devil is in the detail and it is important to reduce the number of errors, one example being in the assignment of correct ligand tautomers. Practical approaches to avoiding common pitfalls in ligand fitting were suggested.

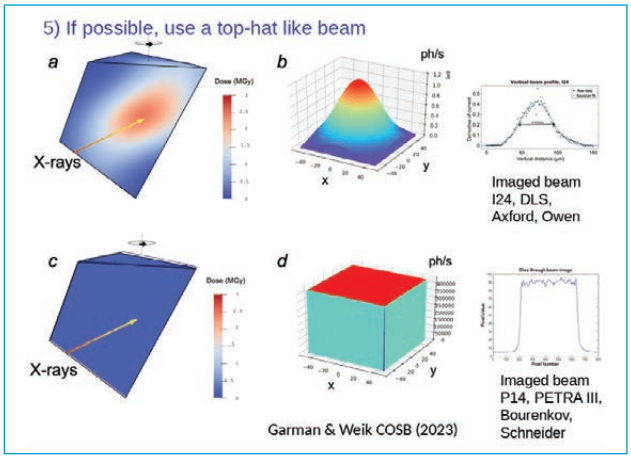
In the seventh and final session entitled "Structural analysis: climbing the data mountain" **Helen Ginn** (DESY, Hamburg) talked on the subject of "Teasing out the secrets of subtle protein dynamics" using RoPe (**r**epresentation **o**f **p**rotein **e**ntities) – a powerful tool which enables visualisation of conformational space from experimental data and how this space can be used to drive protein refinement against the electron density. Next, **Briony Yorke** (Leeds) presented on the subject of "Probing crystallin using UV/X-ray crystallography" by the serial approach to investigate photostability and photodamage in human γD crystallin. Crystallins are proteins which have evolved to retain transparency over the course of a human life span in the absence of cellular regeneration and with daily exposure to UV. Finally, **Ashwin Chari** (Max Planck, Germany) talked about "Analysing models from ultra-high resolution crystallography" with the aim of supplementing time resolved studies with ultra high resolution data from macrocrystals of highly homogenous mechanistically trapped states.

The meeting was closed by **Helen Ginn** (DESY, Hamburg) and **Nick Pearce** (Linköping, Sweden) who thanked all the speakers, organisers and session chairs for their excellent contributions to the meeting. The workshop highlighted that macromolecular X-ray crystallography is still highly relevant and, together with other techniques, will continue contributing to our knowledge on biological functions.

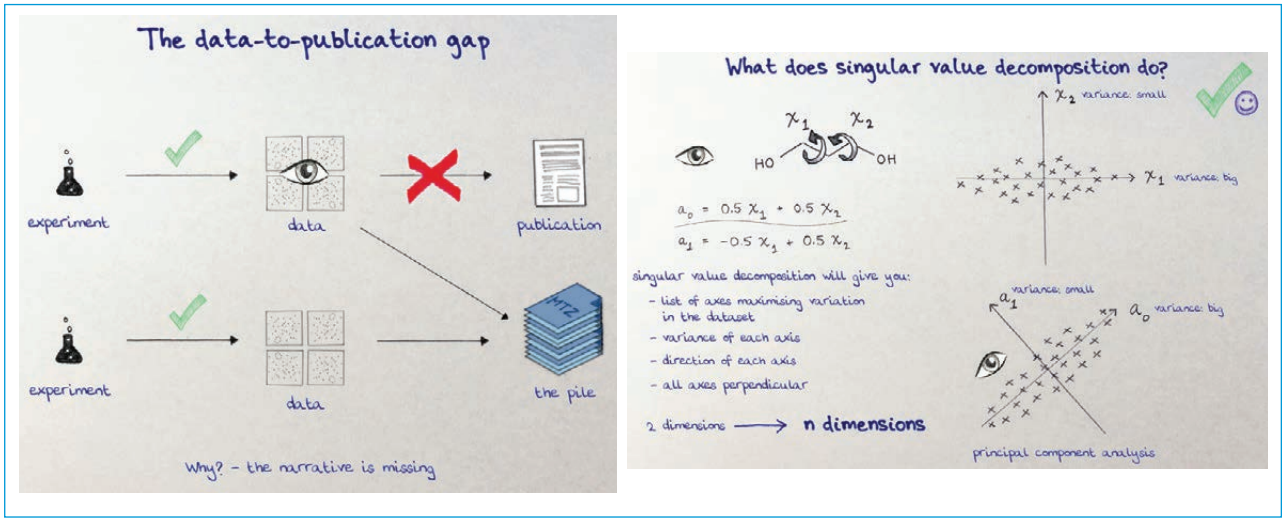
Ben Bax, Cardiff
Shabir Najmudin, Kings/Nottingham/City-St George's



Elspeth Garman (Oxford) presented on the RADDOSE-3D software tool which allows the dose for a planned diffraction experiment to be visualised. Dose distributions for a range of data collection strategies are shown here.



*Using a top-hat beam gives a more homogeneous dose distribution and avoids 'hot spots' of high damage caused by the peak of a more Gaussian shaped beam. Slide by **Elspeth Garman** (Oxford).*



Helen Ginn (Hamburg) presented artistically on the data-to-publication gap, giving a brief summary of the difficulties of publishing at the forefront of structural biology and on how singular value decomposition (SVD) can be used as principal component analysis to visualise clustering.

Down memory lane: The Manchester Atlas X-Ray Diffractometer

The background

THE Atlas on-line X-Ray Diffractometer project (X-Rad, for short) was born at a time in the early 1960's when it was becoming clear computers and automation could have a massive impact on the speed and reliability of repetitive scientific processes requiring the collection of large amounts of data. The use of X-ray diffractometers to examine the internal structure of crystals at a molecular level is one such application. The principles were established by W L Bragg and his father in 1912 and have been widely exploited since. In particular, X-ray diffraction techniques have been fundamental in the determination of the 3D structures of complex organic molecules, well known examples being penicillin and insulin. Both these structures were solved by the distinguished scientist Dorothy Hodgkin, awarded the Nobel Prize in 1964 for her work using X-ray crystallography, who visited the Manchester project in its later stage to see the work being done.

The size and cost of early computers made it unrealistic to dedicate a whole machine to a single scientific instrument. The notion of time sharing, as exemplified by Atlas, opened up the opportunity to control data collection just using a fraction of Atlas's capability and made the concept much more attractive. An important follow-on question was just how the work balance should best be shared between Atlas and the data collection system. But first, some background on the X-Rad system and the people involved.

Figure 1 shows the four-circle diffractometer, also called a goniometer, mounted on its cabinet containing the power supply and controls for the X-ray source. Alongside was a standard Atlas cabinet containing the digital and analogue electronics linking the diffractometer to Atlas. The diffractometer, a Y290, was designed by Uli Arndt, then at the Royal Institution and made by the long-established, but sadly now defunct, precision instrument manufacturer Hilger and Watts in north London. An initial attempt to automate the Y290 had proved unreliable and the University of Manchester was given the opportunity to exploit the potential of Atlas in a novel way to achieve real-time data collection.

The equipment in Figure 1 was surrounded by a glazed cubicle, the whole being located about eight yards from the Atlas computer in a separate room previously occupied by a Mercury computer. Owen Mills from the University's Chemistry Department was the client, a specialist in X-ray crystallography and a major computer user. Dai Edwards took the lead responsibility for the Electrical Engineering (EE) Department. The other members of the team were Keith Bowden, who initially was also involved in the Atlas fixed-store design and implementation, and myself. I graduated in EE in 1961 and joined the group as an MSc student under Keith's supervision. My particular responsibilities lay with the position control systems for the diffractometer but, being the junior member, was also involved in the complete design and implementation process. A very satisfying experience.

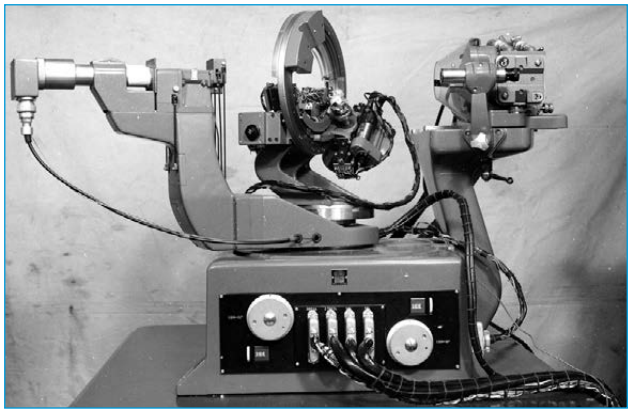


Figure 1. *The four-circle diffractometer at the heart of the X-Rad system. The cables leading off to the right connected with electronics that linked the X-Rad system to the Manchester Atlas computer. This image is courtesy of the University of Manchester.*

The system

The crystal whose structure is to be studied is mounted on a thin support so that it lies at the very centre of the diffractometer. Three separate circular components are visible in Figure 2, the *phi*, *chi* and *omega* circles. These can each rotate independently and be set to any position with an accuracy of 0.01°. So, it is possible to choose any angular position for the crystal in 3-dimensions to a high degree of accuracy. The fourth circle, *twotheta*, carries the X-ray detector. The detector can only rotate in one plane so, for each measurement position, the crystal must be set so the diffracted beam of interest lies in the detector plane. The diffracted beam has a natural spread and its intensity is measured by scanning the detector across the beam for a set time and counting the quanta received. The repetitive operating sequence of the diffractometer is to set a new crystal and detector position, generally involving movement of all four circles, followed by a scan of the beam using just two circles whilst measuring intensity. A data gathering session might involve several thousand measurements and take many hours. Overnight and weekend running was the norm. The results of a run were accumulated in a file (held on magnetic tape) on the Atlas. At the conclusion of a run, an analysis program produced the desired information on the structure of the molecule under test.

The motors for each of the four circles were state-of-the-art DC permanent magnet motors with DC tachometers attached. This was before the days of digitally commutated motors. Conventional transistor power amplifiers drove the motors and speed was controlled by an analogue velodyne system. Angular movement was measured by optical moire fringe systems of the type then being adopted for numerically controlled machine tools. Because the moire fringe system provided relative rather than absolute positioning, a separate set of photocells scanned separate tracks with clear and opaque sections to set the working range of each circle. This allowed the diffractometer to find fixed reference positions from which all further movements were made counting fractions of the moire fringes. Limit switches protected the diffractometer from malfunctions and positioning errors.

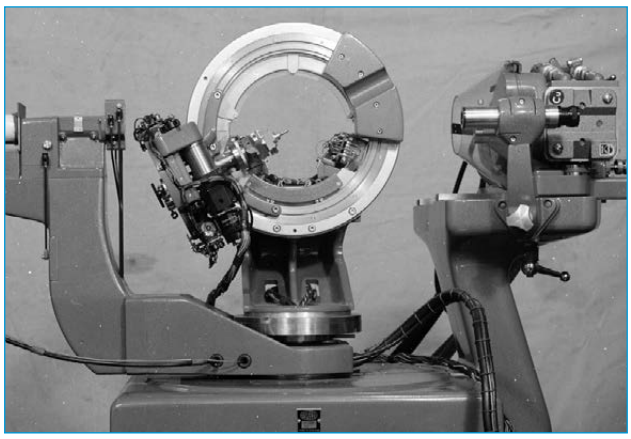


Figure 2. *Close-up of the type Y290 diffractometer or goniometer at Manchester. This image is courtesy of the University of Manchester.*

A party trick for visitors was to allow them to force a diffractometer circle away from its desired position using the manual setting wheels and then watch and feel the digital servo firmly but gently drive it back to exactly the right position.

The whole control system, including both analogue and digital sections, was mounted in a standard Atlas rack with Atlas circuit boards for the digital logic. Because both positioning and beam measurement just required simple arithmetic counting, the digital system was based around a set of registers and a half adder/subtractor. For diffracted beam measurement, 20 bit register capacity was chosen to give adequate statistical accuracy. Signed differences for positioning each circle within a 360° range with 0.01° accuracy requires 17 bits but 18 bit registers were chosen for engineering convenience. So, the register and half adder/subtractor data loop was set at 20 bits.

There is an interesting twist to the design that reflects the relatively high cost of digital circuits at that time. The total functional register capacity is just 72 bits for positioning the four circles and 40 bits for receiving the counts from two detectors (the Manchester chemists chose to use just one but the system was designed for the more general case with two). A mere 104 bits in total. However, it was thought worthwhile to share some registers between functions because not all are in use at one time. The digital position control loops for each of the circles could be kept live even when not moving to new positions by short, 6 bit, 'clamping' registers. The actual gain was minimal but from my memory of the design decisions it was thought worth the slight extra complication to demonstrate the principle.

Communication between the diffractometer system and Atlas was via the standard Atlas V-store system containing three 24 bit registers, two for information and control and the third for testing. In this respect, the X-Rad was just another of the many input/output devices connected to the main computer.

Priority logic accepted asynchronous interrupts from up to eight sources including two quanta detectors, the four goniometer circles and two associated with the V-store. Interrupts could be prioritised and dealt with in around 1 microsecond allowing peak count rates of 1M quanta per second, assuming single detector operation. Average count rates were much lower, around 10k per second. When counting was in progress just two circles would be in motion, the *omega* and *twotheta*, at quite a slow rate, around 0.5°/second. At this speed the interrupt request rates associated with positioning average one every 10 milliseconds and these have minimal impact on peak counting rates. Of course even low priority interrupts must be dealt with in the same time as the highest to avoid potential loss of counts.

The Sequel

The Atlas on-line system worked well and productively for a number of years and benefited from direct digital interfacing between the diffractometer and Atlas. However, with only a small number of Ferranti Atlas computers in existence it did not provide a general solution which could be used to satisfy the increasing demand for automated systems. Around the time the first Atlas system was completed at Manchester, new small and relatively cheap minicomputers became available which could potentially be used to replace a lot of the special hardware with software. Hilger and Watts were keen to take advantage of this opportunity and one of the very first DEC PDP-8 models was purchased. There are claims this was the fourth machine to be sold by the company. It was certainly very early days for DEC in the UK. I remember spending time at the UK headquarters in Reading, then bare-boarded space over a carpet shop in Castle Street, testing bits of software before our production machine arrived. A lot of the floor space was used to store machine manuals which were handed out at exhibitions as sales material. No glossy sales leaflets. One of the technical staff was Geoff Shingles who stayed with DEC as it expanded to be a very large operation in the UK.

As the PDP-8 had a short 12-bit word length, double length working was needed for the circle position and detected quanta count registers. However, with some pre-scaling of the count rate, the machine was quite capable of satisfying the time constraints of the application. The diffractometer inputs were handled by the PDP-8's priority interrupt system, emulating the special hardware of the Atlas X-Rad. A bespoke operating system functionally replicated the X-Rad control hardware and also allowed background pre-processing of positional data. For this, software floating point functions were needed to achieve the necessary accuracy.

However, the PDP-8 certainly did not have the capability to do the processing of collected data and this had to be done off-line on another more appropriate machine. The standard input/output for small machines at that time was provided by the paper tape reader and punch options of the widely used Teletype keyboard and printer device. The initial advantage of using paper tape for input and output was its universality but apparently some later systems were adapted using digital interfaces to achieve more elegant solutions.

The Hilger and Watts PDP-8 system enjoyed considerable commercial success and was used quite widely in the UK, apparently until the 1980s, and abroad. One story suggested two systems went to the USSR but were never heard of again. In 1966 the company gained a Queen's Award to Industry for service to export and in 1968 a second Queen's Award for technical achievement.

Rounding off

The Atlas X-Rad system successfully demonstrated the principles of an automated on-line data collection system tightly integrated with a time-sharing computer. It was intensively used for diffraction studies for several years, fully exploiting the new capabilities of the Hilger and Watts four-circle diffractometer. It was ahead of its time in the sense that as it was very much a part of the Atlas system, possibilities for replication were extremely limited and it never happened.

However, the parallel introduction and explosive growth of relatively cheap mini-computers, such as the PDP-8, made it attractive to design stand-alone systems which could be acquired much more easily by research laboratories. They still automated the data collection process but relied on links to other computers to do the more complex data processing of results. In today's world, networking allows easy interconnection and the paper tape transfers of the PDP-8 age are long gone. Further information can be found in:

A small computer applied to real time data collection, D. B. G. Edwards, K. F. Bowden, J. Standeven and O. S. Mills. Computer Bulletin, Vol 10, No 1 June 1966, and

An Operating System for a Small Computer providing Time-Shared Computing and Control Functions, J. Standeven, K. F. Bowden and D. B. G. Edwards, I.F.I.P. Congress, Edinburgh, August 1968.

John Standeven

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The glowing vial

Uli Arndt FRS, the designer of the Hilger & Watts diffractometers, wrote a very interesting autobiography entitled "Personal X-ray Reflections" (Athena, London, 2006) in which he describes some unusual experiences in his first position at the Royal Institution, working with Dennis Riley a few years after WW2. The laboratory was located in the basement at the RI which housed what was allegedly the world's most powerful X-ray machine, along with many remnants of the work of Michael Faraday and James Dewar whose equipment was by then some 50 - 100 years old. Arndt describes how he happened to leave a box of X-ray film on the instrument maker's bench. When he used the films a few days later he found that they were all heavily fogged. Use of a Geiger counter in the lab where the film had been left showed that a 2 m^2 area of the floor where the instrument maker worked was highly radioactive. This was brought to the attention of the UK Atomic Energy Authority in Culham who sent a decontamination team. Remedying the situation required removing the wooden flooring and drilling up about 15 cm of the concrete beneath. Coincidentally, during this work by the Culham team in full protective gear and breathing apparatus, the lab was visited by an elderly gentleman who had worked there some 50 years previously. He recounted how Dewar had been given some radium chloride by Marie Curie. On coming downstairs from the director's flat one night in his dressing gown to observe the radium glowing faintly in the dark, he had accidentally knocked the bottle on the floor. With a half-life of 1,600 years, we can expect appreciable persistence of the counts! In Ernest Rutherford's biography of Marie Curie[1] he states that she gave an invited lecture at the RI in 1903 and subsequently collaborated extensively with Dewar on the properties of radium. Presumably the breakage was not a major impediment to their work!

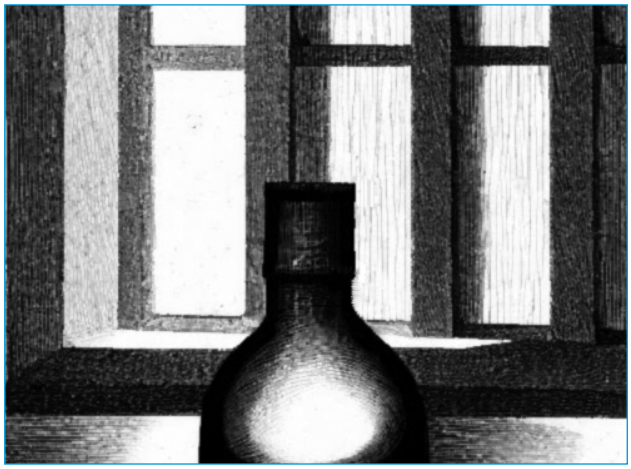
Meanwhile, back to Uli Arndt's new position at the RI where, having found a significant workplace radiation hazard, he then found out that the institution's pride and joy, allegedly the world's most powerful X-ray source, which dated back to the 1930's and drew up to 200A from the mains, was actually significantly less powerful than a regular hospital X-ray tube. The challenge he faced was one of putting it discreetly to the RI management that a certain amount of equipment reappraisal and modernisation might needed in the X-ray department. Fortunately, he was aided in this task by the fact that the new President of the RI (Lord Brabazon of Tara) was highly experienced in corporate backtracking. In fact, a prototype luxury airliner which bore his own name (the Bristol Brabazon) had just been written-off as commercially non-viable and the whole taxpayer-funded project abandoned. Consequently, signing off an old X-ray machine for disposal, presumably in the skip, was not a significant embarrassment.

Interestingly, the Brabazon was conceived during WW2, had 8 engines driving as many counter-rotating propellers and was comparable in size with the largest aircraft of today[2]. However it was slow compared to passenger jet planes which were already in use by the early 50's and it only had capacity for around 100 passengers. The plan included sleeping berths, a dining room, cinema, promenade and bar, which might have made sense as a mode of travel for the upper echelons of society in the immediate pre- and post-war era, but would hardly seem to be the model subsequently adopted for passenger flight by the aircraft industry, although it struck me that it might be one that could in future help us to achieve net-zero! The Brabazon's development required the demolition of the ancient village of Charlton and the rehousing of all its residents in order to extend the runway of Bristol Filton airfield. However, in one final cruel twist of fate, test flights showed that the Brabazon would have operated perfectly well if the runway had been left at its original length. Footage of her official maiden flight in 1949 may be seen by members on YouTube. With its very few irregularly placed portholes and generally scary appearance, it is tempting to speculate that it could have a second life in an austere carbon-neutral future where only the super-rich can fly, albeit perhaps not as fast as we do today. However, in retrospect, maybe the 1930's extravagance of the design was, like that of the RI's prestigious X-ray generator, the main ingredient of its downfall.

Jon Cooper
UCL

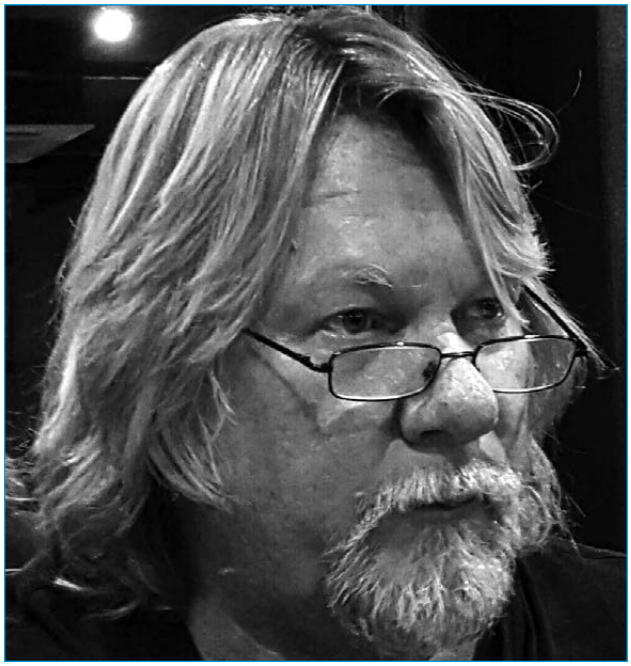
References:

1. Rutherford, E. (1934) "Mme Curie." *Nature* **134**, 90-91.
2. Wikipedia, the free encyclopedia.



A thematic image created by the surreal graphics generator at deepai.org.

Obituary



Richard Alexander Pauptit

Richard Alexander Pauptit 1954–2024

It is with heavy hearts that we write this memorial for Dr Richard Alexander Pauptit, who died on 30 June 2024. Richard was well known and highly respected in protein crystallography circles and contributed hugely to the field. His enthusiasm, passion, and creativity for this area of structural biology was infectious, and those who were fortunate to work, study and collaborate with him will feel a profound loss on his passing.

Richard was born in Amstelveen, in the province of North Holland, Netherlands in 1954. Due to his father's work, he spent his formative years travelling the globe including time in the Middle East, Europe, Australia and Africa, and the love of travel continued throughout Richard's adult life.

Richard completed his schooling at the American Community School in Beirut, Lebanon, before enrolling at the University of Cape Town, South Africa (1973–75) where he received a BSc and excelled in Chemistry and Computing. It was during his time as an undergraduate that Richard's interest in X-ray crystallography was sparked. Richard began working in the field of small molecule crystallography in the laboratory of Professor Luigi Nassimbeni at the University of Cape Town, helping to solve four small molecule structures.

Richard's academic journey continued at the University of British Columbia, Vancouver, Canada, where he undertook an MSc (1976–78) and PhD (1978–1982) in the laboratory of Professor James Trotter. Here, he honed his understanding of crystallography in the field of chemical crystallography, working on organic compounds.

Richard continued to build on his knowledge during a postdoctoral and lectureship position (1982–83) at the University of Auckland, New Zealand, which resulted in the publication of several small molecule structures.

In 1983, moving across the globe again, Richard took up a research position in the Biocenter at the University of Basel, Switzerland with Professor Johan Jansonius. At this stage Richard extended his research activities to the study of macromolecules. Using his broad crystallography background and programming skills, Richard wrote and improved a wide range of computational programs in the area of molecular replacement and protein structure refinement. At the Biocenter, he led and collaborated on many challenging projects including proteases, transaminases and other enzymes as well as the nascent field of membrane protein crystallography on a number of different porins.

In 1991, Richard moved to Heidelberg, Germany, to become a Fellow with the European Molecular Biology Laboratory (EMBL), working with many current leaders in structural biology. At EMBL his scientific collaborations focused on Src homology 3 domains and other related proteins.

Following this research position, in 1992, Richard took up a Team Leader position with AstraZeneca pharmaceuticals (formerly known as ICI Pharmaceuticals), in Macclesfield, United Kingdom. He established protein crystallography facilities and integrated this technique into an ongoing programme of drug design. Together with other scientists, under Richard's leadership, target-compound complex structures were determined which led to development of many drug therapies for disease.

As a Senior Principal Scientist and Associate Director in Discovery Sciences, Richard continued to inspire and innovate, ensuring that scientists could collaborate, within and outside of the company, encouraging rich partnerships with universities and research institutes. He played an important role in various outreach initiatives, including a postdoctoral programme whose aim is to promote a supportive and collaborative research culture for scientists to thrive. Richard brought the crystallography group in AstraZeneca to both national and international arenas. He participated in and led many collaborative and strategic activities including: leadership of the Biological Structures Group of the British Crystallographic Association; he was an active member of the CCP4 committee; a member of Scientific Advisory Board for BIOXHIT (an EU Framework 6 high-throughput crystallography project); was a Member of the Scientific Advisory Committee for the Membrane Protein Structure Initiative (MPSi), a BBSRC SPoRT initiative; and was a peer reviewer for *JMB, Structure* and many other journals, including IUCr Journals where he also acted as a Co-editor on *Acta Crystallographica F.*

Richard instigated communities of practice and founded opportunities to share expertise and research news, including the international Protein Structure Determination in Industry (PSDI) meetings and the CCP4 Glasgow Protein Structure Workshop, a Northern UK regional protein crystallography event involving around 10 academic laboratories and AstraZeneca.

Richard was a leading voice in the world of protein crystallography with a long list of invited lectures at meetings and conferences. With his expertise in drug discovery, he held honorary positions in academia in addition to supervising researchers and being a PhD external examiner. He had an amazing portfolio of collaborations and authored many publications, but the wealth of influence he had on so many projects is priceless.

To have encountered Richard, to have worked with him and interacted in some way along his globe-trotting scientific journey is an unforgettable experience. Many people will have listened to, and have been inspired by, his talks at various conferences and lectures at universities. Colleagues will have sat with him on various committees and organized meetings and conferences with him, and will be marked by these encounters. As his former students, we were fortunate to benefit from his unorthodox yet effective teaching methods. His approach was always centered around the individual, offering a unique perspective on research and teaching: the strong, black coffee he served kept us going through the long periods of data collection; the crystallography tutorials delivered in the safe learning environment of the local pub will be forever etched in our memories; and the nail-biting journeys of course, in a battered, left-hand drive Volvo were character building.

Richard may have introduced us to crystallography, but his influence remains with us over the course of our varied careers. He taught us with humility, he was the most supportive, warm, funny and unusual mentor. He formed a community who were bonded by a scientific goal but also united a team through kindness, generosity and karaoke.

Richard retired from AstraZeneca in 2014 and spent time developing many of his other skills and talents. A big fan of motorbikes and skiing, he once stated that he enjoyed the feeling of the wind fast flowing through his long hair. He had a passion for music, played the guitar and was always keen on introducing people to lesser-known Canadian guitar bands. In latter years, Richard explored his creative side, demonstrating a talent in painting and exhibiting his art several times. He was an active member of a crossword setting community, sharing his method of setting, and solving puzzles on a regular basis. Many readers of *The Independent* will have in fact struggled with cryptic crosswords set by 'Dutch', Richard's alias as a puzzle setter.

Richard is survived by a loving family who have been a constant source of strength and inspiration for him. His children made him proud and will carry his generosity of spirit with them. Richard will be remembered not only for his scientific achievements and creative endeavors but also for his kindness, generosity, and the indelible mark he left on the lives of those who had the privilege to know him. A unique man, who will be sorely missed.

Caitriona Dennis, Health Professions Education Unit, Hull York Medical School, York YO10 5DD, United Kingdom

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Meetings of interest

WHERE possible, information on the following meetings has been abstracted from the conference websites, where further details may be obtained.

Assistance from the IUCr website is also gratefully acknowledged.

If you have news of any meetings to add to future lists, please send them to the Editor, **jon.cooper@ucl.ac.uk**.

BSG Winter Meeting 2024 – New Advances and Future Directions in Structural Biology

MRC-LMB Cambridge, Friday 6th December 2024

Organisers: **Andrew Carter** (Cambridge) and **Simon Newstead** (Oxford)

Preliminary programme

10:30 – 11:00	Registration (with coffee and pastries)
10:50 – 11:00	Introductory remarks

Session 1

11:00 – 11:25	**John Jumper** (Google Deepmind)
11:25 – 11:40	Poster speaker
11:40 – 12:05	**Kelly Nguyen** (MRC LMB)
12:05 – 12:20	Poster speaker
12:20 – 12:45	**Tracey Gloster** (St Andrews)
12:45 – 14:15	Lunch and Poster Session

Session 2

14:15 – 14:40	**Harry Low** (Imperial)
14:40 – 15:05	**Vicki Gold** (Exeter)
15:05 – 15:20	Poster speaker
15:20 – 15:45	**Helen Cooper** (Birmingham)
15:45 – 16:00	Coffee
16:00 – 17:00	Town Hall Discussion – Future Directions for Structural Biology

- What do we see as the future interface between machine learning and academia
- Advances in high-resolution mapping of cellular function
- Dynamics, flexibility and transient interactions
- How do we get from the molecular scale to understanding systems and disease.

17:00 – 18:00 Drinks and Poster prizes.

CCG and PCG joint Autumn Meeting

The 2024 CCG Autumn meeting will be held jointly with the PCG and the ISIS Neutron and Muon Source in celebration of their 40th anniversary! The meeting will be held on the **27th – 29th October 2024** at the Cosener's House, Oxfordshire.

CCP-EM/Diamond Icknield Workshop

Harwell, 4th – 8th November 2024

This 5-day course is largely aimed at structural biologists with EM maps suitable for model building and refinement. This course will host some of the leading software developers and provide ample contact time to allow delegates to discuss their data in detail alongside traditional lectures and tutorials. This is a comprehensive course for EM model building covering advanced use of LocScale, ModelAngelo, Buccaneer, findMySequence-checkMySequence, EM_placement, Coot/Moorhen, TEMPy-REFF, ISOLDE, Refmac-Servalcat, Privateer, new validation tools and AlphaFold-DB & EMDB/PDBe updates. It will cover all aspects of model building including: map optimisation, automated model building, model fitting, medium resolution refinement, high resolution refinement, interactive refinement, validation and deposition.

Twenty-Seventh Congress and General Assembly of the International Union of Crystallography

Calgary, Canada, 11th – 18th August 2026

IUCr2026 is set to be held in the magnificent city of Calgary, located in the heart of Alberta, Canada, from **11th – 18th August 2026**. Calgary, a city renowned for its breathtaking natural beauty and warm hospitality, has been chosen as the host for this remarkable occasion. Nestled amidst stunning landscapes and boasting a rich cultural heritage, this vibrant metropolis promises to provide an unforgettable experience for all attendees. For details please visit: **www.iucr2026.org**.

For updates and details of all BCA meetings please visit: **www.crystallography.org.uk**

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